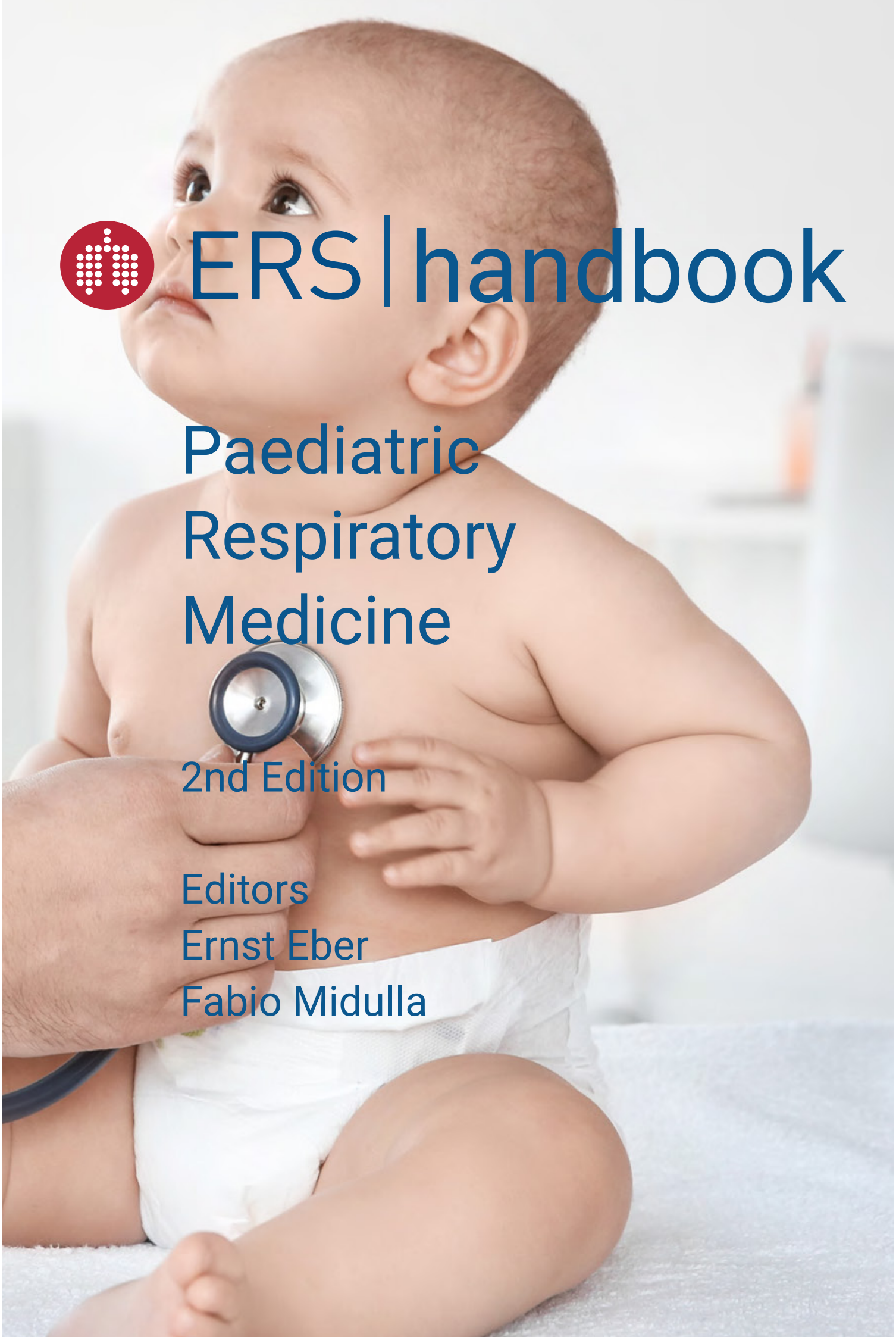

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2nd Edition

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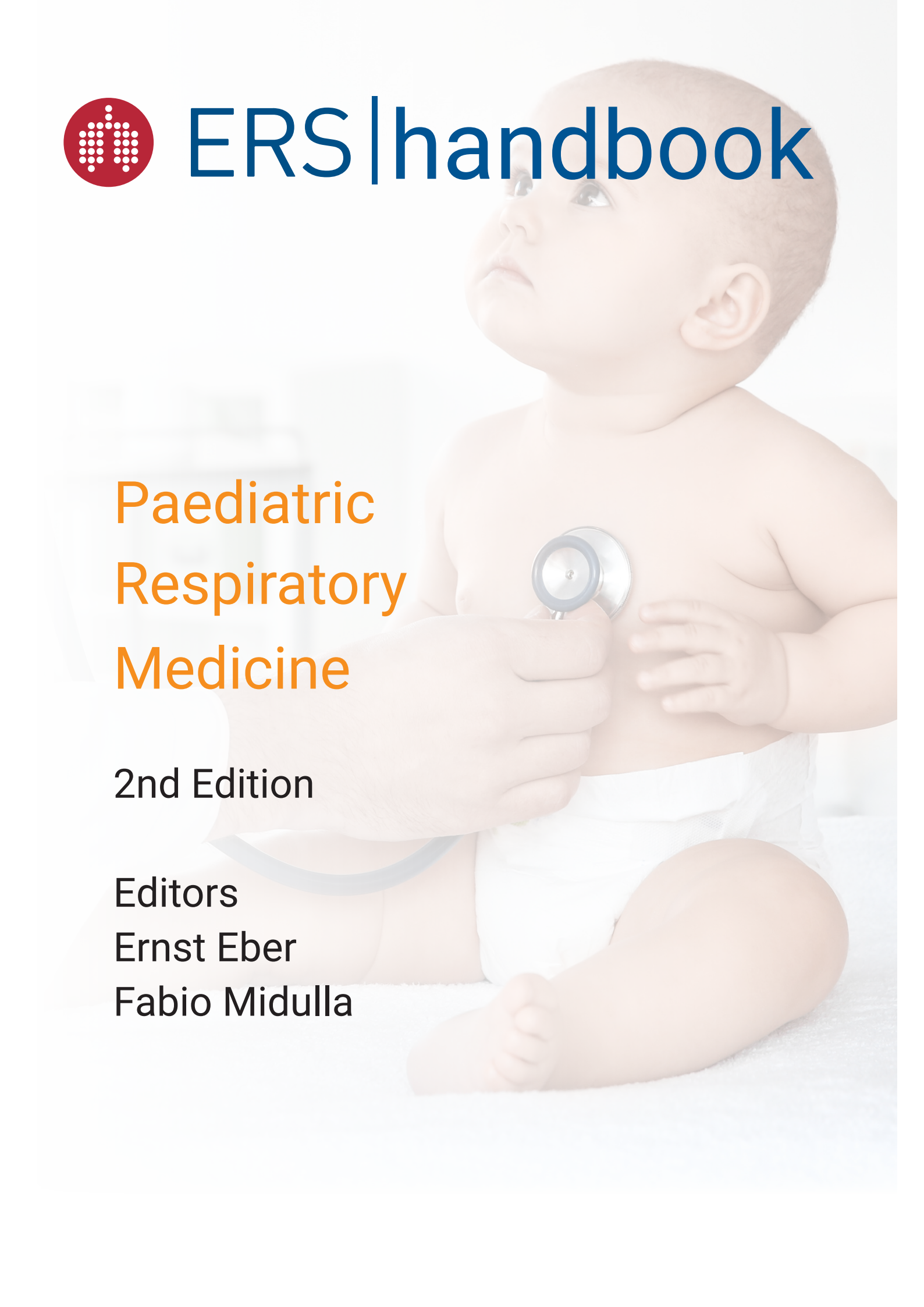

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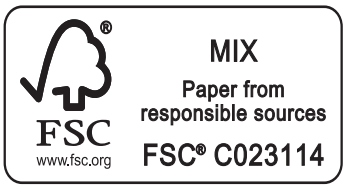

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Preface

"Education is not the filling of a pail, but the lighting of a fire."
(*Uncertain source*)

Dissemination of knowledge and medical and public education constitute fundamental objectives of the ERS mission, and the ERS aims to provide excellence in respiratory medicine education. In 2005, the ERS School started the very ambitious HERMES (Harmonised Education in Respiratory Medicine for European Specialists) project. Since then, HERMES Task Forces have formed to standardise training and education within different specialties of respiratory medicine. To support the implementation of various educational activities, the ERS has produced a series of *Handbooks* as educational tools, with the first edition of the *ERS Handbook of Respiratory Medicine* launched in 2010.

Starting in 2007, the paediatric respiratory medicine task force, using a formal consensus process and working with numerous experts throughout Europe, developed a HERMES syllabus (description of the competencies required) and a HERMES curriculum (description of how competencies should be taught, learned and assessed), as well as a voluntary European examination in paediatric respiratory medicine. With the content reflecting the HERMES syllabus and curriculum (published in 2009 and 2010, respectively), the first edition of the *ERS Handbook of Paediatric Respiratory Medicine* was published in 2013 and, as a compact state-of-the-art textbook, provided a comprehensive update for specialists within this field of respiratory medicine.

This second edition of the *ERS Handbook of Paediatric Respiratory Medicine* reflects the updated European paediatric respiratory medicine syllabus (published in 2019), which has been streamlined and made more relevant to current practice. The *Handbook* again consists of concise, peer-reviewed chapters written by experts in the field. We hope that this second edition will not only inform our trainees and be a valuable resource for those preparing for the paediatric HERMES examination but also provide an easily accessible and comprehensive update for colleagues at all levels of seniority, across paediatric respiratory medicine. Thus, this updated *Handbook* is intended to make a significant contribution to increasing the standards of training in paediatric respiratory medicine throughout and outside of Europe and, ultimately, to improving the care of children with respiratory disease.

We are grateful to the ERS Education Council and to the ERS publications staff who so thoroughly and thoughtfully curated the second edition of this *Handbook*, and last, but not least, to all the contributors who have shared their knowledge and experience with you.

Ernst Eber and Fabio Midulla
Chief editors

List of abbreviations

AHI	Apnoea–hypopnoea index
AIDS	Acquired immunodeficiency syndrome
BAL	Bronchoalveolar lavage
BMI	Body mass index
BPD	Bronchopulmonary dysplasia
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CT	Computed tomography
ECG	Electrocardiogram
ENT	Ear, nose and throat
FEV_1	Forced expiratory volume in 1 s
FRC	Functional residual capacity
FVC	Forced vital capacity
GOR	Gastro-oesophageal reflux
HIV	Human immunodeficiency virus
HRCT	High-resolution computed tomography
ILD	Interstitial lung disease
K_{CO}	Transfer coefficient of the lung for carbon monoxide
LCI	Lung clearance index
MRI	Magnetic resonance imaging
NIV	Noninvasive ventilation
OSA(S)	Obstructive sleep apnoea (syndrome)
P_{aCO_2}	Arterial carbon dioxide tension
P_{aO_2}	Arterial oxygen tension
PCD	Primary ciliary dyskinesia
PCR	Polymerase chain reaction
PEEP	Positive end-expiratory pressure
PFT	Pulmonary function test
PSG	Polysomnography
P_{tcCO_2}	Transcutaneous carbon dioxide tension
RV	Residual volume
S_{aO_2}	Arterial oxygen saturation
S_{pO_2}	Oxygen saturation measured by pulse oximetry
TB	Tuberculosis
TLC	Total lung capacity
T_{LCO}	Transfer factor of the lung for carbon monoxide
V'_E	Minute ventilation

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Anatomy and development of the respiratory system

Pinelopi Anagnostopoulou and Johannes C. Schittny

To understand how the lungs are built and how they develop is a prerequisite for paediatric respiratory medicine. In this chapter, we will first discuss aspects of anatomy, then this will be followed by an introduction to development of the respiratory system.

Anatomy of the respiratory tract

The respiratory system extends from the nose and mouth openings to the most distant alveoli. Its main purpose is gas transfer and gas exchange. The left and right lungs are housed in the ribcage (thorax). The expansion of the ribcage causes an expansion of the lungs and air flows into the lungs (inhalation). When the ribcage reduces its size, exhalation takes place. The air enters *via* the nose/mouth, passes through the throat (pharynx), the larynx and the trachea into the lungs, and travels through the bronchial tree. The latter includes conducting airways (trachea, bronchi and bronchioles) and gas-exchanging airways (respiratory bronchioles and alveolar ducts); conducting airways transport the air into the gas-exchanging airways. Gas exchange takes place in the alveoli, which cover the surface of the gas-exchanging airways.

The upper respiratory tract

The upper respiratory tract includes the nose, the nasal cavity, the paranasal sinuses, the mouth and the pharynx.

Key points

- While the conducting airways transport air from and to the respiratory zone, the alveoli in the alveolar ducts, in the terminal saccules and in the respiratory bronchioles are responsible for gas exchange.
- The conducting and respiratory airways are prenatally formed by repetitive cycles of outgrowth and branching of epithelial tubes (branching morphogenesis).
- Most of the gas-exchange surface area is formed by the formation of new septa dividing the existing airspaces (alveolarisation, also called septation).
- Alveolarisation starts prenatally and continues until young adulthood.

Larynx

The larynx is the border between upper and lower respiratory tracts. In neonates it is funnel-shaped, found at the level of C2–C3 cervical vertebrae, and it reaches the C1 when elevated, thus enabling simultaneous breathing and suckling at this age. In adults, it is found lower, at the level of C3–C6. It is composed of three single (cricoid, thyroid, epiglottis) and three double (arytenoid, cuneiform, corniculate) cartilages, as well as ligaments, membranes and muscles. Blood supply and innervation of the larynx are shown in table 1.

The larynx may be divided into three parts: supraglottis, glottis and subglottis. The supraglottis includes (from anterior to posterior) the epiglottic tip, the arytenoid folds and the arytenoid cartilage. The vocal apparatus is located at the glottis level and includes the pearly white true vocal cords that lie on each side of the opening (rima glottidis) and, above and lateral to each of them, the pink vestibular folds (false vocal cords) covered by vascular mucosa. The subglottis is continuous with the trachea.

The lower respiratory tract

The lower respiratory tract is located in the thorax and includes the trachea, the main bronchi and the lungs.

Table 1. Blood supply and innervation of the most important elements of the respiratory tract

	Blood supply	Innervation
Larynx	Superior and inferior laryngeal arteries	Vagus nerve
Trachea	Inferior thyroid arteries Bronchial arteries	Pulmonary plexus
Lung	Pulmonary circulation Two pulmonary arteries from the pulmonary trunk (right heart) send the deoxygenated blood to the alveoli for reoxygenation The oxygenated blood returns *via* the pulmonary veins to the left heart While the arteries run in parallel to the airways, the veins run inter-axially at the surface of the pulmonary units like acini, the subsegments and the segments Systemic circulation Bronchial arteries (from the aorta) supply lung regions not participating in gas exchange (*e.g.* bronchi and bronchioles) The bronchial veins drain into the azygos system	Pulmonary plexus Sympathetic fibres Sympathetic trunk (cervical and upper thoracic ganglia): causes bronchodilation Parasympathetic fibres Vagus nerve
Pleura	Arteries Bronchial arteries (visceral pleura) Subclavian artery (cervical pleura) Intercostal arteries (costovertebral pleura) Diaphragmatic vascular plexus (diaphragmatic pleura) Veins Venous drainage to the superior vena cava	Parietal pleura Intercostal nerves, phrenic nerve Visceral pleura Pulmonary plexus, no sensory nerves

Trachea and main bronchi

The trachea lies between the oesophagus and the sternum and consists anterolaterally of C-shaped incomplete cartilaginous rings and posteriorly of a fibromuscular wall. Just before the pulmonary hila, at the carina, it bifurcates into the right and the left main bronchi. The right bronchus is shorter, larger in diameter and lies more vertically compared to the left one.

Pulmonary hila

The root of each lung is known as the hilum (plural hila). The hilum connects the lung to the heart and trachea and includes the following structures: main bronchus, pulmonary artery, two pulmonary veins, bronchial artery and vein, pulmonary autonomic plexus and lymph nodes.

The lungs

The two lungs are similar, but not entirely symmetrical. The left lung is lower in volume and narrower (shorter transverse dimension) compared to the right lung, due to the presence of the heart in the left thoracic cavity. The right lung is relatively shorter (shorter longitudinal dimension) due to the liver, and thus the right hemidiaphragm is higher than the left. Lung volumes are sex specific (higher in boys compared to girls) and ethnicity specific, and height is a major determinant.

Right lung

The right lung consists of three lobes (superior, middle and inferior), divided by two fissures. The oblique fissure separates the inferior from the superior and the middle lobe, and the shorter horizontal fissure separates the superior from the middle lobe.

Left lung

The left lung consists of two lobes (superior and inferior) separated by the oblique fissure. The lingula is a small process of the superior lobe, usually found at the end of the cardiac notch.

Bronchopulmonary segments

Each main bronchus divides into lobar bronchi, which subdivide into segmental bronchi. Each segmental bronchus is a functionally independent lung unit (bronchopulmonary segment), which has a high clinical relevance (*e.g.* collapse or infection of a segment will not affect the whole lung). The segments are separated partially by connective tissue. Both lungs have 10 segments each (table 2), which vary in volume and shape. In some cases, segment VII of the left lung is very small

Table 2. Bronchopulmonary segments of the lung

Right lung		Left lung
Apical (I) Posterior (II) Anterior (III)	**Superior lobe**	Apical (I) Posterior (II) Anterior (III) Superior lingular (IV) Inferior lingular (V)
Lateral (IV) Medial (V)	**Middle lobe**	
Superior (apical) (VI) Medial basal (VII) Anterior basal (VIII) Lateral basal (IX) Posterior basal (X)	**Inferior lobe**	Superior (apical) (VI) Medial basal (VII) Anterior basal (VIII) Lateral basal (IX) Posterior basal (X)

and is viewed as part of segment VIII. The two lingular segments of the left lung are considered as equivalent to the right middle lobe and sometimes an additional partial fissure can be seen there.

The bronchial tree subdivides further by dichotomous branching. The proximal airways (bronchi) contain cartilage plates in their walls. Towards the periphery, the size of the cartilage plates decreases and eventually no cartilage is present. Beyond this point, the conducting airways are called bronchioles (figure 1). The branching pattern probably follows the shape of the chest cavity, and there is evidence that it is genetically determined. On average, the bronchial tree contains ~23 generations of airways, ranging from ~17 (upper lobe segments) to ~32 (posterior basal segments). On average, the first ~10 generations are bronchi, followed by ~4 generations of conducting bronchioles and ~4 generations of respiratory bronchioles. The exact number of generations per type of airway depends on the individual length of the pathway. Thus, on average, the first 14 generations, up to the terminal bronchioles, are purely conducting, and together with the upper respiratory tract they represent the anatomical dead space of the respiratory system, where only gas transfer takes place. Distal to the terminal bronchioles, the gas-exchange area begins, including several generations of respiratory bronchioles, alveolar ducts and saccules. The alveoli, where gas transfer takes place, cover the walls of the saccules and alveolar ducts, and partially cover the walls of the respiratory bronchioles (figure 1). The small tree of airways distal to the terminal bronchioles is called the acinus (plural acini) and

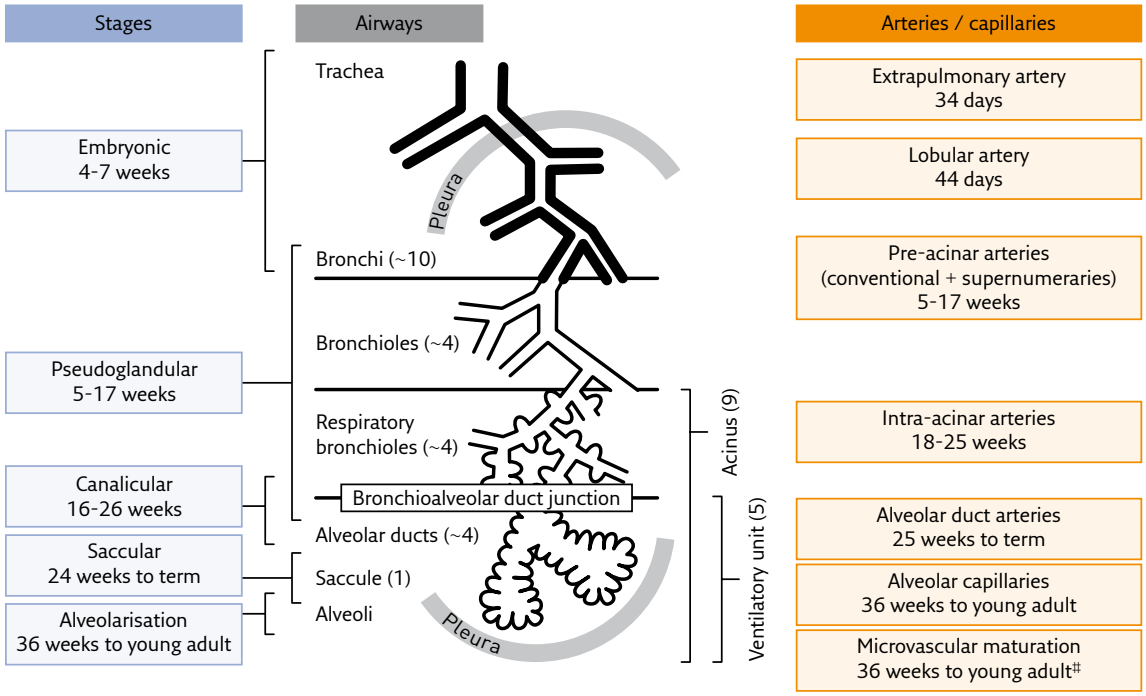

Figure 1. Layout of the bronchial tree and overview of lung development. The bronchial tree starts at the trachea, follows with the bronchi, bronchioles and alveolar ducts, and ends in the saccules. Gas exchange takes place in the alveoli, which completely cover the walls of the saccules and alveolar ducts, but only partly cover the walls of the respiratory bronchioles. The bronchial tree is formed during pre- and post-natal lung development. The stages of airway formation are given in blue, and the appearance and maturation of the vascular tree in orange. Timings of development, in days and weeks, are given post coitum for humans. Numbers of airway generations are shown in parentheses; on average, a human airway ends after 23 generations in an alveolar saccule; however, a range of 17–32 generations has been observed. ‡: own unpublished data. Modified from Hislop (2005) and reproduced and modified from Schittny (2018) with permission; © J.C. Schittny.

represents the functional/respiratory unit of the lung parenchyma. Inside the acini, the transition from the respiratory bronchioles to the alveolar ducts takes place. The point of transition is called the bronchioalveolar duct junction and hosts stem cells that are important for lung regeneration.

Blood supply

The pulmonary circulation drives the non-oxygenated blood from the right heart to the lung for oxygenation. Obviously, it cannot supply a sufficient amount of oxygen to the lung tissue. Therefore, the larger structures of the lung are supplied by the systemic circulation *via* the bronchial arteries. For an overview of the blood supply of the respiratory system see table 1.

Innervation

The innervation of the lower respiratory tract is mentioned in table 1.

Non-pulmonary structures of the thorax

Apart from the lungs, the thoracic cavity includes the chest wall, the mediastinum, the diaphragm and the pleura (table 3).

Chest wall

The neonatal thorax has a rounded circumference, which becomes dorsoventrally flattened later in life. The chest wall is about five times more compliant than the lungs in neonates, and is therefore easily deformable. This difference becomes progressively lower, so that the compliance of chest wall and lungs becomes equal in adults. The workload for breathing is significantly higher in neonates than in older children and adults. Therefore, neonates show an elevated vulnerability to develop respiratory muscle fatigue.

Pleura

The pleura is a serous membrane that covers the lungs. The inner layer (visceral pleura) adheres directly to the lung surface, except for the hilum area. The outer layer (parietal pleura) is adjacent to the structures that cover the lung. According to its location it is called costovertebral, cervical, mediastinal and diaphragmatic. A thin pleural cavity lies between the two layers. The pleural fluid serves as a lubricant and allows the two layers to slide against each other during respiratory movements without losing the

Table 3. Other structures of the thoracic cavity

Chest wall	Bones: 12 thoracic vertebrae, 12 paired ribs, sternum Muscles: intercostal (external, internal, innermost)
Respiratory muscles	Main respiratory muscles: diaphragm and intercostal muscles Accessory respiratory muscles: scalene muscles, sternocleidomastoideus, *etc*.
Diaphragm	Peripheral muscular part Central fibrous part (centrum tendineum)
Pleura	Visceral and parietal pleura
Mediastinum	Organs: thymus, pericardial sac and heart, trachea, oesophagus Vessels: ascending aorta, aortic arch and its branches, descending thoracic aorta, pulmonary arteries and veins, vena cava (superior and inferior), azygos and hemiazygos venous system, thoracic lymph nodes and thoracic duct Nerves: thoracic sympathetic trunk with splanchnic nerves, vagus nerve, phrenic nerve

mechanical coupling between the lungs and the thoracic wall. Pleural recesses are locations where the pleural surfaces are in direct contact without any intervening lung tissue: the costomediastinal recess (between costal and mediastinal pleura) and the costodiaphragmatic recess (between costal and diaphragmatic pleura).

Diaphragm

The diaphragm is the major inspiratory muscle and separates the thoracic cavity from the abdominal cavity. It consists of a central tendon part and a peripheral muscular part. Relatively flat at birth, it acquires a dome shape as the thoracic cavity grows and expands. Many structures (*e.g.* aorta, oesophagus, inferior vena cava, *etc.*) pass through the diaphragm *via* diaphragmatic openings. Failure of fusion of muscle fibres may cause a congenital diaphragmatic hernia, commonly at the left posterolateral diaphragmatic corner (Bochdalek hernia). The blood supply comes from phrenic branches that arise from the aorta. The diaphragm is innervated by the phrenic nerve (C3–C5).

Development of the lung

At the beginning of human lung development, the oesophagus and the trachea are not yet separated. The trachea and main bronchi derive from the primitive foregut. The right and left main bronchi give rise to the two lungs independently. This occurs *via* a repetitive cycle of outgrowth of epithelial tubes into the surrounding mesenchyme, then branching of these tubes. This process is widespread and highly conserved throughout evolution, and is known as "branching morphogenesis". It forms all of the conducting and respiratory airways, including the saccules, until term (figure 1). It also governs the development of branched glands (*e.g.* salivary, mammary and lacrimal glands) and the renal tubules.

Prenatal lung development is further subdivided into four stages, based on organogenesis, continued branching morphogenesis, epithelial differentiation and formation of primary septa: embryonic (6–9 weeks post-menstrual age (wPMA; weeks of pregnancy/gestation; weeks post coitum+2 weeks)), pseudoglandular (7–19 wPMA), canalicular (18–28 wPMA) and saccular (or terminal sac; 26 wPMA until term) (table 4).

The gas exchange area is increased more than 10-fold by a process known as "alveolarisation" or "septation", which starts before birth but continues post-natally. This process is unique to lung development and subdivides the existing airspaces by the formation of the secondary septa. It continues at least as long as the lung grows, until young adulthood (figure 1 and table 4).

Embryonic period (6–9 wPMA)

Lung

An outpouching of the ventral wall of the primitive foregut gives rise to the right and left main bronchi, which themselves give rise to the two lungs independently. They elongate and start a repetitive cycle of growth into the surrounding mesenchyme and dichotomous branching, which is called branching morphogenesis. The latter requires an intensive epithelial–mesenchymal interaction, which takes place between the ectodermal epithelium of the foregut and the surrounding mesenchymal tissue. At this point, the inner surface of the future airways is covered by an undifferentiated cubic epithelium.

Trachea

The laryngotracheal groove (sulcus) in the lateral wall of the foregut deepens and fuses progressively, thus separating the trachea from the oesophagus. Cartilage formation starts in the mesenchyme surrounding the trachea at the end of the embryonic period

Table 4. Stages of human lung development and their time scale

Stage	Duration	Characteristics
Embryonic	E26–E49 (6–9 wPMA)	Organogenesis: formation of the trachea; primordium (anlage) of the right and left lungs; formation of major airways by branching morphogenesis; formation of pleura
Fetal		
Pseudoglandular	F35–F119 (7–19 wPMA)	Formation of bronchial tree and large parts of prospective respiratory airways; birth of the acinus even if the acinar epithelia are not yet differentiated
Canalicular	F112–F182 (18–28 wPMA)	Completion of branching morphogenesis by the formation of the most distal airways; first air–blood barrier; appearance of surfactant; acini become detectable due to epithelial differentiation
Saccular or terminal sac	F168–F266 (26 wPMA until term)	Expansion of (future) airspaces; formation of immature primary septa
Post-natal		
Alveolarisation[#]		
Classical (first phase)	F252 (38 wPMA) until age 3 years	Formation of secondary septa (septation) resulting in the formation of the alveoli; at the beginning of this stage, all alveolar septa are immature and contain a double-layered capillary network (they mature later, see microvascular maturation)
Continued (second phase)	Age 2 years until young adulthood (17–21 years)	Formation of secondary septa (septation); most of the alveolar septa are mature, containing a single-layered capillary network
Microvascular maturation	38 wPMA until young adulthood[¶]	Remodelling of the capillary bed of the inter-alveolar septa (transformation of the double-layered capillary network into a single-layered one); takes place approximately in parallel to alveolarisation

The timing of stages does not have sharp borders. Regional differences between central and peripheral areas and an overlap between stages are common. E/F: embryonic/fetal day (days post coitum). [#]: alveolarisation starts before birth; [¶]: own unpublished data. Data from Schittny (2018); © J.C. Schittny.

and continues until it reaches the smallest bronchi (27 wPMA). Following the same central-to-peripheral principle, the tracheal glands are formed, followed by the glands of the bronchi.

Pleura

At 7–9 wPMA, the parietal pleura develops out of the somatic mesoderm, a layer covering the inner surface of thoracic body wall. The splanchnic mesoderm gives rise to the visceral pleura.

Diaphragm

At 7 wPMA, the septum transversum is formed from mesenchyme tissue, which separates the pericardial cavity from the abdominal cavity. During the next 2 weeks, the two pleuroperitoneal membranes grow out of the two pleuroperitoneal folds. They fuse with the posterior edge of the septum transversum and form the first primitive diaphragm.

Arteries and veins

Vasculogenesis (*de novo* formation of vessels) starts with the formation of a plexus in the mesenchyme surrounding the lung buds. The plexus is connected caudally to the left atrium and cranially to the aortic sac. As airway branching continues, a new capillary plexus is formed as a halo surrounding each newly formed terminal end of the bronchial tree. Each plexus contributes to the building of the future pulmonary circulation, where the bronchial tree serves as a template for the formation of the vascular tree for blood and lymph vessels. Intussusceptive remodelling, pruning and angiogenesis of the primary formed vessels are necessary to build the final pulmonary circulation.

Clinical aspects of developmental defects in the embryonic period

Defects in organogenesis are often incompatible with life or cause severe pulmonary morbidity. They are related to the primordium of the lungs (pulmonary agenesis, aplasia, *etc*.), to incorrect tracheal/oesophagus separation (tracheo-oesophageal fistula, oesophageal atresia, *etc*.) and to initial lobe formation, as well as to an incomplete closure of the pericardial–peritoneal canal(s) by the pleuroperitoneal membrane (diaphragmatic hernias). In the latter case, the visceral organs move cranially and compress the lung at later stages, which leads to pulmonary hypoplasia. For further details of developmental defects, see section 10 of this *Handbook* "Congenital malformations".

Pseudoglandular stage (7–19 wPMA)

Developmental similarities between the glands and the bronchial tree gave the name to this stage. Branching morphogenesis continues and the bronchial tree is formed; in humans there are on average approximately 23 generations of branches. However, the number of generations formed depends on the length of the pathway of the future airways. Therefore, by the time of the transition from the pseudoglandular to the canalicular stage, the proximal generations of the future alveolar ducts are already present. The distal generations will be formed during the canalicular stage. Glands start to form in the trachea and bronchi at 14–16 wPMA.

Cellular differentiation

The first ciliated, goblet and basal epithelial cells, as well as α-smooth muscle actin-positive cells, are detected during the pseudoglandular stage. Differentiation and appearance of the cells starts proximally and proceeds distally. Once the differentiation continues past the future bronchioalveolar duct junction, alveolar epithelial cells will become visible first. However, this does not occur until the canalicular stage.

Mechanical forces

The α-smooth muscle actin-positive cells form a continuous layer around the future airways, starting at the trachea and ending proximal to the terminal bud of the developing bronchial tree. These cells start spontaneous peristaltic contractions by pushing waves of inter-bronchial fluid into the periphery, thus causing a rhythmic extension of the most distal airways, including the terminal ends. Around birth, these contractile cells change from a peristaltic to a static phenotype and regulate the diameter of the conducting airways.

Fetal breathing movements start in humans at ~12 wPMA. These movements cause an exchange of pulmonary and amniotic fluid and induce lung tissue stretching.

Clinical aspects of the pseudoglandular stage

Branching morphogenesis is highly dependent on mechanical forces. Compression of the lungs due to a diaphragmatic hernia, oligohydramnios, skeletal abnormalities or an embryonic tumour may cause different degrees of pulmonary hypoplasia. Hypoplasia refers to a reduced number of generations of the bronchial tree and may cause severe pulmonary insufficiency. In the case of oligohydramnios (too little amniotic fluid), two mechanisms may apply. First, there may be a direct effect due to the compression of the thorax caused by the lack of amniotic fluid. Secondly, oligohydramnios is often caused by genetic defects that reduce branching of the renal tubules. The same genetic defect could directly reduce branching of bronchial tree, because many of the genes involved contribute to both kidney and lung development.

Laboratory experiments have shown that elimination of fetal breathing movements and reduction of spontaneous peristaltic contractions of the airways reduce the number of generations of the bronchial tree. However, the clinical importance of these results has not been further investigated.

Canalicular stage (18–28 wPMA)

In the canalicular stage, the differentiation of the alveolar epithelia becomes histologically visible, which leads to the recognition of the future alveolar ducts (figures 1 and 2). The cuboidal cells present in the pseudoglandular stage differentiate to type I and type II alveolar epithelial cells. Type I cells are flat, possess a large surface area, and cover most of the alveolar surface. The type II cells stay cuboidal and start to produce surfactant. The first air–blood barriers are formed due to angiogenesis, and due to close contact between type I alveolar epithelial cells and capillaries. All these events are prerequisites for the first gas exchange, which becomes possible at the end of this period. Last but not least, branching morphogenesis stops during this stage (or at the latest at the beginning of the saccular stage), mainly due to differentiation of the cuboidal epithelial cells at the terminal buds of the bronchial tree.

Alveolar ducts/acini

At the bronchioalveolar duct junction, the epithelial layer consistency changes abruptly from ciliated cells and club cells (bronchiolar exocrine cells) to type I and II alveolar epithelial cells. The bronchioalveolar duct junction forms during the canalicular stage, hosts stem cells, and stays constant throughout lung development at the location (generation of the airway) where it was originally formed. The bronchioalveolar stem cells are cuboidal cells located at the transition line where the epithelium of the bronchiole ends and that of the alveolar duct starts. Because the bronchioalveolar duct junction demarcates the entrance to the ventilatory units (figures 1 and 2), the number of ventilatory units also stays constant. This means that the ~10-fold increase of lung volume, which takes place until adulthood, is achieved by growth of the ventilatory units and not by increase in number.

Air–blood barrier

In order to build the first air–blood barrier, the capillaries of the mesenchyme “move” to the surface of the future alveolar ducts, which is by now covered by type I epithelial cells. The basement membranes of the endothelial cells and type I alveolar epithelium fuse and form a very thin sheet-like structure optimised for gas exchange.

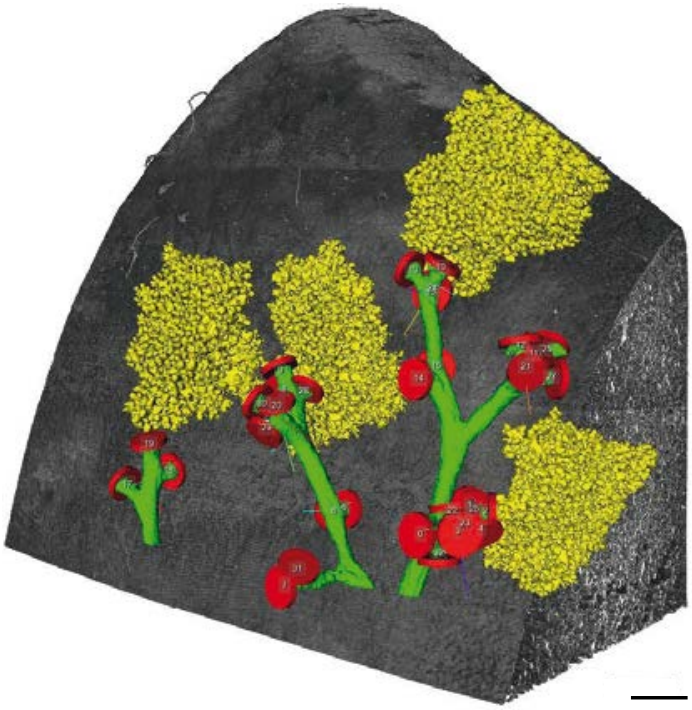

Figure 2. 3D-visualisation of rat acini/ventilatory units branching from terminal bronchioles. The conducting airways are drawn in green and the acini/ventilatory units in yellow, in a view looking from the outside onto the air–tissue surface. Hence, the ventilatory unit resembles the small tree of alveolar ducts distal of the bronchioalveolar duct junction (labelled by segmentation stoppers (red discs), which are disks of a defined grey value that are added into the 3D dataset by hand; they separate the grey-value-based segmentation of the conducting airways from that of the acinar airways). Because rats do not have respiratory bronchioles, each acinus has only one ventilatory unit. In humans, who possess respiratory bronchioles, one acinus has 8–16 ventilatory units, because the respiratory bronchioles belong to the acinus (figure 1). Only four out of 24 acini present are shown, in order to recognise individual acini. Scale bar = 0.5 mm. Reproduced from Schittny (2018) with permission; © J.C. Schittny.

Surfactant

During the canalicular stage, type II alveolar epithelial cells start to produce surfactant. Surfactant contains ~80% phospholipids, ~10% neutral lipids and ~10% surfactant proteins (SP-A, SP-B, SP-C and SP-D). By dynamically lowering the surface tension, surfactant is a prerequisite for the first inflation of the lung, directly after birth. It also prevents the lungs from collapsing during expiration, takes part in the regulation of airspace size, increases compliance, and SP-A and SP-D contribute to innate immunity. For more information about surfactant, see chapter "Surfactant dysfunction syndromes and pulmonary alveolar proteinosis", as well as the sections covering respiratory mechanics, immunology, BPD and ILD.

Clinical aspects of the canalicular stage

Survival is possible if birth occurs towards the end of the canalicular stage, but the infant normally needs assisted ventilation and has a high risk for developing BPD. Defects in the canalicular stage can lead to a condition called alveolar capillary dysplasia. This represents a very rare lethal congenital disease, where pulmonary blood vessels, in particular alveolar capillaries, are greatly reduced.

Saccular stage (26–40 wPMA)

During the saccular stage, the mesenchyme further condenses, the acinar airways grow in length and width, and primary immature septa are formed in all locations

where two airspaces meet. A thin layer of connective tissue separates the sheet-like capillary networks of both surfaces of the septum. In parallel, platelet-derived growth factor (PDGF)-receptor-α-positive myofibroblasts move into the primary septa, produce elastin fibres and collagen fibrils, and initiate alveolarisation.

Clinical aspects of the saccular stage

As for the canalicular stage, neonates born at the early phase of the saccular stage present respiratory insufficiency that needs assisted ventilation and are at risk of developing BPD. The risk decreases for every post-menstrual week (see section 11 of this *Handbook* "Bronchopulmonary dysplasia").

Alveolarisation (38 wPMA until young adulthood)

After completion of branching morphogenesis at the end of the canalicular stage or beginning of the saccular stage, the lung volume increases by a factor of ~10 and the alveolar surface by a factor of ~20 until adulthood. In order to achieve the enormous increase in surface area, a lung-specific mechanism is applied. Existing airspaces (sacculi) of the future alveolar ducts are subdivided by the formation of new, secondary septa (figure 3). This process is either called alveolarisation, which means the formation of new alveoli, or septation, which means the formation of new septa. During alveolarisation, the alveolar surface area is enlarged by both lung growth and formation of new alveoli/alveolar septa. Lung growth accounts for ~20% of the enlargement of the alveolar surface area. The remaining 80% of the enlargement is due to the formation of new septa.

Classical alveolarisation

During classical alveolarisation, thick immature primary septa, containing a double-layered capillary network, are folded to create subdivisions of the pre-existing airspaces, and the first alveoli are formed. PDGF-receptor-α-positive myofibroblasts accumulate in the primary septa and produce elastin fibres and collagen fibrils, and alveolarisation is initiated at these sites. The new septa are formed by folding one of the two sheet-like capillary layers, and thus also contain a double-layered capillary network. The two layers are then reduced to one sheet-like capillary network during microvascular maturation. The latter step is believed to increase the efficiency of the gas exchange.

Continued alveolarisation

Microvascular maturation and alveolarisation take place roughly in parallel. However, alveolarisation continues and new alveolar septa are formed from pre-existing mature septa containing only a single-layered capillary network. Again, at sites where elastic fibres, collagen fibrils and PDGF-receptor-α-positive myofibroblasts accumulate, new septa are formed by a fold of the capillary layer. The resulting gap in the pre-existing capillary layer is immediately closed by angiogenesis, resulting in a local duplication of the capillary network at the base of the newly formed septum. Again, the newly formed septum possesses a double-layered capillary network, which will mature by microvascular maturation soon after. The concept of classical and continued alveolarisation is mainly based on rat data. However, it is known that fundamental mechanisms, like branching morphogenesis and alveolarisation, are highly conserved between species. Therefore, it may be hypothesised that the same mechanism applies in humans.

Alveolarisation of the respiratory bronchioles

Alveolarisation of the respiratory bronchioles has been studied only in rhesus monkeys. It starts in parallel to classical alveolarisation, at the most proximal

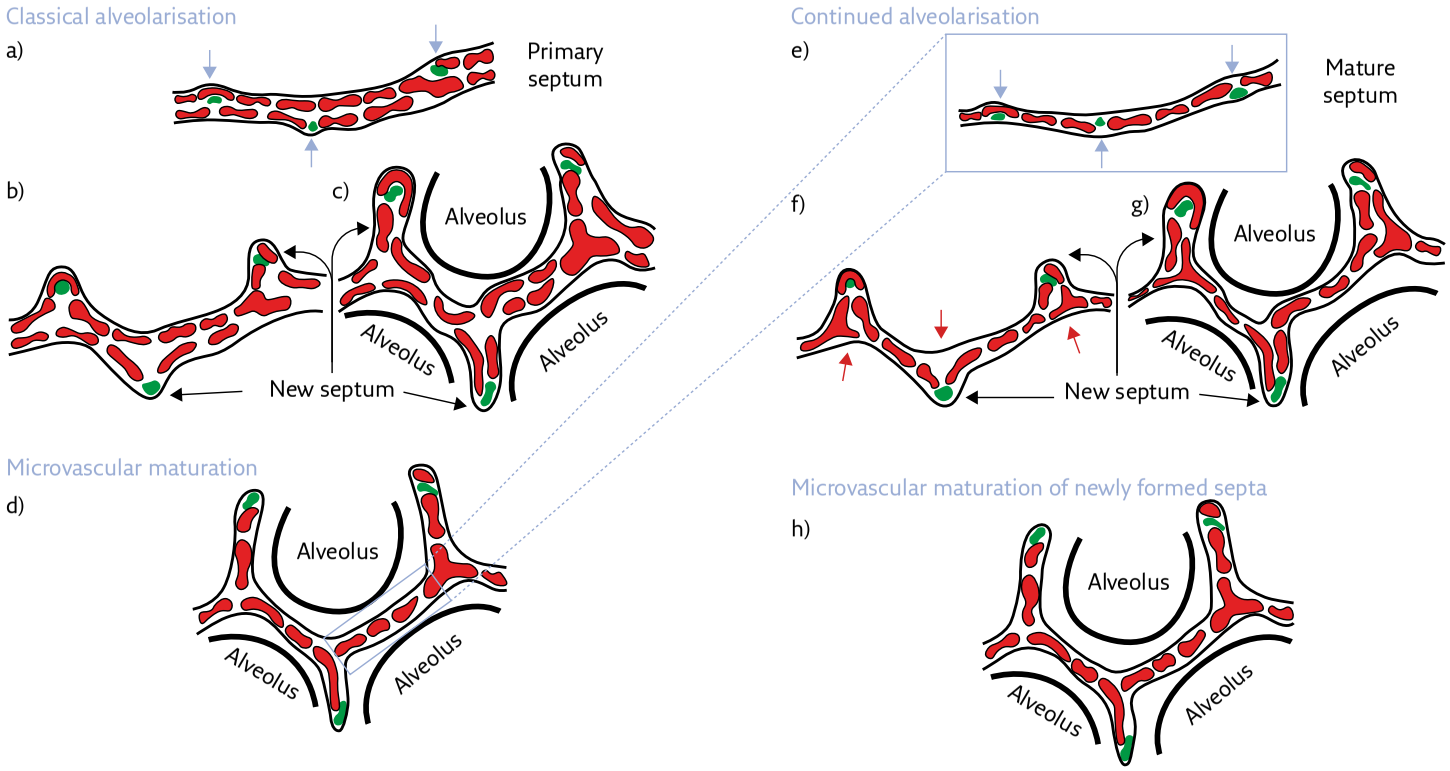

Figure 3. Classical and continued alveolarisation. The blue arrows indicate sites where new septa will be formed, where elastic fibres, collagen fibrils and PDGF-receptor-α-positive myofibroblasts (green) accumulate. Black arrows indicate folding to create new septa. a) At the beginning of classical alveolarisation, thick, immature primary septa exist, containing a double-layered capillary network (red). b) The new septa are formed by folding of one of the two sheet-like capillary layers. c) Pre-existing airspaces subdivide and the first alveoli are formed. The newly formed septa also contain a double-layered capillary network. d) During microvascular maturation, the two layers are reduced to one sheet-like capillary network. e) Alveolarisation continues and new alveolar septa are formed from pre-existing mature septa containing only a single-layered capillary network. f) New septa are formed by a fold of the capillary layer. The resulting gap in the pre-existing capillary layer is immediately closed by angiogenesis, resulting in a local duplication of the capillary network at the base of the newly formed septum (red arrows). g) The newly formed septum possesses a double-layered capillary network that will mature soon after, by h) microvascular maturation. Reproduced and modified from Schittny (2018) with permission; © J.C. Schittny.

respiratory bronchioles, and takes only 5 days. It resembles the formation of the air–blood barrier during the canalicular stage. Alveoli are formed by an out-pocketing into the mesenchyme. The alveoli are first lined with a cuboidal epithelium, which later flattens to form the air–blood barrier.

Clinical aspects of alveolarisation

For humans, rhesus monkeys, rats and mice, it has been convincingly shown that new alveoli are formed as long as the lungs grow, even after lobectomy in adults. This potential has a high clinical relevance, because it shows that, in principle, structural damage could be repaired, *e.g.* a late recovery of BPD or compensatory growth after lobectomy. However, the really interesting question remains open: "Why does it work only in some but not in all structural lung diseases?"

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Applied respiratory physiology

Monika Gappa and Nicole Beydon

Knowledge of respiratory physiology is essential for understanding changes in disease and for the application and interpretation of PFTs. Application of this knowledge should be common practice for a paediatric respiratory specialist; this chapter can only highlight a few key points and the reader is encouraged to go into more detail elsewhere.

The underlying concepts have changed little over recent years. The purpose of the respiratory system is gas exchange with delivery of oxygen and removal of carbon dioxide to maintain homeostasis at the cellular level. Infants are particularly prone to respiratory failure because of developmental disadvantages; these include a floppy chest wall, more horizontal positioning of the ribs and diaphragm, and the small airway diameter, which leads to a dramatic increase in respiratory resistance when the diameter is reduced by bronchial mucosal oedema or mucus in various clinical conditions.

Pathological changes in lung physiology will vary according to disease, but common patterns can be observed according to whether the condition is primarily obstructive or restrictive in nature. This dichotomy may be overly simplistic for describing some of the conditions that the respiratory paediatrician will have to manage but can serve as a useful starting point (figure 1). Spirometry remains a cornerstone of assessment, but measurement of lung volume is vital for full interpretation. This chapter will briefly summarise the underlying measurement principles and discuss how to approach clinical questions and symptoms by applying available PFTs. Assessing lung function

Key points

- Distinguishing obstructive and restrictive disorders is a simplistic but helpful starting point.
- The choice of PFT will depend on the clinical question (diagnosis and/or symptoms) and the age of the patient. A combination of spirometry and body plethysmography is considered useful.
- Visual inspection of the flow–volume curve, including the inspiratory part, is essential.
- Assessment of inflammation is becoming increasingly recognised as an important part of the overall evaluation.

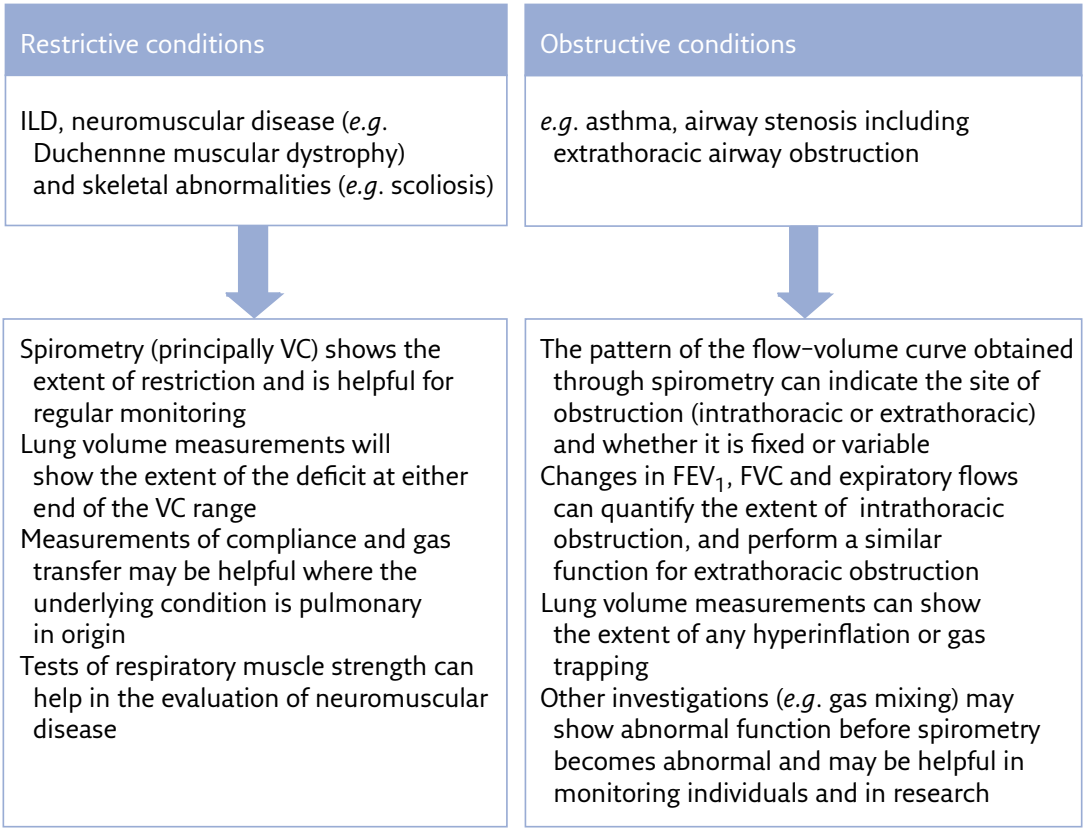

Figure 1. Consideration of abnormalities as either restrictive or obstructive in nature. These are not mutually exclusive, and individuals may show elements of both. VC: vital capacity.

generally requires some degree of cooperation, and therefore tests may be difficult to perform in young children. However, standards exist and preschool children as young as 3 years old may successfully perform most PFTs. Depending on the technique applied, interpretation may be limited because of a lack of reference values and/or because of the higher variability in this age group. Independent of the technique applied and the age group tested, it is essential to select appropriate reference values and to express results as z-scores, as these take age-related variability of the technique and of measured indices into account, which also facilitates tracking of lung function over time. The most robust reference data have been collated by the Global Lung Function Initiative (GLI). However, normative preschool data from the GLI are limited to the following indices: $FEV_{0.75}$, FVC, $FEV_{0.75}$/FVC, forced expiratory flows at 75% and 25–75% of FVC (FEF_{75} and FEF_{25-75}, respectively). The same applies to older children and adolescents, where FEV_1 instead of $FEV_{0.75}$ is available. When assessing the progression of lung disease and changes in lung function over time, it is important to consider inter-test variability, which is higher in disease than in health. The inter-test coefficient of variation in forced volumes measured 3 months apart has been shown to be 17% in healthy children but 42% in children with CF. In young school children, natural variability over 1 year may be as high as 1.2 z-scores. In addition, PFTs will never be the only means for establishing a diagnosis but will be part of the puzzle of approaching a patient with different signs and symptoms.

Spirometry and the flow–volume curve

Spirometry is the recording of the amount (volumes) and speed (flow) of inspired and expired air during the respiratory manoeuvres.

Children who are able to cooperate with testing will be asked to make an airtight seal around the mouthpiece and breathe steadily, and will then be coached to perform a

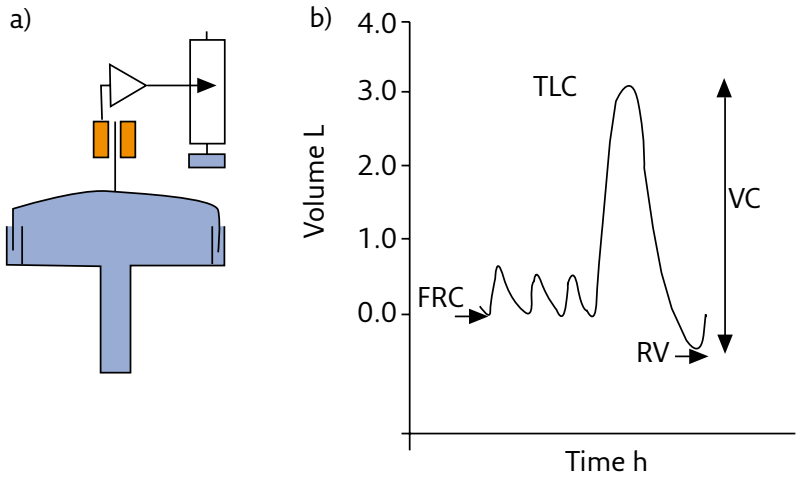

Figure 2. a) Original type of mechanical spirometer and b) associated recording of changes in volume. The recording shows three tidal breaths at FRC, followed by inspiration to TLC and expiration of VC to RV.

maximum unforced expiratory manoeuvre to RV, followed by a maximum inspiratory manoeuvre to TLC, followed by a full forced expiration. If this manoeuvre is difficult, a full inspiratory manoeuvre can be performed from tidal breathing, followed by a forced maximal expiration. The recordings of volume change showing tidal breathing and a maximum (slow) respiratory manoeuvre are shown in figure 2. In addition to a slow manoeuvre, a full forced manoeuvre is generally recorded. The derivation of an expiratory flow–volume curve from the volume–time recording (spirogram) is shown in figure 3. The manoeuvres are repeated several times in order to achieve the best (highest) values and assess repeatability. More details can be found in chapter "Static and dynamic lung volumes".

Measurements of lung volume

The principal means of measuring absolute lung volumes are plethysmography, gas dilution (usually helium dilution) and nitrogen washout, all of which measure FRC and derived lung volumes. The underlying principle for plethysmography differs from

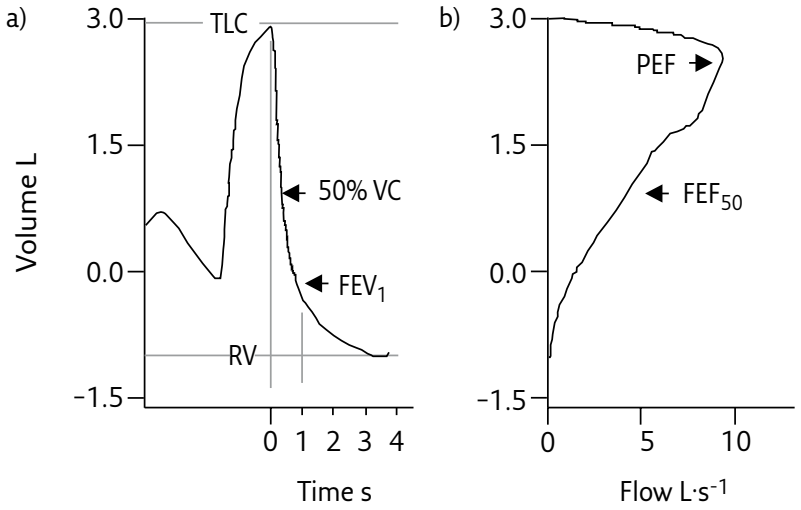

Figure 3. Relationship between a) a spirogram and b) an expiratory flow–volume curve, showing inspiration to TLC, followed by forced expiration to RV. Peak expiratory flow (PEF) occurs early in the manoeuvre, followed by a smooth decline in flow to RV. Note that FEV_1 or any other timed volume can only be derived from the spirogram.

the gas dilution and washout techniques, and this may be utilised to characterise the pathophysiology in different disease states.

Equipment and procedure

Whole-body plethysmography measures all the air in the chest, whether in communication with the airway and ventilated or not. In recent years, it has been agreed to use the term FRC for all lung volumes measured during tidal breathing at end-tidal expiration; therefore, the abbreviation FRC_{pleth} (FRC by plethysmography) has been introduced. In contrast, FRC measurements using gas dilution or washout techniques quantify only lung volumes in free communication with the airway opening and therefore ventilated air (FRC_{gas}, *e.g*. nitrogen or helium).

One limitation of body plethysmography is that the shutter manoeuvre is rarely feasible in young children below school age. In addition, reference values for volumes measured by body plethysmography are relatively old and limited, especially in younger age groups.

The principle of nitrogen washout is to quantify the volume of nitrogen within the lungs and then, knowing the alveolar concentration of nitrogen, calculate the corresponding lung volume. The principle behind the test is not restricted to nitrogen, and it is possible to use other inert tracer gases.

Which measurement of lung volume is most appropriate?

The measurement of choice will depend on the question to be answered. Measurements based on dilution or washout measure the volume of lung that is being ventilated (*i.e.* functional and available for gas exchange). Trapped gas will not be included. Plethysmography measures trapped gas in addition to the ventilated portions of the lung, because all the air in the thorax (whether trapped or not) is subjected to the changes in pressure and volume that are used in the calculation. In healthy individuals, the differences in FRC are small, but in sick individuals they can differ considerably, and the size of the difference may be informative. When performing a gas washout, the time taken to complete the measurements can be informative, with a longer time required if airways disease is present. The inefficient distribution of ventilation can be quantified by indices of ventilation inhomogeneity such as the LCI, which has been shown to be much more sensitive to early changes within the small airways than indices obtained using full forced expiratory manoeuvres, particularly in patients with CF (see section 9 of this *Handbook* “Cystic fibrosis”).

Assessment of airway obstruction

Patients with obstructive disorders form the largest component of the workload of the respiratory paediatrician, with diseases involving also the more peripheral airways (mainly asthma and CF) being the most common. The hallmark of obstructive disorders is airflow limitation, which can occur during expiration, inspiration or both. The typical patient with obstructive respiratory disease will have an expiratory flow–volume curve that shows a distinct concave shape, such that flows at high lung volumes (peak expiratory flow and FEF_{25}) will be relatively spared and those at lower lung volumes (FEF_{50} and FEF_{75}) will show a greater reduction. Visual inspection of the flow–volume curve is an essential part of the evaluation.

When FEV_1 and FVC are compared with predicted values, both indices may be within normal limits, but in obstructive airway disease the FEV_1/FVC ratio is typically reduced and this can be helpful in interpreting spirometry. However, FEV_1/FVC should not be

considered in isolation, because it cannot convey whether one or both components are within normal limits or not (*i.e.* both volumes may be reduced to a similar degree in restrictive disorders). According to the most recent American Thoracic Society (ATS) recommendations on spirometry reports, the bronchodilator effect should be assessed by the absolute and percentage change in FEV_1 and FVC.

Physiological studies using bronchial catheters have demonstrated that the forced expiratory flow–volume curve will not detect changes beyond the eighth generation of the bronchial tree ("silent lung zone"), explaining why spirometry may still be normal when only peripheral airways are affected by disease.

Airways obstruction may also be measured using tests of respiratory mechanics such as the oscillation technique (see chapter "Forced oscillation techniques"), the interrupter technique or measurement of airway resistance by body plethysmography. These techniques assess resistance that opposes the airflow by simultaneous recording of the airflow and the change in airway pressure. Because these tests require tidal breathing only, they may be more suitable for use in younger children. However, the variability of these tests is higher than for most spirometric indices, which has to be considered when interpreting the results.

Clinical symptoms and applied physiology

Intrathoracic *versus* extrathoracic airway obstruction

The approach to a patient with stridor, particularly a young infant, is mainly clinical. However, inspection of the shape of the flow–volume curve during tidal breathing or maximal manoeuvres may help with the differential diagnosis. Where there is an extrathoracic variable obstruction such as laryngomalacia, which classically will be symptomatic with a variable inspiratory stridor, the abnormality will be evident on the inspiratory limb of the flow–volume curve (figure 4a) and expiration may be unaffected. During expiration, the positive-pressure gradient extending from the lung down to the airway opening will tend to maintain the extrathoracic airway open, so the abnormality will not be evident. During inspiration, the pressure gradient will be reversed and the tendency may be for unstable regions of the extrathoracic airway to be sucked inwards.

With a fixed obstruction, such as a subglottic stenosis, which may be clinically symptomatic with inspiratory and expiratory stridor, the maximum flow that can be achieved will be determined by the physical dimensions of the airway at its narrowest point and will be similar at inspiration and expiration. Depending on the underlying cause of the obstruction, this may change little as the child grows, so that the absolute peak inspiratory and expiratory flows remain constant from one year to the next, with progressive worsening of the flows when related to predicted values. The flow–volume curve will appear flattened on both the inspiratory and expiratory limbs, with loss of a well-defined peak flow and no significant response to a bronchodilator (figure 4b).

It is important to note that PFTs should not be performed in acute airway obstruction or any other acute respiratory condition, as the patient's respiratory status may be further compromised.

If the obstruction is located within the thoracic cage (intrathoracic), the obstruction will be more evident on the expiratory part of the flow–volume curve, because during inspiration, the intrathoracic pressure will decrease and become negative, thereby "opening" the airway. In variable obstruction, such as tracheomalacia, the flattening of the flow–volume curve will be evident during expiration, while inspiration may appear normal. In the case of a fixed intrathoracic obstruction such as tracheal stenosis from

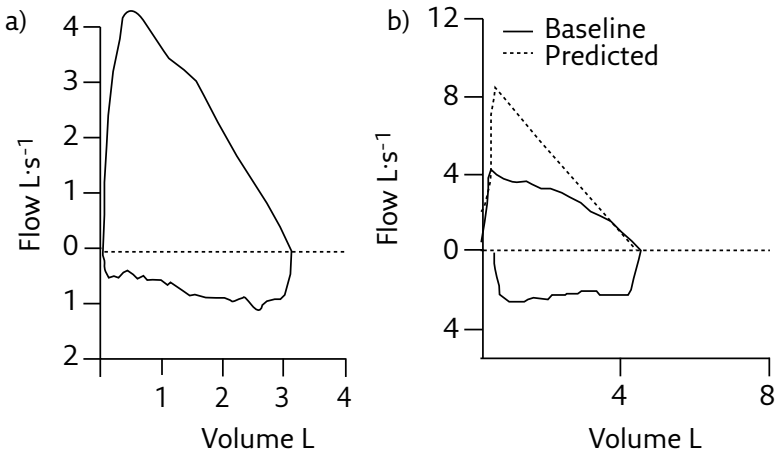

Figure 4. a) Variable upper airway obstruction (laryngeal polyp), illustrating reduced flow through inspiration but a normal pattern for the expiratory curve. b) Fixed obstruction (tracheal stenosis), with flattening of both the inspiratory and expiratory curves. On expiration, the flow is reduced primarily at high lung volume, with normal flow in the last quarter of VC.

vascular abnormalities (*i.e.* pulmonary sling; see chapter "Vascular malformations"), both the inspiratory and expiratory part of the flow–volume curve may be affected. PFTs may be insensitive if airways are completely obstructed. In addition, PFTs should not be considered to diagnose foreign body aspiration.

Expiratory wheeze: asthma and other wheezing disorders

During an acute episode of asthma or in acute virus-induced wheezing, there is no need for PFTs. In acute episodes, the clinical response to a bronchodilator inhalation may be more informative. Depending on diagnosis, disease severity and age of the patient, airway obstruction may be apparent during expiration with a concave appearance of the expiratory part of the flow–volume curve, even when the patient is clinically stable, becoming more marked with increasing severity of the obstruction. In cases where there is severe obstruction of the small airways (*e.g.* an exacerbation of asthma, severe asthma or advanced CF), the distribution of lung volumes may also become abnormal. During the course of expiration, the airways become narrower as the lung volume decreases, and when the airways are abnormally narrowed (*e.g.* due to oedema, excessive mucus or contraction of the smooth muscles within the airway wall), they may close completely (at closing volume) at an early stage in the manoeuvre. When closing volume increases, RV is increased and vital capacity (VC) may be reduced ("pseudorestriction").

A reduction in VC should be an indicator to measure absolute lung volumes in such patients to differentiate between true restriction and a decrease in VC because of early airway closure. The technique of choice to detect restriction (or pseudorestriction) should be plethysmography, as this technique measures true TLC and FRC. Combining measurements of FRC using both plethysmography and a gas-washout technique allows the detection and quantification of hyperinflation and trapped gas volume. However, in the most extreme cases, where patients have extensive airflow obstruction and uneven distribution of pressure changes within the chest, the assumptions underlying plethysmography may no longer be valid; in these individuals, there is usually clear clinical evidence of hyperinflation and central obstruction.

It is important to note that RV is not measured directly but is calculated from measured FRC (by either gas washout or plethysmography) minus expiratory reserve volume. The expiratory reserve volume depends on cooperation, and the manoeuvre may be difficult to perform, especially for younger children. Therefore, the technician

should report patient cooperation, and volumes must be checked for plausibility before interpreting results.

The hallmark of asthma is variable airflow obstruction and bronchial hyperreactivity from chronic mucosal inflammation. If the spirometric measurement shows reduced values, a bronchodilator test should be performed to assess reversibility; an increase in FEV_1 of ≥12% is considered significant according to European Respiratory Society/ATS standards. However, in children, the sensitivity and specificity of this cut-off are low. In preschool children, a bronchodilator response in $FEV_{0.75}$ of 11% provides a positive predictive value of 47% and a negative predictive value of 89%, and a negative bronchodilator test does not rule out asthma and should prompt a bronchial provocation test if the clinical suspicion is asthma. In children, the most specific test for asthma is a submaximal exercise challenge on a treadmill. Direct provocation tests using methacholine or histamine are more sensitive but less specific. Other diseases such as CF, BPD and acute infection may show bronchial hyperresponsiveness (BHR; see chapter "Reversibility and bronchial provocation testing"). Assessing lung function may assist in but not be sufficient for establishing a diagnosis; for example, in preschool wheeze, previous and family history are the most important parameters, while a diagnosis of BPD will be established according to post-natal history, and PFTs will help to assess the nature and degree of pulmonary impairment.

PFTs in children with asthma should be supplemented by measurement of the fraction of exhaled nitric oxide (F_{ENO}; see chapter "Exhaled nitric oxide, induced sputum and exhaled breath analysis"). Elevated F_{ENO} supports the diagnosis of atopic asthma. The role of F_{ENO} in routine clinical practice to monitor and guide therapy remains unclear. Elevated F_{ENO} indicates persistent eosinophilic inflammation, which may indicate uncontrolled asthma due to low adherence to treatment recommendations or because of persistent inflammation due to intrinsic disease severity or continued allergen exposure, for example; in this setting, a reduction of the dose of inhaled corticosteroids may lead to an exacerbation and should be considered carefully. Implementation of F_{ENO} measurement in the diagnostic work-up of suspected asthma is now recommended by most asthma guidelines.

Pulmonary restriction in neuromuscular and orthopaedic diseases and ILDs

True restriction is defined as a reduction in TLC, either due to parenchymal changes (*e.g.* ILDs) or due to decreased thoracic movements in neuromuscular or orthopaedic conditions. Usually, reduced VC in the forced expiratory manoeuvre will prompt further assessment of lung function to diagnose or exclude true restrictive respiratory disease. The subject may report shortness of breath on exertion with poor exercise tolerance, or in severe cases on mild exertion or at rest. Where the underlying condition is known, such as a skeletal or neuromuscular disorder, spirometry will be part of the assessment, usually on a regular basis. A single assessment is usually of limited value, as the range of predicted values is wide. Serial measurements are more informative, for example in the early stages of Guillain–Barré syndrome as a pointer to the probable need for mechanical ventilation, or to monitor the progression of Duchenne disease.

The shape of the expiratory flow–volume curve in pure restrictive disorders in children will generally show a linear or even a convex descending portion, in contrast to that observed in obstructive disorders. It is also important to understand how the flow–volume curve is shown on the screen: if it is aligned at TLC rather than RV (figure 5), it may give the erroneous impression that the reduction in VC occurs due to elevation of RV and not by a reduction in TLC. Flows at high lung volumes (*e.g.* FEF_{25}) are reduced in restrictive disease, not because of airway obstruction but because the volumes at which they are measured are constrained.

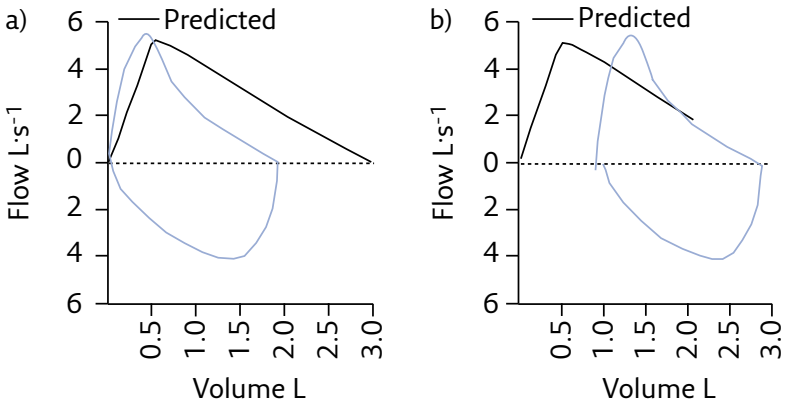

Figure 5. Flow–volume curve from a child with restrictive disorder, including a schematic of the predicted expiratory flow–volume curve with a VC of 3.0 L predicted. a) The actual flow–volume curve aligned with the schematic at TLC. The expiratory flow appears to be substantially below the predicted flow. b) The actual flow–volume curve aligned at RV, showing that the measured expiratory flow coincides with the predicted flow over much of the VC. Note that the precise positioning of the actual curve on the schematic requires measurement of absolute lung volumes.

Measurement of absolute lung volumes will confirm whether the deficit in VC is exclusively at the upper end (*i.e.* reduction in TLC only) or whether RV is increased, as may happen in skeletal abnormalities. RV may also be elevated in severe obstructive disease, but clinical history and post-bronchodilator changes in spirometry may distinguish between these patterns. Where the restriction is due to a neuromuscular condition, spirometry may be more variable and the flow–volume curve can give the impression of inconsistency of effort; in these cases, the operator must be alert to the tiring effect of repeated forced manoeuvres and avoid too many attempts at achieving higher values of VC.

When the restrictive pattern results from a muscular condition, such as muscular dystrophy, if the diaphragm is involved the VC may be further reduced when the patient lies supine when compared with an upright posture. If the diaphragm is weak or incompetent, the abdominal contents move up into the thorax when the patient lies down, whereas when the subject is upright the gravitational force prevents this from happening. Assessing the posture-related change may therefore be relevant if surgery is contemplated. Although sequential measurements of VC are undoubtedly helpful in monitoring changes in the function of patients with muscle disease, it may be difficult to interpret them if it is not possible to make an accurate measurement of body height, as is often the case in nonambulatory patients who may also have developed scoliosis. A measurement of VC may have increased in absolute terms from one annual review to the next, but the net effect may yet be deterioration if the increase in VC has not kept up with linear growth. In these patients, the arm span should be measured to substitute height, such that predicted values may be calculated based on arm span to allow a more realistic assessment of the progression of disease. In the case of contractures/ankyloses, it is important to measure all parts of the arm span or alternatively to use ulnar length. An alternative approach to assess respiratory function in patients with neuromuscular disease is to measure maximum inspiratory and expiratory pressures directly, which has the advantage that predicted values can be related to age rather than to height.

ILDs are rare in children but also result in a restrictive pattern with a reduction in TLC, although FRC and RV may be normal. In these children, the ability of gases to diffuse from the alveoli into the blood may be reduced. Assessment of T_{LCO} from its components of K_{CO} and alveolar volume can be informative in children able to perform

the necessary manoeuvre. T_{LCO} relies mainly on: 1) the surface and the diffusion properties of the alveolar capillary membrane, 2) the carbon monoxide–haemoglobin chemical reaction rate, and 3) the volume of alveolar capillary blood. The most common technique is the single-breath method where the subject breathes out to RV and then takes a full inspiration of a gas mix that includes 0.3% carbon monoxide and a proportion of an inert, insoluble gas (usually helium or neon), followed by a 10-s breath-hold (6 s in younger children or in those with markedly reduced lung volumes) and a steady exhalation. The rate at which carbon monoxide is transferred out of the lungs and into the blood can be calculated and related to the volume of the lungs, determined from the dilution of the inert gas. The cooperation required for successful measurements means that T_{LCO} cannot be measured in very young children, but it may be possible in some as young as 6 years of age.

Assessment of inflammation in the lung function laboratory

Applied respiratory physiology has historically been limited mainly to studies of pulmonary mechanics and gas exchange but should include an assessment of the degree of inflammation, particularly in asthma. The only "inflammometry" available for routine clinical use is measurement of F_{ENO}, which is a marker of eosinophilic inflammation, and in this regard it may be of most help in asthma. The measurement of F_{ENO} may contribute to confirming a diagnosis of asthma or to assessing the response to steroids, and may help to assess the risk of exacerbations. Failure of high levels of F_{ENO} to respond to steroids may alert the clinician to poor adherence on the part of the child with asthma or the parents. Nasal nitric oxide measurements are relevant in screening for PCD, because levels are lower than in healthy individuals. A detailed review of the technical aspects and clinical applications is available (see chapter "Exhaled nitric oxide, induced sputum and exhaled breath analysis").

Looking at the profile of inflammatory cells or other biomarkers in sputum may be informative (see chapter "Exhaled nitric oxide, induced sputum and exhaled breath analysis"), but the value of various biomarkers is still being evaluated. Sputum may be produced spontaneously, particularly in patients with CF, but can otherwise be obtained by sputum induction with hypertonic saline. In children where this is not possible, BAL can be used to obtain a sample in those individuals where the importance of the sample merits the invasiveness of the procedure.

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Immunology and defence mechanisms

Johanna Theodorou and Bianca Schaub

The immune system is a system of interdependent cell types that collectively protect the body from various diseases with increasing specificity of immune regulation. In general, it is composed of two major parts, the innate and the adaptive immune systems, also designated the first and second lines of defence, respectively. In order to keep a healthy immune balance, the innate defence system needs to be regulated efficiently by itself but also in closely connected regulation with the adaptive system.

Innate defence mechanisms

Innate immunity of the lung

The lung is exposed to a multitude of airborne pathogens, allergens and pollutants, although only a few cause respiratory infections, demonstrating the efficiency of the lung's defence system. The innate immune system is composed of a mechanical, physical and chemical barrier, which act together in the defence against invading micro-organisms (figure 1).

The first defence mechanism of the lung is an initial mechanical barrier to avoid the invasion of particles >5 µm into the upper airways. This barrier comprises a surface of nasal hairs and nasopharynx channels. The surfaces of the upper and lower airways including the glottis, trachea and small branches of the bronchi and bronchioles also contribute to host defence.

Key points

- Innate immune mechanisms comprise a mechanical, physical and chemical barrier, which act together in the defence against invading micro-organisms.
- The airway epithelium forms a physical barrier against inhaled substances and contributes to host defence by producing mediators of the chemical barrier, including chemokines, cytokines, antimicrobial peptides, proteinase inhibitors and surfactant proteins.
- Adaptive immune mechanisms include T-cell-mediated responses of different subpopulations and components of the humoral and mucosal immune systems.
- Interaction of innate and adaptive immune regulation is required for specific defence against respiratory diseases, involving prenatal and post-natal factors.

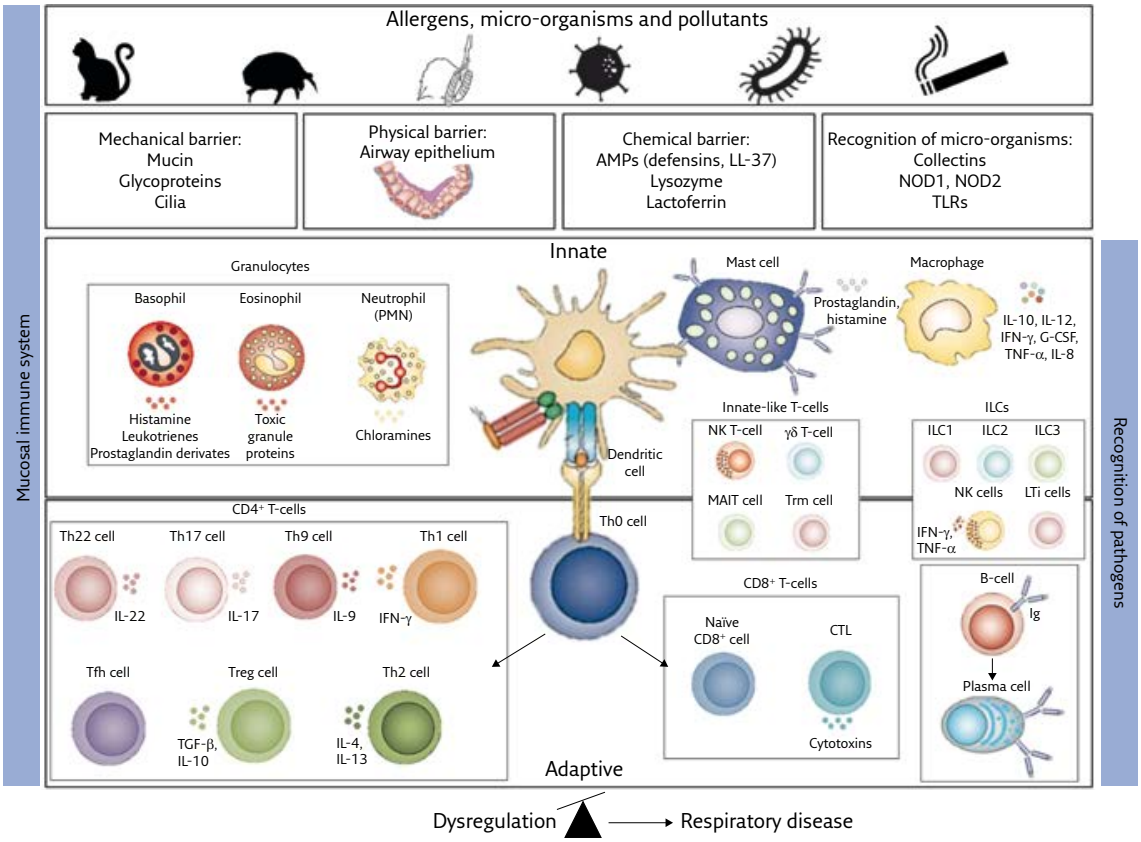

Figure 1. Overview of the initiation and interaction of the innate and adaptive immune systems. AMP: antimicrobial peptide; LL-37: cathelicidin; NOD: nucleotide-binding oligomerisation domain; TLR: Toll-like receptor; PMN: polymorphonuclear neutrophil; IL: interleukin; IFN: interferon; G-CSF: granulocyte colony-stimulating factor; TNF: tumour necrosis factor; NK: natural killer; MAIT: mucosal-associated invariant T-cell; Trm: tissue-resident memory T-cell; ILC: innate lymphoid cell; LTi: lymphoid tissue-inducer; Th: T-helper; Tfh: T follicular helper; Treg: regulatory T-cell; TGF: transforming growth factor; CTL: cytotoxic T-lymphocyte.

The surface of the airways is covered with mucus, consisting mainly of secreted and membrane-associated mucin glycoproteins, which trap micro-organisms and pollutants. By regulating intracellular signalling pathways, membrane-associated mucins also have antimicrobial and anti-inflammatory properties. These complexes are then cleared by the ciliary movement of the mucus to the oropharynx, resulting in efficient removal of the pathogens and pollutants. Dysregulation of mucus production is often a symptom of severe respiratory diseases such as CF or asthma.

The airway epithelium is the point of contact for smaller inhaled substances such as allergens, micro-organisms and pollutants. It is the interface between the external environment and the internal milieu. This epithelium forms a physical barrier and also contributes to host defence in a number of ways, such as the production of chemokines, cytokines and antimicrobial peptides (AMPs), as well as protease inhibitors, all of which form a chemical barrier. In particular, the epithelium-derived T-helper type 2 (Th2)-promoting cytokines interleukin (IL)-33, IL-25 and thymic stromal lymphopoietin are associated with the development of allergic airway diseases. The airway epithelium expresses several pathogen recognition receptors (PRRs) including membrane-bound Toll-like receptors (TLRs) and collectins such as surfactant proteins. In this way, it is also involved in the regulation of inflammatory signalling pathways following binding of micro-organisms.

Antimicrobial peptides

Airway epithelial cells secrete large numbers of different molecules involved in the inflammatory process. These molecules kill micro-organisms, induce wound healing and angiogenesis, and orchestrate the adaptive immune response (figure 1). The term AMP summarises a class of innate effector molecules secreted by airway epithelial cells and neutrophils, with a broad spectrum of activity against bacteria, fungi and enveloped viruses. AMPs are classified according to their size, predominant amino acids or conformational structure. In the respiratory tract, the principal families are defensins and cathelicidins.

Defensins are highly structured compact peptides, classified into α- and β-subgroups depending on their folding. The α-defensin human neutrophil peptides 1–4 are present on neutrophils and have a nonoxidative microbicidal activity. The β-defensins are widely expressed throughout the epithelia and form a general defence against bacterial infection. In general, defensins induce proliferation of the airway epithelial cells and are involved in wound repair. These AMPs also show a synergistic activity with other host defence molecules, such as the large antimicrobial proteins lysozyme and lactoferrin, which are present in airway fluids. Lysozyme acts by lysing bacterial membranes, whereas the antibacterial activity of lactoferrin is mediated by its iron-binding property, which sequesters free iron, necessary for bacterial metabolism. The function of these antimicrobial substances in host defence has been demonstrated in several animal experiments. For example, mice in which the LL-37 homologue CRAMP (cathelicidin-related AMP) is deleted show an impaired defence against invasive bacterial infections. Moreover, AMPs play an important role in several lung diseases, such as pneumonia, diffuse panbronchiolitis and CF. In CF patients, AMPs may become inactivated as a result of the high salt concentration in the epithelial lining fluid. AMPs show a concentration-dependent toxicity towards eukaryotic cells, and higher-than-normal concentrations have been described in CF, neonatal and adult pneumonia and diffuse panbronchiolitis patients, where they contribute to exuberant inflammation, potentially through lysis of lung epithelial cells, induction of IL-8 production and restriction of defensin-induced cytotoxicity. Induction of AMPs such as human β-defensins and the subsequent protection against microbial pathogens are of particular interest in therapeutic approaches to overcome the growing resistance to conventional antibiotics. For example, the cyclic and highly cationic peptide novexatin, which is used to target fungal infections, is based on human α- and β-defensins.

Cell types participating in innate immunity

Several cell types participate in initiating and maintaining the innate immune response and link the innate and adaptive parts of the immune defence (figure 1). Macrophages engulf and digest pathogens by phagocytosis and initiate the adaptive immune response. Dendritic cells are a link between the innate and adaptive immunity, as they ingest, process and present antigens to further cell types of the adaptive immune system. Granulocytes are a group of white blood cells containing cytoplasmic granules. They are divided into three types: neutrophils, eosinophils and basophils. Neutrophils participate in phagocytosis and immediate killing of micro-organisms, independent of previous exposure, whereas basophils are highly specialised in the synthesis and secretion of several pharmacologically active products such as histamine, proteases, leukotrienes and prostaglandin derivatives. Eosinophils are recruited to the site of inflammation during a Th2-type immune response, where they produce a variety of cytokines and lipid mediators and release their toxic granule proteins. Mast cells

participate in inflammatory processes by releasing characteristic granules and hormonal mediators upon activation (*e.g.* histamine and prostaglandins).

Thrombocytes act primarily in blood clotting but also initiate innate immune functions by secretion of pro-inflammatory molecules.

Alveolar macrophages

Alveolar macrophages represent the first line of phagocytic defence against particles that evade the mechanical defence. These cells combine important phagocytic, microbicidal and secretory functions, and initiate inflammation and further immune responses.

Communication between alveolar macrophages and other immune cells is of great importance in launching an efficient immune response (figure 1). Cytokines play a major role in pulmonary host defence, especially IL-10, IL-12, interferon (IFN)-γ, granulocyte colony-stimulating factor and tumour necrosis factor (TNF)-α, the key mediator in recruiting polymorphonuclear leukocytes (PMLs) into the healthy airways. Defence against micro-organisms that are resistant to microbicidal activity requires cell-mediated immunity associated with the recruitment of large numbers of PMLs into the alveolar space by generating mediators, such as the arachidonic acid metabolite leukotriene B_4, and complement or chemotactic peptides such as IL-8. In fact, leukotriene B_4 and IL-8 have been identified as being centrally involved in the pathophysiology of respiratory diseases such as bacterial pneumonia and CF.

Neutrophil recruitment and enhancement of phagocytic defence

PMLs represent the largest population of intravascular phagocytes, with greater phagocytic activity than alveolar macrophages. In response to inflammatory stimuli such as tissue-released mediators and microbial-derived compounds, they migrate into the infected tissue site. Following phagocytosis, fusion of the phagosome and lysosome and add-on fusion of azurophilic granules with the phagolysosome generate highly toxic antimicrobial compounds such as chloramines, defensins, and lysozyme and other proteases. During pulmonary infection and inflammation, PMLs also participate in the regulation of local host responses by secreting TNF-α, IL-1β, IL-6 and macrophage inflammatory protein 2.

Recognition of pathogens by the airway epithelium

As a response to pathogen exposure, the innate immune system releases AMPs into the lumen of the airways and chemokines, as well as cytokines, into the submucosa. These mediators initiate inflammatory reactions accompanied by the recruitment of phagocytes, dendritic cells and lymphocytes, which in turn help to initiate adaptive immune responses. In order to initiate this cascade, micro-organisms first need to be recognised. Micro-organisms have characteristic conserved molecules on their surface, called pathogen-associated molecular patterns (PAMPs), which can be recognised by PRRs. These receptors comprise soluble forms, such as collectins. Eight collectins have been identified so far, including mannan-binding lectin and the surfactant proteins SP-A and SP-D. These collectins play a key role in the first line of defence by binding to invading micro-organisms, thereby enhancing migration, chemotaxis and phagocytosis by alveolar macrophages. SP-A and SP-D also activate other immune cells including dendritic cells, T-cells and granulocytes. The other groups of PRRs are the intracellular nucleotide-binding oligomerisation domain (NOD) proteins NOD1 and NOD2, which are involved in peptidoglycan recognition, and transmembrane molecules, such as TLRs, which directly mediate a cellular response after microbial

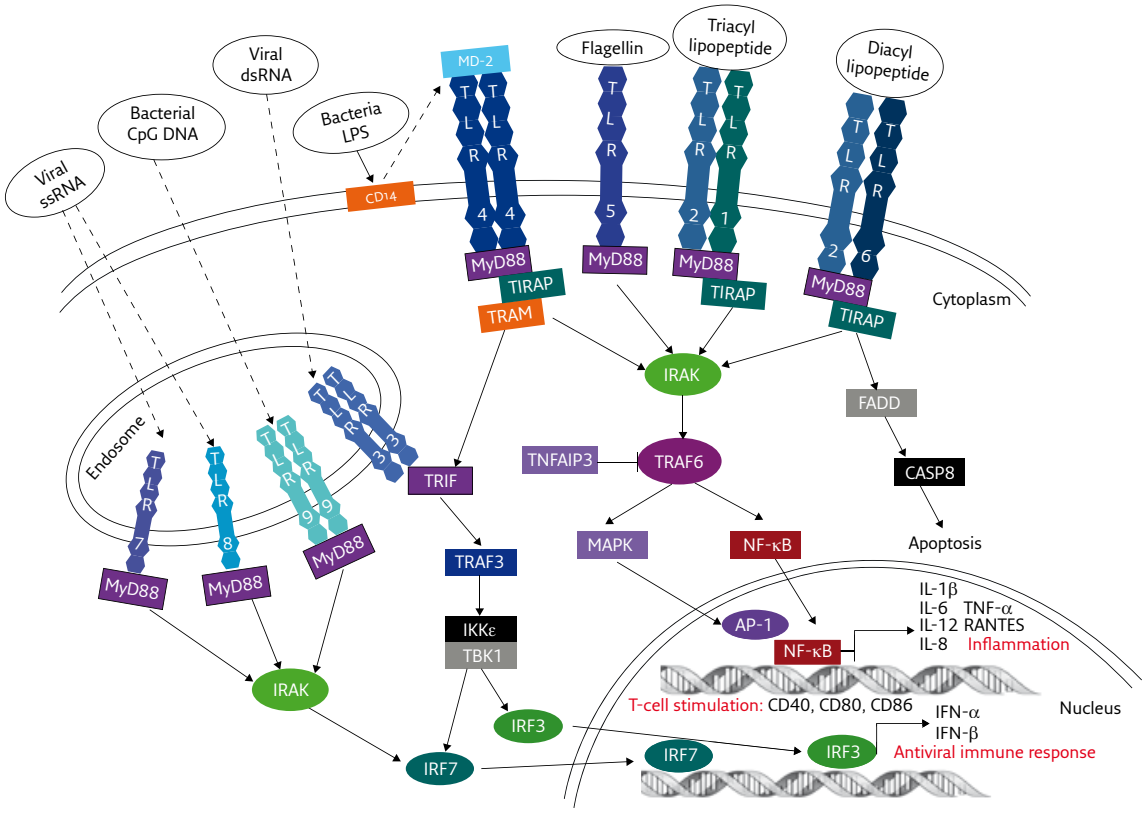

Figure 2. TLR signalling cascade. The myeloid differentiation primary response gene 88 (MyD88)-dependent pathway can be used by all TLRs except TLR3. The MyD88-independent pathway is utilised by TLR3 and TLR4. ssRNA: single-stranded RNA; dsRNA: double-stranded RNA; LPS: lipopolysaccharide; MD-2: myeloid differentiation factor 2; CD: cluster of differentiation; TIRAP: Toll/IL-1 receptor (TIR) domain-containing adaptor protein; TRAM: translocation-associated membrane protein; IRAK: IL-1 receptor-associated kinase; FADD: Fas-associated death domain; TRIF: TIR domain-containing adapter-inducing IFN-β; TNFAIP3: TNF-α-induced protein 3; TRAF: TNF receptor-associated factor; CASP8: caspase 8, apoptosis-related cysteine peptidase; MAPK: mitogen-activated protein kinase; IKKε: IκB kinase-ε; TBK: TANK-binding kinase; AP-1: activator protein-1; NF-κB: nuclear factor-κB; RANTES: regulated on activation, normal T-cell expressed and secreted; IRF: IFN regulatory factor.

exposure. The TLR signalling cascade is shown in figure 2. TLRs are the homologues of the Toll receptor in *Drosophila* flies. To date, 13 TLRs have been identified in mammals and 10 of these have been shown to be expressed in humans.

TLRs are abundant on nearly all cells of the body. They are responsible for initiating an adequate response following microbial exposure, and are involved in the regulation of cytokine, chemokine and AMP expression and the production of reactive oxygen species. The different TLRs can detect a variety of bacterial, viral and fungal products, as well as damage-associated molecular patterns (DAMPs) that are released by cells undergoing necrosis. While binding of commensal bacterial species to, for example, TLR2 results primarily in the induction of tolerance mechanisms, TLR ligands of pathogenic micro-organisms promote inflammatory signalling. This TLR signalling pathway is divided into two main signalling cascades: the myeloid differentiation primary response gene 88 (MyD88)-dependent and -independent pathways. In the MyD88-dependent pathway, all TLRs except TLR3 recruit the adaptor molecule MyD88 upon stimulation and induce nuclear factor (NF)-κB and mitogen-activated protein kinase (MAPK) through IL-1 receptor-associated kinase (IRAK) 1 and IRAK4

and TNF receptor-associated factor (TRAF)-6. This leads to activation of NF-κB and MAPKs (JNK and p38), followed by translocation of NF-κB and activator protein 1 (AP-1) to the nucleus and the upregulation of pro-inflammatory genes. Additionally, TLR2 and TLR4 require the adaptor molecule TIRAP (TIR domain-containing adaptor protein), which acts as a bridging molecule between the receptor and MyD88.

The MyD88-independent signalling pathway, which depends on the adaptor molecule TRIF (TIR domain-containing adaptor inducing IFN-γ), is utilised by TLR3 and TLR4. TRIF forms a complex with TRAF-3 and subsequently activates IFN regulatory factor (IRF) 3 and IRF7, which locate to the nucleus and activate IFN-inducible genes. The adaptor molecule TRAM (TRIF-related adaptor molecule) is solely involved in TLR4 MyD88-independent signalling, where it recruits TRIF to the TLR4 complex.

TLRs can also form homo- or heterodimers, such as TLR2 with TLR1 and TLR6. The dimers have different ligand specificity. Moreover, additional coreceptor molecules increase ligand sensitivity. Four different adaptor molecules exist: MyD88, TIRAP, TRIF and TRAM. This variety of adaptor molecules might allow them to recruit different transducers, resulting in specific downstream signalling. For TLR4 signalling, CD14 facilitates the presentation of lipopolysaccharide (LPS) to myeloid differentiation factor 2 (MD-2), a coreceptor required for LPS recognition by TLR4.

The most studied TLR, TLR4, is the central component in the response to LPS, a unit of the outer membrane of Gram-negative bacteria. TLR2 recognises a wide array of bacterial and fungal substances. TLR2 is also expressed on regulatory T-cells (Tregs), a type of T-cell that suppresses the activity of pathogenic T-cells and prevents the development of autoimmune responses and allergic lung diseases. TLR2 stimulation is supposed to reduce the suppressive function of Tregs. Moreover, single-nucleotide polymorphisms in TLRs such as TLR2 and TLR4 have been shown to play an important role in the development of immune-mediated lung diseases in childhood. Specifically, asthmatic children with polymorphisms in TLR2 have different expression of Treg markers in cord blood, while asthma-protective effects have been demonstrated for genetic variants of TLR4 in farm-exposed children. Variants in TLR1 and TLR10 genes are associated with bronchiolitis followed by subsequent asthma.

TLRs are regulated by several microRNAs, noncoding RNAs that bind mRNAs and suppress their translation. The dysregulation of microRNAs has been shown to be involved in inflammation, T-cell activation and other immunological pathophysiological mechanisms.

Summary of the innate immune response

The innate immune system is crucial for an immediate defence against infection. Previously, this innate part of the immune system was thought to have no immunological memory function, which represents a key feature of the second, adaptive, part of the immune defence. However, recent publications have shifted this paradigm by suggesting that the innate immune system might also have the ability to remember recurring stimuli by epigenetic reprogramming, summarised as trained immunity or innate immune memory. In particular, monocytes, natural killer (NK) cells and innate lymphoid cells (ILCs) seem to react with a tailored response upon recognition of known PAMPs.

Innate/adaptive system crosstalk

The adaptive immune system requires a couple of days for an efficient, specific immune defence. This system gets switched on when the innate defence mechanisms are not

sufficient. The adaptive immune system is induced by different cellular processes and activation of the innate immune response. While some infections can be controlled through activation of the innate immune system, the adaptive immune system is essential for a number of respiratory tract infections. However, close cooperation between the two systems is needed for a healthy immune response. Recently, several types of immune cells have been identified that form the link between these two systems, namely ILCs and innate-like T-cells. In addition, cytokines, chemokines and AMPs connect the two arms of the immune system by activating both innate and adaptive immune cells. Cathelicidin (LL-37) displays a similar activity to defensins and attracts neutrophils, monocytes, activated mast cells and $CD4^+$ T-cells. In addition, the humoral immune system also interacts with adaptive immune cells. For an IgA response, two major mechanisms exist: an innate T-cell-independent mechanism, which provides a first line of protection, and a T-cell-dependent adaptive response, which takes longer and produces high-affinity antibodies.

Innate lymphoid cells

ILCs are a new lineage of cells recently identified as innate counterparts of T-cells and are associated with protective immunity by secreting effector cytokines and regulating other innate and adaptive immune cells without expressing specific antigen receptors. They can be divided into three subgroups, ILC1, ILC2 and ILC3, based on their phenotype, origin and the cytokines they produce. ILC2s are associated with the pathophysiology of asthma and other allergic diseases due to their secretion of IL-13, triggering Th2 differentiation.

NK cells, a type of cytotoxic lymphocyte, are included in the ILCs and are involved in a fast immune reaction and killing of cells, together with lymphoid tissue-inducer cells, which induce the development of secondary lymphoid organs.

Innate-like T-cells

Innate-like T-cells including invariant NK T-cells, mucosa-associated invariant T-cells and γδ T-cells as well as tissue-resident memory T-cells (Trms) are part of the innate immune system. Due to their complex biology, they are suggested to be involved in both the innate and adaptive immune systems, as they exhibit characteristics of both. Whereas NK T-cells are mainly responsible for the recognition of lipid antigens, mucosa-associated invariant T-cells recognise bacterial metabolites such as riboflavin precursor. γδ T-cells are a small subset of T-cells that have a receptor composed of a γ- and δ-chain instead of the more frequently occurring α- and β-chains. In addition, Trms accelerate pathogen clearance immediately by activating innate and adaptive immune cells and limiting pathogen spread by granzyme B expression.

Adaptive defence mechanisms

Basic principles of adaptive immune defence

As well as T-cell-mediated immune responses, the humoral and mucosal immune systems play a prominent role in the adaptive immune defence.

T-cell-mediated immune response

After development in the thymus, T-cells reach the blood circulation, migrate through peripheral lymphatic tissue, circulate through the blood and tissue, and return *via* the lymphatic system to the blood circulation. Migration is supported by CCR7, a chemokine receptor, which binds the ligand CCL21 and is produced by stroma cells

in the T-cell zone of the peripheral lymphoid organs. After rolling of T-cells, adhesion, diapedesis and migration into the T-cell zone, antigen presentation takes place.

To complete the adaptive immune response, naïve T-cells need contact with a specific antigen. After presenting the processed antigen peptides *via* major histocompatibility class II molecules (to the T-cell receptor), the costimulatory cascade is initiated, which consists of complex interactions of several T-cells and antigen-presenting cells (APCs). The most potent APCs are dendritic cells; their interaction with T-cells is a key factor in the induction of efficient immune responses. Subsequently, T-cell differentiation into effector T-cells and proliferation take place. These effector cells operate with other cells, not with the pathogen itself.

T-cells

T-cells can be roughly classified into the subpopulations of $CD4^+$ and $CD8^+$ T-cells. $CD4^+$ T-cells consist of Th1, Th2, Th9, Th17, Th22, T follicular helper (Tfh) and Treg cells (figure 1). Th1 effector cells support activation of macrophages and express cytokines, which induce a class switching to antibody class IgG3. Th2 cells express B-cell-activating effector proteins and secrete cytokines, regulating the class switching to IgG4 and IgE, which is responsible for antiparasitic and allergic immune responses.

Tregs are relevant for maintaining the balance of different T-cell populations (Th1/Th2) and thus for a healthy immune balance. Th17 and Th22 cells operate in a pro-inflammatory fashion, as far as is known, and are essential for acute inflammatory processes by activating or recruiting neutrophils to the local infection. Th9 cells, currently grouped in the Th2 subpopulation, constitute a new subpopulation and produce the cytokine IL-9. The different T-cell populations secrete a more or less specific cytokine pattern (figure 1). Tfh cells, located in B-cell follicles, are responsible for the formation and maintenance of the germinal centre, as well as B-cell differentiation into antibody-forming plasma cells and memory B-cells. The cytotoxic $CD8^+$ T-cells recognise and eliminate virus-infected cells by secreting cytotoxins such as perforin, granulysin and granzymes.

The humoral immune system

The humoral immune system response to infections consists of the production of antibodies by plasma cells, which derive from B-lymphocytes, binding of the antibody to the pathogen, and elimination by phagocytosis and molecules of the humoral immune system. For production of antibodies, antigen-specific Th cells are important. B-cell proliferation and differentiation take place in the T-cell/B-cell periphery in the secondary lymphatic tissue, followed by the T-cell periphery and the germinal centre. IgM is produced by mature B-cells. IgM in the blood circulation is essential for protection against infections, whereas the IgG isotype diffuses into the tissue. Overall, the humoral defence system operates through the production of specific antibodies. Effector cell mechanisms are determined by the "heavy chains" of the isotype and antibody classes.

Secretory immunoglobulins

The secretory immunoglobulins (IgA and IgM) are secreted by epithelial cells of the mucus gland into the lumen, while IgG and IgE diffuse passively. During an immune response, different functions and amounts of immunoglobulin can be detected. Secretory IgA is the main immunoglobulin in the respiratory tract, while secretory IgM decreases during maturation. IgM can efficiently agglutinate particulate antigens and make microbes more susceptible to phagocytosis, while IgA is essential for binding of antigens without activating an inflammatory response. IgA comprises two subclasses, IgA1 (80% in the respiratory tract) and IgA2, which together protect

against viruses and bacteria by inhibiting bacterial adherence, blocking toxins and neutralising viruses. The former is sensitive to bacterial proteases (*e.g. Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis*). By binding to antigens before transcytosis, IgA can additionally activate cells by binding to the Fc receptors. IgG is produced locally, binds subepithelial antigens and leads to local inflammation after complement fixation. It also exists in the bronchial lumen.

The adaptive immune response requires at least 96–100 h to establish antigen contact for T- and B-cells and for differentiation and proliferation of effector cells. After activation of adaptive immune responses, antibodies and effector T-cells are distributed *via* the circulation and recruited to the relevant tissue, in this case the lung. An effective adaptive immune response is characterised by protection and immunological memory. This manifests itself *via* an improved chance to react against familiar pathogens and to eliminate them successfully. Memory T- and B-cells are developed. This protection can be generated artificially by vaccination.

The mucosal immune system

The mucosal immune system is of considerable size and includes the gastrointestinal tract, the lower respiratory tract, the genitourinary tract and other exocrine glands such as the pancreas, conjunctiva, eye glands, salivary gland and the breast during lactation. Due to its physiological functions (*e.g.* gas exchange in the lungs), surfaces are thin and barriers are permeable. Its main role is an efficient defence against invading infectious agents.

The mucosal immune system probably contains 75% of all lymphocytes of the body and produces the majority of immunoglobulins in healthy individuals. Specific features of the mucosal immune system include the interaction between mucosa, epithelium and components of the lymphatic tissue. Moreover, activated cells and cells with memory function also exist without prior infection, and nonspecific natural effector T-cells and Tregs are present. Immune regulatory processes actively downregulate immune responses, and inhibitory macrophages and tolerance-inducing dendritic cells are present. Following antigen overload, particular compartments of the mucosal immune system induce immune responses including antigen intake and presentation, microfold cells and especially dendritic cells, while special "homing receptors" are relevant.

Pathogenic micro-organisms use different strategies to invade the body, such as inclusion of antibodies, inflammatory mechanisms and modulation of different components of the immune system. The immune system of the mucosa has to distinguish between potentially harmful and harmless antigens. Accordingly, it can induce an efficient effector response to pathogens and will not respond to colonisation by common airway micro-organisms. As bacterial colonisation with commensals does not generally exert any detrimental effect on humans, there has to be "coexisting, nonharmful" immune regulation. In the mucosal immune system, antigen presentation to the T-cell is the main component for the decision between tolerance and defence. In the absence of inflammation, antigen presentation occurs without complete costimulation. Mostly, differentiation of Tregs occurs, which guarantees a healthy immune regulation. If pathogens invade, an inflammatory response is induced, activation of antigen presentation and costimulation occurs, and a protective T-cell response is initiated.

Relevance of interaction of innate and adaptive immune regulation for specific defence against respiratory diseases

While exogenous and environmental factors can influence the susceptibility to pulmonary diseases, modulation and interaction of innate and adaptive immune

responses play a prominent role in the defence and regulation of a "healthy immune response".

For asthma, one of the most common chronic diseases in childhood, a close interaction of the innate and the adaptive immune system early in life, often in the first year or during intra-uterine development, is responsible for whether a child develops asthma or transient wheezing, or stays healthy.

A few examples demonstrate the clinical relevance of the innate and adaptive interaction for asthma development. The most convincing results originate from epidemiological studies. Multiple cross-sectional and longitudinal studies have shown that prenatal exposure (during pregnancy) to an environment rich in microbial substances can decrease the risk for asthma, hay fever and atopy for the offspring. It has been shown that activation of the innate immune system *via* TLRs modulates the adaptive immune response, which can subsequently be protective against the development of Th2-mediated immune diseases such as asthma. Besides activation of innate TLRs, activation of Tregs seems to be essential as an important adaptive defence mechanism. In addition, TNF-α-induced protein 3 (TNFAIP3) regulation, which has recently been shown to be critical in childhood asthma development, can be positively modulated by environmental exposure. While newborns with subsequent asthma and manifest asthmatic children express lower levels of this negative regulator of the NF-κB signalling pathway, farm dust and LPS exposure can shift the impaired levels to healthy expression levels.

A further example is respiratory infections early in life, which can lead either to subsequent protection or to a higher risk for chronic airway diseases. This seems to depend on the specific pathogen. Exposure to environmental pollution during pregnancy is an example of an exogenous risk factor that changes structural processes of the lung and has an impact on early immune maturation. This multifaceted field of research demonstrates that many complex interactions of innate and adaptive immune regulation are required to induce an effective immune response.

Development of defence mechanisms

Defence against potentially harmful substances and pathogens is crucial for healthy development. As development of the immune system occurs during the prenatal stage, the specific defence mechanisms of the lung are probably already developed at this stage.

Prenatal period

During the prenatal period, immune regulation is complex, and it is probable that "immune programming" occurs at this early stage. Various studies suggest that exposure to different components of the environment can interfere with early programming. These include infections, smoke exposure and certain maternal dietary habits. Bidirectional interactions between the mother and the fetus seem to be key for post-natal immune maturation; however, this field of research is still evolving. Besides genetic factors, in particular epigenetics, the environment and its interactions seem to influence this early immune response.

Regarding modulatory mechanisms of intra-uterine immune regulation, there may be different explanations. Potential exposure of fetal cells to allergens can occur through the transfer of amniotic fluid *via* the placental tissue starting at 20 weeks of gestation. Furthermore, indirect modulation through influences on the maternal immune system is likely, as the fetal–placental transfer occurs *via* an

active mother–child regulation. Immune cells in decidual tissue of the mother (*e.g.* macrophages, $CD8^+$ and γδ T-cells, and large granulated lymphocytes) can induce rejection of paternal histocompatibility antigens. Additionally, novel data indicate that maternal–fetal tolerance to paternal alloantigens is an active process in which peripheral Tregs specifically respond to paternal antigens to induce tolerance. Overall, maturation of the infant adaptive immune system probably starts between weeks 15 and 20 of gestation and can be antigen specific.

Post-natal period

During the post-natal period, influences similar to those during the prenatal period are present, in addition to ongoing immune maturation. Contact with environmental factors such as smoke exposure or respiratory pathogens probably directly changes the development of immune regulation in the airways. Airway APCs seem to be important during the late phase of inflammation. They are most likely involved in the local damage during inflammatory processes of the airways and are therefore also important for programming of T-cell responses after their migration to the lymph nodes.

In dendritic cells, age-dependent immaturity is associated with a decreased ability to react to inflammatory conditions. During the first year of life, no dendritic cells are present in the airways if no inflammation occurs. In the case of severe respiratory infection, some mature dendritic cells are present. Thus, local impacts on lung structures, such as infectious processes, seem to affect dendritic cell maturation and subsequently T-cell activation.

Early infections of the respiratory tract (*e.g.* rhinovirus) are associated with allergic inflammation later in childhood. However, this early "priming" of the airways seems to depend on the type of infection, as other infections are rather protective against the development of allergic airway inflammation.

Thus, early exposure to infections seems to influence the maturation of local immune networks, which can switch on Th1-mediated immune responses and are, in turn, relevant for efficient defence, while Th2-related immune responses are most likely decreased. However, more studies are needed to elucidate which infections at which local part of the airway (upper/lower respiratory tract) are relevant besides genetics, epigenetics and other environmental triggers. Moreover, the role of the microbiome and its metabolites has been shown to highly influence both immune activation and tolerance by regulating target molecules, especially host receptors. Recent studies have shown that bacterial short-chain fatty acids enhance the chemical barrier by activating AMPs such as regenerating islet-derived protein 3-γ (REgIII-γ) and β-defensins and enhancing the formation of mucus. As well as bacterial influences, the virome also has the capacity to regulate the host immune system in either a harmful or a beneficial way. In addition, members of the prokaryotic domain Archaea have been shown to have immunogenic effects and specifically protective effects on childhood asthma development.

A multifaceted influence on early immune development of a child is most likely critical for the development of allergic airway disease or, *vice versa*, for potential protection against childhood asthma, for example. All of these influences can occur prenatally and are key for later immune development and potentially for disease development.

In the pathophysiology of inflammatory respiratory disorders involving this complex system of innate and adaptive players, dysbalance of Th1/Th2 responses, as well as an impaired regulation of pro- *versus* anti-inflammatory signalling pathways, is known to be involved.

Summary

The innate and adaptive immune systems need to work efficiently individually, while closely connected to each other, in order to provide a successful defence against invading pathogens or inflammation in general. In the case of default regulation in any part of the system, either partial or absent defence can result in different forms of immune-mediated disease such as infections or more chronic diseases such as allergies.

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History and physical examination

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Respiratory medicine, particularly when applied to young children, relies much more on clinical information than on precise laboratory results. Even in today's world of technological wonders, there is no substitute for a patient history and physical examination. This chapter discusses basic issues of paediatric medical history and physical examination of the respiratory system, and briefly addresses the pathogenesis of physical findings.

Medical history

A patient history in paediatric respiratory consultation is governed by the same principles as any other medical history. The child's parents are the primary source or, at the very least, important contributors to the history. However, when obtained by proxy, the subjective nature of the information can be obscured. The undefined use of terms for respiratory symptoms (such as "wheezing") adds to the confusion. Nevertheless, useful information may be obtained from children as young as 3 years of age, while from the age of 8 years the child should be the principal source of the history. Privacy of older children and adolescents must be respected.

The physician should ask open-ended questions and, depending on the complaint, further questioning will focus and expand on specific points. A general structure

Key points

- In respiratory consultations, the patient history is focused on the respiratory system and is adapted to patient circumstances (*e.g.* emergency situations, complaints, chronic problems, age). However, other pertinent organ systems should not be neglected, and the structure of the history is important in order to avoid missing helpful clues.
- A respiratory physical examination of the chest includes inspection, palpation, percussion and auscultation. Lung sounds should be classified, as they differ in pathogenesis and clinical relevance. However, the nomenclature of lung sounds is a subject of considerable confusion.
- A structured physical examination (applied with flexibility in paediatric patients) is fundamental to the evaluation of the respiratory patient. It should include the upper respiratory system, the evaluation of cyanosis, the skin, the digits and other pertinent organ systems.

of the required information needs to be kept in mind in order to cover all the issues relevant to the presenting illness. Such a structure should include the major concern that prompted consultation (chief complaint) and a chronological description of the problem. Clarification should be sought of its onset, frequency, timing, duration and severity, relation to specific circumstances, and response to medication already used. Other relevant signs and symptoms need to be asked for and previous assessments and laboratory results reviewed. The past medical history is quite important: recurring or persistent respiratory problems, emergency visits, hospitalisations, surgery, vaccination status, prenatal, perinatal and neonatal circumstances, including prematurity, mode of delivery and birthweight, all need to be assessed. Family and social history are not to be neglected, and review of other organ systems is no less important in paediatric patients than it is in adults. The all too common presentation of a young child who appears "chesty all the time" and "continuously coughing and wheezing" exemplifies the importance of a detailed history.

Chief complaint and past medical history

The most common chief complaints are wheezing and coughing. However, it is important to discern from the beginning what a parent means by "wheezing". Is it a "whistling" expiratory sound, or is it reminiscent of "rattling" of the chest? The proverbial "all that wheezes is not asthma" holds true, but then again "all that wheezes is not a wheeze". Regarding cough, it is important to clarify whether it is dry and irritating or whether it sounds wet (or "productive"), as well as whether it is often accompanied by wheeze. Cough variant asthma is unusual, and chronic (>4 weeks' duration) wet cough is the most common presentation of chronic bronchitis, *e.g.* persistent (protracted) bacterial bronchitis, which may require more extensive investigation.

If a diagnosis of asthma cannot be made with reasonable certainty, further probing may be in order, for example with the following line of questions:

- What was the reason that prompted specialist consultation?
- Was the onset of wheeze and/or cough acute or progressive?
- Was it related to a viral cold or a sudden episode of choking while eating or playing with small objects?

Viral infections in young children are the most common trigger of such symptoms; 6–8 colds per year (mostly during the cold months) are not unusual at a young age. However, an excessive number of severe infections, recalcitrant nappy rash and oral candidiasis beyond 6–12 months of age may indicate immunodeficiency.

Careful questioning should attempt to discern whether the current episode is actually different from previous ones and in what respect. Additional suggested questions could be structured as follows:

- What is the duration of the episode, as well as that of similar previous episodes?
- Are the episodes only triggered by colds, or are there other triggers, such as exercise, aeroallergens, laughter, strong odours, *etc.*? Cough and wheeze after exercise are associated with airway hyperresponsiveness, while intolerance to exercise, poor feeding and oedema are consistent with congestive heart failure.
- Do the episodes occur during night sleep and do they wake up the child?
- Do the symptoms display seasonality (*e.g.* related to the viral or pollen season)? Evidence of eczema, allergic rhinitis and/or allergic sensitisation should be addressed.

- Does the child vomit and does vomiting always follow coughing, or is it related to meals and the recumbent position (*i.e.* reminiscent of GOR)?
- Have inhaled medications been used and do they appear helpful? If already on medication, dose, inhalation technique, patient's compliance and adherence should be evaluated. The history of hospitalisations or emergency department visits and physicians' diagnoses should be obtained.
- What was the age of onset of symptoms? If close to birth, congenital malformations or genetic inheritance should be considered. Weight and height graphs need to be reviewed and adequate growth ascertained; if the weight lags behind, information on stool consistency should be sought and the diagnosis of CF considered.

The history of prematurity, intubation, mechanical ventilation, prolonged oxygen dependence and corrected oesophageal atresia or tracheo-oesophageal fistula is crucial for interpreting the child's respiratory symptoms; the diagnoses of BPD, subglottic stenosis, tracheomalacia and GOR need to be considered accordingly. The history and duration of breastfeeding and GOR, as well as of problems of poor feeding or failure to thrive, should be addressed.

In diagnosed asthma, questionnaire-based clinical tools, such as the age-appropriate Asthma Control Test and Asthma Control Questionnaire, which have been validated in children, may be utilised in the evaluation of asthma control.

Chief complaints such as cyanotic episodes, hoarseness, stridor, snoring and/or apnoea, haemoptysis, chest pain, dyspnoea, exercise intolerance and nasal symptoms will require further specific probing by the respiratory specialist.

Family, environmental and social history

Family history of asthma, allergies or CF is very helpful. It is important to investigate for consanguinity of parents, miscarriages and childhood deaths (including sudden infant death of a sibling) in the family, as well as history of HIV or TB infection.

Environmental history can be quite revealing. Exposure to indoor tobacco smoke, wood stove heating or gas cooking can trigger bronchitis symptoms and asthma exacerbations. Questioning should address exposure to other inhaled irritants and presence of pets and indoor plants, as well as dampness. Wall-to-wall carpeting, an old housing environment or recent renovation may be important contributors to the child's symptoms. This also holds true for exposure to outdoor air pollution. Vaccination history is important.

Social history may help to determine the quality of historical information and the patient's household circumstances, and aids the physician to form realistic management choices and compliance expectations.

Physical examination

Upper airways

The upper respiratory tract should be examined and facial or buccal deformities should be noted (*e.g.* micrognathia, retrognathia, depressed nasal bridge, clefts, bifid uvula, size of tonsils). Examination of nasal passages can be performed with a nasal or a large ear speculum. It may reveal mucosa that is acutely inflamed and bright red (more consistent with infectious rhinitis), or pale and boggy (more consistent with allergic rhinitis). The presence of nasal polyps before the age of 12 years should prompt investigation for CF, while in adolescents they are often the result of allergic rhinitis or chronic sinusitis.

The frequent upward rubbing of the nose due to itching ("allergic salute") and the resultant crease across the front of the nose are signs of allergic rhinitis. The patient may use the facial muscles in order to relieve nasal itching ("rabbit nose" or the "bewitched" sign). Skin creases on the lower eyelids are also consistent with allergy ("allergic crease"). Erythematous, itchy conjunctivae and nasal symptoms are characteristic of hay fever. The classic signs of dark circles under the eyes and a constantly open mouth (often associated with a history of snoring and sleep apnoea) identify children with upper airway obstruction but not necessarily of allergic aetiology. Evidence or history of eczema is also helpful. Therefore, the predominant sites of atopic dermatitis (*e.g.* flexures of upper and lower limbs) should be carefully examined.

Chest

Inspection

The patient's chest should be exposed and inspected for congenital or acquired deformities (*e.g.* pectus excavatum, pectus carinatum or kyphoscoliosis). Hyperinflation of the thorax (*e.g.* air trapping due to asthma or another chronic lung disease) or asymmetry of the two hemithoraces (*e.g.* due to pneumothorax or cardiomegaly) should be sought; asymmetrical excursion of the hemithoraces due to paralysis of the hemidiaphragm may occur.

Chest expansion, respiratory rate and pattern of breathing should be noted, and increased work of breathing (as evidenced by tachypnoea, retractions, use of accessory respiratory muscles and paradoxical respiration) should be assessed. In chronic obstruction, the Hoover sign may be observed. This consists of (untoward) indrawing of the lateral chest during inspiration at the level where the flattened diaphragm attaches to the ribcage. However, it does not reliably reflect the degree of obstruction.

Palpation

Palpation of the chest is mainly used to confirm the findings of inspection. Areas of tenderness and masses (*e.g.* lymph nodes) may be identified. The position of the trachea, *i.e.* the tracheal "tug", is more easily felt than observed.

Chest excursion should be evaluated, and asymmetrical movement can be identified by placing the palms of both hands in a manner "wrapping" the child's chest symmetrically from behind, thumbs placed posteriorly and the rest of the fingers anteriorly. The physician "follows" the chest excursions during breathing with his/her hands, comparing the two sides by observing the movement of the thumbs away from the midline.

Vibrations generated by the voice, *i.e.* "tactile fremitus", and felt with the palm of hands, are more difficult to realise in children due to the higher frequency of their voice. Low-pitch, high-amplitude sounds, such as repeating "ninety-nine" or "one-one-one" (or equivalent vocalisations in other languages) rather loudly, will result in increased tactile fremitus in cases of parenchymal consolidation (*e.g.* pneumonia) and in reduced tactile fremitus in cases of pneumothorax, air trapping or pleurisy.

Percussion

Since its initial description 2.5 centuries ago, dedicated teachers have taught the art of percussion to medical students. The method is based on the match (or mismatch) of the vibratory characteristics of adjoining tissues. When there is great mismatch (*e.g.* chest wall overlying a pneumothorax), there will be resonance and the sound is perceived as "tympanic". Conversely, when there is little acoustic difference between the bordering tissues (*e.g.* pleural fluid underneath the chest wall), the energy of

the impulse propagates quickly and the sound is "dull". Most paediatricians use the indirect method of percussion, whereby the surface of the chest is vertically tapped with the long finger of one hand (plexor), two or three times in each position; tapping is performed on the distal interphalageal joint of the middle finger of the other hand, which is firmly superposed to the skin over an intercostal space (pleximeter). Direct percussion of the chest is sometimes used in younger children. The chest should be percussed symmetrically.

Auscultation

In children, respiratory sounds heard at a distance or auscultated over the chest may provide valuable clues. The stethoscope has practical and symbolic value for the general physician and the pulmonologist alike. Auscultation provides the most detailed information of the entire physical examination. The binaural stethoscope is favoured by most physicians and can adequately serve the specialist. The diaphragm of the head piece, when pressed firmly on the skin, filters out the lower frequencies and allows for better perception of the high-pitched sounds. Conversely, the bell should be applied lightly (to avoid stretching the skin) in order to select for lower frequencies. Appropriately sized chest pieces for different chest sizes should be selected.

The infant should be examined in a quiet and warm room, undressed, on the lap of the parent. To have young children cooperate for proper auscultation is an art; still, it may not always be possible to listen adequately over all the lung segments. The upper lobes are best auscultated over the upper anterior chest, lower lobe sounds are best heard over the posterior lower chest, and the middle lobe and lingula are best represented on the respective sides of the lower third of the sternum. Over the lateral chest, in the axillae, all lobes can be auscultated.

Sounds

To date, there is no definitive nomenclature for respiratory or lung sounds. A European Respiratory Society task force has established a database of high-quality audio-visual recordings of respiratory sounds, as a reference to standardise nomenclature (https://dev.ers-education.org/e-learning/reference-database-of-respiratory-sounds/). Respiratory sounds are related to chest air movement, normal or adventitious, heard at the mouth, the trachea and the chest; they include sounds produced by cough, snoring, sneezing or respiratory muscle contraction, but exclude voiced sounds. Lung sounds are the respiratory sounds heard over the chest. A summary of respiratory sounds is given in table 1 and further details can be found in the chapter "Evaluation and management of wheezing, stridor, snoring and hoarseness".

Normal sounds

Normal breath sounds are respiratory sounds that arise from breathing, excluding adventitious sounds. They consist of vesicular breath sounds (a misnomer as they do not originate in vesicles, *i.e.* the alveoli) and bronchial sounds. Normal breath sounds are characterised by a broad frequency spectrum according to the location of auscultation. Tracheal sounds are normally auscultated over the extrathoracic trachea, with short inspiratory and long expiratory duration. However, this is an abnormal sound when auscultated more peripherally over the lung, *e.g.* on locations distant to the manubrium due to consolidated lung parenchyma. Muscle sounds are low-frequency, low-intensity sounds related to the contraction force of thoracic skeletal muscles, which blend into the normal breath sound spectrum. Often, the terms "respiratory sounds", "breath sounds" and "lung sounds" are used interchangeably.

Table 1. Respiratory sounds

Name	Description
Normal	
Lung sounds	Respiratory sounds heard over the chest
Breath sounds	Respiratory sounds that arise from breathing; broad frequency spectrum according to the location of auscultation
Vesicular	Quiet, low-frequency, non-musical; audible over the chest during inspiration and hardly audible during normal expiration
Bronchial	Higher frequency and intensity; audible over the upper anterior chest wall; approximately equal duration in inspiration and expiration
Tracheal	Normally auscultated over the extrathoracic trachea; short inspiratory and long expiratory duration
Adventitious	Additional sounds, usually associated with pulmonary disorders
Continuous	Musical
Wheeze	Periodic waveforms, predominately of high frequency; can be heard at the mouth or at a distance; usually associated with airway obstruction; expiratory wheeze always signifies flow limitation but inspiratory wheeze mechanism is unclear; also heard in healthy individuals
Stridor	Harsh, loud, usually inspiratory; can be heard at the mouth or at a distance; can be auscultated over the chest; sign of extrathoracic/upper airway obstruction
Rhonchi	Lower frequency wheezes; term also used for alternative sounds so may be obsolete
Discontinuous	Non-musical
Crackles	Usually auscultated during inspiration; also known as "crepitations" or "rales"
Fine crackles	High pitch, low intensity, short duration; gravity dependent; rarely heard at mouth; typical of fibrotic lung disease
Coarse crackles	Low pitched, higher intensity, longer duration; gravity independent; usually audible at the mouth; heard in bronchitis, bronchiectasis, chronic airway obstruction, pneumonia during recovery phase, cardiac failure
Squawk	Inspiratory; composite of wheeze preceded by crackle
Pleural friction	Similar to coarse crackles

Adventitious sounds

Adventitious sounds are additional sounds superimposed on normal breath sounds; they are usually associated with pulmonary disorders. Adventitious sounds are primarily divided into continuous sounds (musical, wheezes) and discontinuous sounds (non-musical, crackles).

Wheeze is characterised by periodic waveforms (continuous and of musical quality), predominately of high frequency. Lower frequency wheezes have different pathogenesis and are often termed rhonchi. In general, wheezes may be audible at the patient's mouth or at a distance. They are usually associated with airway obstruction due to various mechanisms, such as bronchoconstriction, airway wall oedema, intraluminal obstruction (*e.g.* foreign body), external compression or dynamic airway collapse. Expiratory wheeze always signifies flow limitation, while the mechanism underlying the generation of inspiratory wheeze remains unclear. In healthy individuals, wheeze may also be produced by turbulent flow-induced airway wall vibration, without flow

limitation. Of note, there is no correlation between wheeze intensity and the degree of obstruction. Wheeze may be classified into monophonic and polyphonic.

Other continuous sounds, summarised in table 1, are stridor and rhonchi (singular rhonchus). The latter are low-pitched continuous (musical) sounds, generated by intraluminal secretions and collapse of large airways. However, the term rhonchi has also been used for expiratory "gurgling or bubbling sounds" originating in the large airways (*i.e.* what most authorities would term "coarse expiratory crackles"). It is perhaps time that this term be abandoned.

Crackles (also called "crepitations" or "rales") are discontinuous, non-musical sounds, usually auscultated during inspiration. Fine crackles ("crepitant" crackles) are characterised by high pitch, low intensity and short duration. They are caused by the explosive opening of small airways collapsed by surface forces (increased elastic lung recoil pressure or inflammation/oedema). Fine, late inspiratory crackles are typical of fibrotic lung disease. Coarse crackles ("subcrepitant" crackles) are scantier, low pitched, higher intensity and longer duration sounds, which are generated by movement of thin secretions in the bronchi. They start early and continue until mid-inspiration but may also be heard during expiration. A typical example of coarse crackles can be heard in bronchitis, bronchiectasis and chronic airway obstruction (*e.g.* CF). Similar auscultatory findings can be found focally in pneumonia during the recovery phase. Acoustic analysis has also characterised the crackles of cardiac failure as coarse.

Further adventitious sounds include squawk and pleural friction. A squawk is a "composite" inspiratory sound with a musical character (short wheeze) that is preceded by a crackle. It is thought to result from the vibrations set in motion by the sudden opening of a collapsed airway. Squawks are not associated with airway obstruction but rather with pulmonary fibrosing diseases. Pleural friction sound (or friction rub, often described as "leathery") is similar to coarse crackles. It results from the "friction" between inflamed parietal and visceral pleura. It can be auscultated during inspiration or in both phases of breathing and does not disappear with cough. Pleural friction precedes pleural effusion and disappears when fluid is formed.

Voice sounds

Voice transmission is filtered by normal lung parenchyma so that speech becomes indistinct (*i.e.* perceived as "mumble") when auscultating the chest. When there is underlying consolidation, higher frequencies are more effectively transmitted, and syllables become distinct during auscultation; this is termed bronchophony. Aegophony is a similar change in transmission but has a nasal quality with a change of "e" sound to "a". Whispered pectoriloquy is an unusually clear transmission of whispered sounds during auscultation in case of severe consolidation.

Cyanosis and clubbing

Cyanosis

Cyanosis is the bluish-purple discoloration of the skin or the mucosa caused by high concentration of reduced haemoglobin (Hb) in the capillary bed. The value of reduced Hb required for cyanosis to occur is 3 $g \cdot dL^{-1}$ (arterial blood). Depending on the Hb content, cyanosis will occur at different levels of S_{aO_2}: at 65% for Hb 8 $g \cdot dL^{-1}$ (anaemia), 78% for Hb 14 $g \cdot dL^{-1}$ (normal), and 85% for Hb 20 $g \cdot dL^{-1}$ (polycythaemia). Fetal Hb (HbF) shifts the oxygen dissociation curve to the left, thus preventing cyanosis in the neonate; the opposite is true for sickle Hb (HbS) in sickle cell disease. The detection of cyanosis is also influenced by factors such as type and intensity of light,

skin pigmentation, peripheral perfusion and ambient temperature. Ideally, cyanosis should be evaluated in daylight in a comfortably warm environment.

Central cyanosis is seen at the ear lobes and the mucous membranes (buccal, tongue, nasal) and represents reliable evidence of hypoxaemia. Peripheral cyanosis or acrocyanosis (circumoral, distal phalanges of fingers and toes) is more common and does not necessarily imply hypoxaemia. Differential cyanosis may be observed in congenital heart disease, *e.g.* cyanosis of the lower part of the body in preductal coarctation of the aorta, cyanosis of the upper part of the body in transposition of the great arteries. The sensitivity of cyanosis in the evaluation of hypoxaemia is poor; therefore, hypoxaemia should be assessed by measuring the P_{aO_2} or, more readily, the S_{pO_2}.

Clubbing

Clubbing is the thickening of the connective tissue in the distal phalanges of the fingers and toes. It can be detected clinically in three ways: 1) the Schamroth sign, which is the obliteration of the diamond-shaped opening at the base of the nail beds that is normally created by precisely opposing the dorsal surface of the distal phalanges of similar (right–left) fingers; 2) the inversion of the phalangeal depth ratio, *i.e.* the ratio of the distal phalangeal diameter (measured at the level of the eruption of the nail) over the interphalangeal diameter (measured at the crease between the two distal phalanges), which is normally <1; and 3) the increase of the hyponychial angle (defined by the plane of the nail and that of the adjacent skin at the eruption of the nail) to >180º.

Clubbing is an important indicator of lung disease, more commonly seen in CF and non-CF bronchiectasis, empyema or lung abscess, but may also occur in association with heart (congenital or endocarditis), liver or gastrointestinal disorders. It may reflect the course of disease over time and may be associated with (usually painful) periostosis in the context of hypertrophic osteoarthropathy.

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Evaluation and management of acute and chronic cough

Julie M. Marchant, Anne B. Chang and Ahmad Kantar

Globally, cough is the most common symptom leading people to seek medical attention. Cough in children is symptomatic of a broad range of respiratory diseases, ranging from the common cold to serious chronic diseases. Understanding the mechanisms behind cough is essential for effective management.

Physiological aspects of cough

Cough is a complex protective (airway defence) mechanism that occurs through the involuntary activation of the cough reflex. However, it can also be a voluntary manoeuvre. During cough, multiple peripheral and central neural circuits of the cough reflex are activated (afferent, central and efferent limbs). The efferent limb involves both respiratory and extrarespiratory muscles (*e.g.* pelvic sphincter). This protective reflex is a component of normal respiratory physiology that prevents foreign material entering the lungs, including gastric contents. A second protective component is clearance of excessive and retained airway secretions, reducing the risk of infection and effects of pollutants from the respiratory tract. The importance of cough in maintaining respiratory health is evident in clinical situations such as neuromuscular diseases, where the cough is ineffective or impaired.

An effective cough has three mechanical phases: inspiratory, compressive and expiratory. The compressive phase involves an increase in intra-abdominal and intrathoracic pressures through glottis closure. Once the expiratory phase starts

Key points

- Red flags or specific cough pointers should be looked for when evaluating any child with a cough.
- A chronic (duration >4 weeks) daily wet or productive cough in a child should not be ignored.
- The aetiologies of chronic cough in children are different from those in adults. Children with chronic cough should be systematically evaluated but may not always require treatment.
- Exacerbating factors, such as exposure to tobacco smoke, should always be addressed in any child with a cough.

on glottic opening, it involves high airflow velocities and expiratory pressures for maximum airway clearance. Vibration of the larger airways and the laryngeal structures during this expiratory phase cause the coughing sound during turbulent flow. Mucus in the larger airways, as opposed to the smaller airways, is required for a detectable difference in cough sound quality, as the rheological properties of mucus influence cough sounds. Numerous studies have highlighted the helpfulness of the cough quality in guiding the diagnostic approach in children, as will be discussed later in this chapter, as well as why cough quality is an essential part of clinical evaluation of children with cough.

Like other systems, physiological and anatomical aspects involving cough undergo maturation and, thus, there are developmental aspects of cough. Maturation of the cough reflex, modifications in the structure of the respiratory tract and immunological changes are the main factors that explain why the common causes of cough in children are different from those in adults.

Pathological aspects of cough

Problems related to cough can be divided into impaired and excessive cough. Impairment or absence of the coughing mechanism can be harmful and even eventually fatal. Abnormalities in cough can occur in any limb of the cough reflex. Abnormalities in the afferent limb, such as in children with neurological disorders, lead to a predisposition to silent aspiration and subsequent chest infections. Similarly, abnormalities in the efferent limb, such as in neuromuscular disorders, lead to an ineffectual cough and risk of chest infections. Hence, the assessment of cough effectiveness is important when assessing children, particularly those with neurological or neuromuscular disorders.

Excessive cough is troublesome for parents and its presence, when it is persistent, may be the first overt sign of disease of the airways or lungs, *i.e.* it may become a helpful pointer of potential disease for both patient and physician. Indeed, cough is a common symptom of both acute and chronic respiratory illnesses. Also, it consistently remains among the most frequent reasons that parents seek healthcare for their children.

Cough definitions

When evaluating a child with cough it is important to establish the duration and nature of cough, in order to determine appropriate management. Acute cough is defined as a cough of <2 weeks' duration. Chronic cough is defined as >4 weeks' duration. This is based on evidence that shows >90% of upper respiratory tract infections have resolved by 3 weeks. In addition, it means children with serious illnesses, such as a retained foreign body, are evaluated promptly.

An evaluation of cough in children also involves determination of the cough quality, particularly whether it is wet or dry. A wet cough indicates the presence of airway secretions. Other classic cough qualities need to be assessed and include presence of a barking or brassy cough, a paroxysmal cough with or without whoop, or suppressible cough not present in sleep.

Acute cough

Acute cough is defined as a cough lasting up to 2 weeks. Although there are a wide range of aetiologies of acute cough, it is most commonly due to viral infections. Viral infections of the respiratory tract cause early release of many inflammatory

mediators, disrupting the respiratory epithelium, and sensitising chemosensitive cough receptors and the neuronal pathway of the cough reflex. Usually cough resolves spontaneously within 1–3 weeks following viral infection and there is limited evidence that any therapy is beneficial. In many respiratory infections, cough is often the last symptom to disappear. Provided the child is otherwise well with no hypoxia, pyrexia, tachypnoea, findings on auscultation and/or dehydration or feeding difficulties, it is usually appropriate to wait for the illness to take its course, *i.e*. natural resolution. Some acute cough has classically recognisable cough sounds, such as the barking or brassy cough of croup with or without inspiratory stridor or the paroxysmal cough (with or without inspiratory whoop) of *Bordetella pertussis/parapertussis* infection, which will aid in diagnosis.

Children aged 2–5 years may have up to 6–8 episodes of respiratory infection, especially if they attend day care. Persistent coughing after each bout may thus blend into the next infection and this may be reported erroneously as chronic cough. Other causes include bacterial infection of the upper and lower respiratory tract, foreign body inhalation and exacerbation of a chronic disease such as asthma.

Retained inhaled foreign bodies are most commonly seen in young children <5 years of age. Food, particularly nuts and seeds, may be the cause of obstruction in children who have incomplete dentition, immature swallowing coordination or the tendency to be distracted when eating (*e.g*. by playing, running or laughing). This diagnosis should be suspected if there is a history of choking followed by prolonged cough and/or nonresolving pneumonia. The yield from physical examination and radiological studies in the diagnosis of foreign body aspiration is relatively low but the cough is initially dry (may be wet if there is prolonged retention of the foreign body) and there may be associated wheeze, typically unilateral and/or monophonic. When a foreign body is suspected, immediate endoscopic evaluation of the airway is recommended, with removal of the foreign body when found. Delayed diagnosis has serious consequences, such as chronic cough, recurrent pneumonias and, eventually, localised areas of bronchiectasis. Hence, while foreign body aspiration is significantly less common than an acute cough due to viral infections, an inhaled foreign body should always be considered in a child with cough, particularly when there is a history of choking episodes and/or an acute cough becomes chronic in a young child.

An acute exacerbation of asthma can result in an acute cough that is typically dry, unless there is a concurrent lower airway infection. These children exhibit other signs of asthma, such as tachypnoea or bilateral expiratory wheeze with or without hypoxaemia. The cough may be exercise induced and other features such as atopy may be present. Importantly, these children have no focal unilateral findings on examination. A positive response to bronchodilators confirms the diagnosis and, when possible, spirometry may demonstrate a reversible obstructive pattern. However, in children with mild asthma, spirometry is usually normal. Undertaking a bronchoprovocation challenge and/or exhaled nitric oxide measurement may be appropriate.

In summary, acute cough is usually a self-resolving illness in children but can indicate serious illness in the minority of children, *e.g*. due to an inhaled foreign body or complicated pneumonia. Red flags in the assessment of children with acute cough include the presence of respiratory distress (such as chest indrawing, tracheal tug or nasal flaring), tachypnoea, hypoxia and systemic signs (such as a toxic-looking child, rigors, vomiting, inability to eat or drink and dehydration). These children need further investigation and/or specialist referral when warranted.

Chronic cough

Chronic cough is a commonly encountered symptom presenting to paediatric respiratory specialists, and, while prevalence is estimated at 10% of children aged <12 years, the true prevalence of this condition in the community is difficult to define. The prevalence depends on the population being considered, the age of the child and the diagnostic tools used. Although often disregarded by doctors, chronic cough causes a substantial burden of illness. Before receiving appropriate management, many children with chronic cough and their families experience unnecessary or recurring medical consultation, with a great impact on their quality of life and adverse effects from inappropriate use of medications. Chronic cough may represent an underlying serious respiratory disorder. Indeed, an Australian multicentre study found that 12% of the 346 children presenting for the first time to respiratory specialists with chronic cough had a serious underlying disease (*e.g.* bronchiectasis or CF).

Chronic cough in adults is universally defined as a cough that lasts >8 weeks. In children, a daily cough for 4 weeks is the most commonly used definition. There are few data on the cut-off for defining chronic cough based on cough duration. For several reasons (mainly safety and impact of cough on quality of life), the American College of Chest Physicians (CHEST) and most international guidelines define chronic cough as daily cough of at least 4 weeks' duration. However, the British Thoracic Society guideline published more than a decade ago uses duration of >8 weeks. The definition of chronic cough as >4 weeks is used in children as the majority of upper respiratory tract infections have resolved within this timeframe, and this definition allows for prompt diagnosis of serious conditions, such as a retained foreign body.

Table 1. Rarer but important causes of chronic cough in children

Aspiration
Primary or secondary
Swallowing disorders
Airway abnormalities such as tracheo-oesophageal cleft
Retained inhaled foreign body
Discussed in section on acute cough, but should always be considered in chronic cough
Chronic pneumonia
Causes such as TB or fungi need to be considered in certain children and particular geographical areas
Eosinophilic lung disease
Primary or secondary
Airway or peripheral blood eosinophilia
Parasites can play a role in certain areas
Fungi, such as *Aspergillus*, can play a role
ILD
Cough is typically dry
Chest examination shows fine crackles and tachypnoea
Failure to thrive may be present
Nonpulmonary causes that are rare in children
Medications
Cardiac causes
Ear disease

Depending on the setting, the most common causes of chronic cough in children are post-infectious nonspecific cough, asthma and protracted bacterial bronchitis (PBB). These are discussed in the following sections of this chapter. It is important to note that these causes differ from the most common in adults, where GOR disease and upper airway cough (post-nasal drip) syndrome are among the three most common causes, in addition to asthma. GOR and upper airway cough syndrome are thought to be rare causes in children. There are also geographical differences in the causes of cough, such as in areas with endemic TB, which should always be considered.

Other rarer but important causes of chronic cough in children, which will be elucidated by careful evaluation of cough pointers, are shown in table 1. Apart from these, there are multiple other rarer causes, *e.g*. tumours causing airway compression. Additionally, mention should be made of tic cough (habit cough) and somatic cough disorder (psychogenic cough). Both are disorders in which the cough is suppressible, repetitive and distinctive in nature, with a dry cough and characteristic honk or bark. Importantly, this cough is not present in sleep. Treatment involves suggestion therapy.

Asthma

Asthma can present as an acute or a chronic cough in children. Invariably, these children have other symptoms of asthma, including:

- A typically dry cough
- Bilateral polyphonic wheeze
- Exertion dyspnoea
- Atopic features (eczema, rhinitis)
- Family history of asthma or atopy
- Episodic attacks precipitated by triggers such as respiratory illness
- Chest radiograph that may show bilateral hyperinflation
- Spirometry that may show reversible obstructive pattern with response to bronchodilators

Importantly, isolated chronic cough in children with none of the above features is very unlikely to be asthma.

Post-infectious self-resolving cough

Children who have had a respiratory illness can be left with a chronic dry cough. These children do not have any specific cough pointers (listed in table 2) and will resolve over time without treatment. Management involves reassurance and reassessment to ensure no specific pointers develop. Children can be left with a similar illness after *B. pertussis* or *parapertussis*, *Mycoplasma pneumoniae* or *Chlamydiae* infection. The cough post-pertussis can be classically recognisable, with paroxysmal coughing attacks with or without whooping, although this is not always the case.

Chronic endobronchial infection

The most common cause of a chronic wet cough in many paediatric cohorts is PBB. PBB forms part of a proposed spectrum of chronic endobronchial infection that presents with wet cough in children, with PBB at one end of the spectrum and irreversible bronchiectasis at the other. The pathobiological model that explains this progression involves airway infection and neutrophilic airway inflammation.

PBB is defined in children as a chronic wet cough with no other specific cough pointers and normal investigations (apart from bilateral peribronchial thickening in some children on chest radiography). The children have been shown to have

Table 2. Specific cough pointers

History
Chronic wet or productive cough
Haemoptysis
Wheeze
Dyspnoea
Recurrent pneumonia
Symptoms from neonatal period
Onset after choking episode
Cough worsens when child anxious; improves with distraction; can be voluntarily suppressed
Child has thoughts disproportionate to symptoms
Cardiac disease
Developmental/neurological abnormalities
Swallowing difficulties
Failure to thrive
Exposure to TB, *B. pertussis*, travel history
Immunodeficiency or history of deep infections
Autoimmune disease
Angiotensin-converting enzyme inhibitor use
Chronic fever
Examination
Wet or productive cough
Classically recognisable cough sounds
Digital clubbing
Chest wall deformity
Auscultatory findings (wheeze, crepitation, differential breath sounds)
Hypoxia
Cardiac abnormalities (including murmurs)
Investigations
Abnormal chest radiograph
Abnormal spirometry

typical respiratory organisms in their airway (*Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*) and neutrophilic airway inflammation. The chest is clear on auscultation, although a "rattle" of secretions in the large airways can be heard. Treatment involves a course of appropriate antibiotic therapy (typically amoxicillin-clavulanate) for a minimum duration of 2 weeks, with some children requiring up to 4–6 weeks of antibiotic therapy for total cough resolution. Some children will go on to have recurrent episodes of PBB, and these should always be further investigated for other potential causes, such as a missed retained foreign body or bronchiectasis.

The spectrum of chronic endobronchial infection proposed suggests chronic suppurative lung disease and bronchiectasis as possible sequelae of untreated PBB or recurrent episodes. Chronic suppurative lung disease is a condition in which children have chronic wet cough that does not respond to oral antibiotics, but an HRCT scan does not show evidence of bronchiectasis. Bronchiectasis is diagnosed on HRCT, which shows an increase in broncho–arterial ratio, bronchial dilation and wall thickening of peripheral airways. See chapter "Protracted bacterial bronchitis and non-CF bronchiectasis" for further details.

Diagnosis of childhood cough

The initial review of any child with cough involves a thorough history and physical examination. Based on several cohort studies and a single randomised controlled trial, there is now evidence to support using paediatric chronic cough management protocols (or algorithms) to improve clinical outcomes. However, all these studies enrolled children from specialist clinics. Using an algorithm involves a systematic evaluation that includes attention to signs and symptoms associated with red flags or cough pointers suggestive of a specific diagnosis. Spirometry, with or without tests of bronchodilator responsiveness, should be attempted in children who are old enough, typically >6 years of age. An attempt should be made to observe the cough. In a child with acute cough, this may be all that is necessary to rule out potentially serious illnesses, while a "watch and wait" approach is adapted with review for development of new symptoms. A study showed that 30% of children enrolled with acute cough who were still coughing at 4 weeks had a serious chronic lung disease; hence, medical review is always advised if symptoms persist.

In children with chronic cough, initial evaluation should follow the aforementioned approach but should also include a chest radiograph. A targeted history addressing possible presence of cough pointers (table 2) is necessary. These cough pointers are signs and symptoms that suggest a specific cause for the cough. One of the most important markers in chronic cough is the presence of a wet cough, which alerts the clinician to the presence of excessive airway secretions. In addition, classically recognisable cough sounds should be considered. These include the barking or brassy cough of tracheomalacia or tic cough, the honking suppressible cough of tic and psychogenic cough, and the paroxysmal cough (with or without inspiratory whoop) of *B. pertussis/parapertussis* infection.

Management of childhood cough

Cough in children disrupts both the parents' and child's daily activities and is associated with impaired quality of life in the child and significant stress in parents, which improves with cough resolution. Hence, the aim of managing a child presenting with cough is to identify and treat its cause. Early diagnosis is important, as delayed diagnosis (*e.g.* of a foreign body) may cause chronic respiratory morbidity, whereas early diagnosis of chronic disease leads to appropriate management and subsequent resolution of cough and improved quality of life. The removal of exacerbating factors should always be addressed, particularly indoor and outdoor air pollution such as from heating (fires) or tobacco smoke from parents. Finally, the use of cough suppressants should always be advised against, as there is no evidence for their effectiveness in childhood cough and they have the potential to cause serious harm. In acute cough due to viral illness, these measures (ruling out other more serious causes, addressing exacerbating factors and advising supportive management only) are all that is necessary.

In chronic cough, all of these factors remain important and the identification of the cause of cough can be made using a cough algorithm. The use of cough algorithms or pathways can lead to earlier diagnosis and reduce morbidity, unnecessary costs and medication use associated with chronic cough. Internationally, guidelines for managing chronic cough have been developed, and a systematic review of nine studies has shown that there is high-level evidence to support their use. Paediatric-specific guidelines have been evaluated *via* a randomised controlled trial, which showed that children managed *via* the algorithm had shorter cough duration and an improved quality of life. Hence, all children with chronic cough should be evaluated using a paediatric-specific algorithm and treated according to aetiology.

Specific management is dependent on aetiology (the most common of which have been discussed). Irrespective of the treatment, review for cough resolution and development of new signs or symptoms is necessary. Cough has a significant "period" effect; hence, resolution of cough may not always be due to medications used, and a trial off the medication may be necessary to prove efficacy. Finally, the management of parental expectations and the high burden of cough needs to be considered in managing a child with cough. Explanation of the natural history of diagnosed conditions and expected time to cough resolution are important aspects of management.

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Evaluation and management of wheezing, stridor, snoring and hoarseness

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Wheezing, stridor and snoring are common causes of noisy breathing, particularly in infants and young children, and their presence indicates some degree of airway obstruction. Noisy breathing is a loose term that refers to the adventitious sounds heard from a distance (rather than through the stethoscope) and it includes wheezing and stridor, as well as other "abnormal" breathing sounds such as grunting, snuffling, rattling and snoring. Although the evaluation of noisy breathing is not always straightforward, the proper identification of these noises is of major clinical importance, since it can assist in localising the site of the obstruction and thus in the differential diagnosis of the potential underlying causes (table 1). Further details can be found in the chapter "History and physical examination".

The cause is often obvious from the history and the clinical examination, and the final diagnosis can be reached with a minimum of diagnostic procedures. However, an interventional approach may sometimes be necessary to effectively diagnose the cause, especially if a lower airway lesion is suspected.

Key points

- Wheeze is a continuous, usually high-pitched whistling sound that is accompanied by prolongation of the expiratory phase; it is believed to originate from the oscillation of large and medium-sized airways in response to turbulent airflow in partially blocked intrathoracic airways.
- Stridor is a musical, monophonic, high-pitched sound that can be heard without a stethoscope; it is caused by narrowed large, extrathoracic airways. Its presence suggests significant obstruction of airflow in the larynx and/or proximal trachea.
- Snoring is produced during sleep and is due to obstructed air movement in nasopharynx and oropharynx. Children who snore tend to have more collapsible airways and/or increased size of adenotonsillar tissue.
- Hoarseness (or dysphonia) is a disorder of phonation and is used to describe a change in the quality of the voice; it is not usually associated with airway obstruction.

Table 1. Different kinds of noisy breathing, site of origin and common causes

Noise	Site of origin	Common causes
Wheezing	Intrathoracic airways (primarily expiratory)	Asthma, viral wheeze, bronchiolitis, foreign body aspiration, protracted bacterial bronchitis, tracheo/bronchomalacia
Stridor	Extrathoracic airways (primarily inspiratory)	Croup, epiglottitis, laryngomalacia, tracheomalacia, vocal cord paralysis, inducible laryngeal obstruction
Snoring	Oro-/nasopharyngeal airway	Collapsible airways with large-sized adenoids and tonsils, obesity, craniofacial disorders
Rattles	Intra- and extrathoracic airways	Acute viral bronchitis, protracted bacterial bronchitis, neurological disorders with swallowing dysfunction and/or chronic aspiration
Grunting	Glottis	Respiratory distress syndrome (neonates), pneumonia, bacterial infection
Snuffles	Nasal passages	Upper respiratory tract infections, allergic rhinitis

The difficulty in correctly recognising abnormal sounds arises from the different types that may be present in the same patient at the same time or at different points in time, and from the fact that they are frequently intermittent and not heard during the clinical examination, making the clinician rely only on the parent's description. The parent's description is often inaccurate, and their use of terms to describe the sound(s) can be quite misleading. Nevertheless, a detailed history by the parents on the exact nature of the respiratory noise, with special attention to whether it occurs during inspiration, expiration or both, whether it is low or high pitched, or has a musical quality and is accompanied by vibrations of the chest wall, and perhaps the imitation of the various sounds by the physician, will undoubtedly assist in differentiating between the various noises.

Inaccurate classification of sounds can quite often also be a problem among physicians, as there is still ambiguity in the terminology used for respiratory noises in the medical literature, a fact that stresses the need for a common nomenclature in each language. The work of a recent European Respiratory Society task force may well be a first firm step towards this goal, as this has established a database of high-quality audio-visual recordings of respiratory sounds, as a reference to standardise nomenclature (https://dev.ers-education.org/e-learning/reference-database-of-respiratory-sounds/). The RALE Repository (Respiration Acoustics Laboratory Environment; www.rale.ca) also presents digital recordings of respiratory sounds in health and disease.

Computerised acoustic analysis technology has been used to evaluate the acoustic properties of sounds and, in the future, may provide an objective clinical tool for correctly characterising respiratory sounds and assessing disease activity through the serial recording and quantification of these sounds. However, for the time being, this technology is used only for research purposes.

In this chapter, we will discuss wheezing, stridor and snoring, and there will be a brief discussion of some other quite common types of noisy breathing, namely rattles,

grunting and snuffles. Hoarseness (or dysphonia), which is a disorder of phonation and is not usually associated with airway obstruction, will also be discussed.

Wheezing

Wheeze is a continuous, usually high-pitched, whistling sound with a musical quality. It can be heard throughout the respiratory cycle but is more common during expiration and is accompanied by prolongation of the expiratory phase. It is believed to originate from turbulent airflow (caused by partially blocked intrathoracic airways) that oscillates the airway wall and gives rise to this sound.

Although, in theory, wheezing can arise from throughout the conducting airways, it requires a sufficient airflow, which practically restricts the site of its production to the large and medium-sized airways. However, it is common to find that wheezing is audible in cases of extensive small airway narrowing, as is the case with asthma and occasionally with bronchiolitis. This could be due to air trapping in the lung periphery and the higher pleural pressures required to overcome the narrowing. Thus, wheezing is thought to be produced by the resultant external compression of the larger airways, especially during infancy when the walls of the central bronchi are more collapsible.

Since the noise is produced from a multitude of airways throughout the lungs, wheeze consists of a variety of distinct harmonics (differing acoustic characteristics) and is, therefore, "polyphonic". Conversely, when the sound is generated by one large airway (*e.g.* due to a foreign body or stenosis), or just a few airways at most, it consists of a much more limited number of harmonics and is termed "monophonic" (or perhaps, more precisely, "oligophonic"). The "focal" nature of the monophonic wheeze may explain the decrease of its loudness as the distance of the auscultation site on the chest wall from the sound source (the obstruction) increases.

Assessment of wheezing

The most common cause of intermittent episodes of polyphonic wheeze in children is asthma. The prompt response of the wheeze to a trial of bronchodilator is of great importance, since it strongly supports the diagnosis of asthma. In infants, especially if crepitations predominate on auscultation, and particularly if it is the first episode of diffuse airway obstruction, the most likely diagnosis is bronchiolitis. The response to bronchodilators and the presence and/or family history of atopy may help to differentiate bronchiolitis or viral wheeze from asthma. Simple noninterventional investigations, like chest radiography, allergy testing and spirometry, may be useful in older children, whereas more elaborate investigations are rarely necessary.

Acute onset of monophonic wheeze raises the possibility of foreign body aspiration. The absence of a choking event is not reassuring, since about 15% of cases are not associated with a clear history of a choking episode. Monophonic progressive wheeze implies either a focal endobronchial lesion (endobronchial TB, adenoma, *etc.*) or extraluminal compression of central airways by a lymph node or other mass, and should always prompt further investigation. In general, monophonic wheeze needs a thorough investigation with chest radiography, flexible bronchoscopy and/or CT scan.

If there is a strong suspicion of foreign body aspiration, urgent rigid bronchoscopy should be carried out, while mere suspicion should prompt investigation of the airways with a flexible bronchoscope. Rigid bronchoscopy is the modality of choice

for extracting a foreign body, whereas flexible bronchoscopy is used primarily for diagnosis. However, accumulated evidence has shown that, in experienced hands, flexible bronchoscopy can be used successfully for the extraction of foreign bodies. The clinical usefulness of flexible bronchoscopy is even more prominent in cases of objects wedged in distal regions of the bronchial tree.

Stridor

Stridor is a musical, monophonic, high-pitched sound, albeit much harsher (fluctuations) than wheeze, which can be heard without a stethoscope, especially during inspiration. It is caused by oscillations of narrowed large, extrathoracic airways, and its presence suggests significant obstruction of airflow in the larynx and/or the extrathoracic trachea. The generation of stridor can be explained by the dynamics of inspiration/expiration (particularly when forced) and the Bernoulli principle, which, simply put, states that the pressure (dynamic energy) exerted by a moving fluid or gas on a surface decreases as the velocity (kinetic energy) of the fluid increases. Inhalation generates negative intrapleural pressure (relative to that of the atmosphere), which in turn is applied to the trachea. In normal individuals, this results in a minimal and not clinically relevant collapse of the extrathoracic airways. However, if the airway is partially obstructed there is a disproportionally large drop in the intraluminal pressure, which is created by the respiratory muscles in order to overcome the obstruction. This pressure drop is further augmented by the turbulent flow through the "constricted" laryngeal/tracheal tube due to the Bernoulli principle, which further deteriorates the narrowing (a floppy extrathoracic airway will deteriorate the collapse even further). The Bernoulli effect, which creates high-frequency fluctuations of intraluminal pressure, is also, most likely, primarily responsible for the vibrations of the airway wall that are responsible for the creation of the particular sound. Conversely, exhalation induces a positive intraluminal pressure of the extrathoracic airway, which tends to distend the extrathoracic trachea, alleviate the tracheal obstruction, and reduce expiratory flow resistance. These mechanisms explain why stridor is predominantly inspiratory, although it can also be present during expiration if the obstruction is severe enough (figure 1).

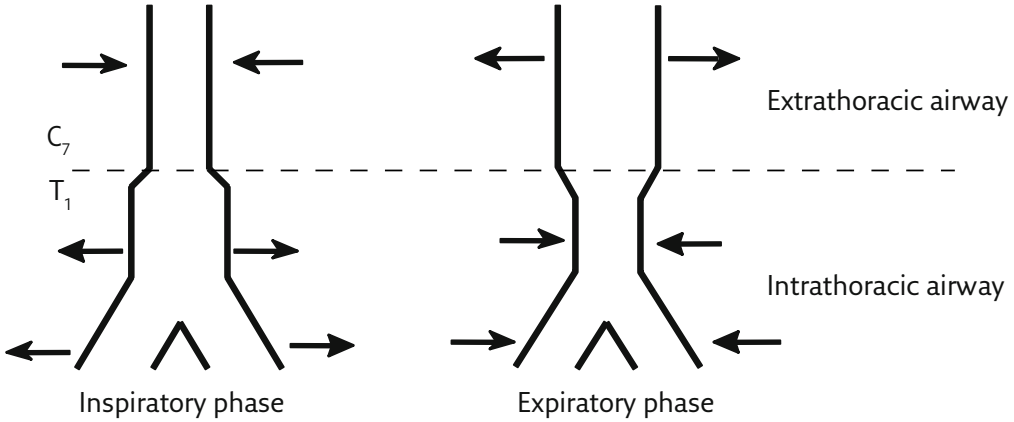

Figure 1. During inhalation, a negative intraluminal pressure (relative to that of the atmosphere) is generated in the extrathoracic airways. This results in a minimal collapse, which, in normal individuals, is not clinically relevant. Exhalation induces a positive intraluminal pressure, which tends to distend the extrathoracic airways. Regarding the intrathoracic trachea and bronchi, the negative intrathoracic pressures during inhalation tend to expand them. Conversely, the compression of the thorax during exhalation produces positive pressures within the thoracic cavity and the airways tend to become narrower.

Assessment of stridor

History and physical examination provide information on the persistence of stridor (chronic *versus* acute), acuity of onset (abrupt *versus* gradual), timing during the respiratory cycle (inspiratory, expiratory, biphasic), accompanying symptoms (fever, coryza), hoarse and/or weak cry, cyanotic episodes, positional differences in the intensity of noise, interval symptoms between episodes and severity of respiratory distress.

The most common cause of acute stridor is viral croup, which presents with stridor accompanied by hoarseness, dry barking cough and respiratory distress. Croup is usually preceded by coryzal symptoms and improves within a few days. It accounts for >90% of all cases of stridor in children. It is unlikely to occur before 6 months of age. Most episodes are mild and only a minority of children need hospital admission. The obstruction is due to subglottic oedema and, in most cases, stridor occurs during inspiration, although it can be biphasic in severe disease. Other quite exceptional infectious causes of acute stridor are epiglottitis and bacterial tracheitis.

Foreign body aspiration should always be suspected when the beginning of stridor is abrupt and accompanied by severe respiratory distress. As discussed in the section on wheezing, rigid or flexible bronchoscopy can be used for extracting a foreign body.

The most common cause of chronic stridor in infancy is laryngomalacia. It usually manifests days or weeks after birth and symptoms usually resolve by 12–18 months. The noise varies in intensity with the respiratory effort and the position of the patient. The obstruction is due to the prolapse of the epiglottis or the loose mucosal tissue overlying the arytenoid cartilages into the laryngeal inlet. Laryngeal walls collapse due to the subatmospheric pressure generated during inspiration. On expiration, the positive luminal pressure overcomes the obstruction, thus keeping the airway open. Therefore, if there is expiratory stridor, an alternative diagnosis needs to be sought.

Intermittent, sudden-onset, daytime episodes of stridor in school-aged children or adolescents may indicate inducible laryngeal obstruction. In this condition, which may coexist with asthma, the vocal cords are held in a paradoxical adducted position. Patients present with significant inspiratory stridor and respiratory distress. Symptoms usually appear during exercise, especially in highly competitive young athletes, but may also appear without any identifiable cause.

Rare causes of chronic stridor include vocal cord paralysis (congenital or acquired), laryngeal clefts, subglottic stenosis (congenital or acquired), haemangiomas, laryngeal cysts and laryngeal webs.

For acute episodes of stridor that are typical of croup, there is no need for investigations other than clinical evaluation. However, children who have unusually prolonged or recurrent episodes or are not completely asymptomatic between episodes require endoscopic evaluation, as do children aged <6 months.

In infants with chronic inspiratory stridor who are thriving and do not have significant respiratory distress, cyanotic episodes, chronic cough, hoarseness or weak cry, the most likely diagnosis is laryngomalacia and there is no need for further investigations. However, if any of these additional characteristics are present, a more thorough investigation is in order. Endoscopic evaluation can be performed with either rigid laryngotracheoscopy or flexible bronchoscopy. The main advantage of rigid laryngotracheoscopy is that it allows a better view of the posterior aspects of the

larynx and upper trachea, whereas flexible bronchoscopy is superior in evaluating the airways dynamics. The entire airway should always be examined, despite the finding of a lesion in the larynx that can explain the stridor, since in about 15% of patients an additional lesion will coexist in the lower airways.

If inducible laryngeal obstruction is suspected, spirometry may show "truncated" inspiratory and expiratory flow–volume loops. However, a definite diagnosis can be set only with direct visualisation of the cords with laryngoscopy during an episode.

Snoring

Snoring is a sound that is produced during sleep from the increase in resistance to the airflow in the upper airways and more specifically, in the region of the nasopharynx and oropharynx. Children who snore tend to have more collapsible airways and relatively larger adenotonsillar size. During rapid eye movement (REM) sleep the tone in pharyngeal muscles is reduced, resulting in the increase of the frequency and severity of obstruction. Snoring is more pronounced on inspiration but it can also be audible during expiration. It is considered to be common in children, with the reported prevalence ranging from 5% to 20%. Its severity ranges from the so-called "primary snoring" with no evidence of ventilation abnormalities to severe OSAS. The latter is characterised by episodes of complete or partial upper airway obstruction leading to hypoxaemia and/or hypercapnia, and frequent nocturnal arousals. The spectrum of disorders from primary snoring to OSAS is characterised as sleep disordered breathing.

Assessment of snoring

The main concern in the evaluation of snoring is to define the children who may suffer health consequences related to the pathology underlying this breath sound. This may prove to be difficult. OSAS cannot be diagnosed simply on the grounds of a history of snoring, since not all children who snore have OSAS; neither is the absence of snoring sufficient to exclude OSAS, since parents may not have noticed the snoring of their child. Furthermore, there is some evidence suggesting that "primary snoring" may not be completely benign.

A detailed history is helpful. Children who suffer from OSAS snore almost every night, snoring usually persists throughout the night and there are frequent apnoeic episodes followed by loud snorts and changes in position. They may suffer from daytime tiredness, poor concentration and enuresis. Behaviour and learning problems are not unusual. The clinical examination may reveal adenoidal facies, enlarged tonsils or hyponasal speech. Obesity, prematurity, family history and craniofacial anomalies are all well-known risk factors for OSAS. However, the history and clinical examination are not sufficient to reliably diagnose or exclude OSAS and a definitive diagnosis has to rely on PSG, which is considered the gold standard for evaluating children for sleep disordered breathing. Unfortunately, this method is complex, expensive and time-consuming; these drawbacks restrict its usefulness to a limited number of specialised centres. A simplified alternative method is the continuous recording of oxygen saturations overnight with pulse oximetry. Furthermore, there are several devices that monitor pulse oximetry in combination with one or more other parameters, such as chest wall movement, body movement and airflow. Due to their low cost, simplicity and portability, they can be used for unattended studies at home. In general, these methods have high positive and low negative predictive values, which imply that patients with negative results require full PSG for definitive diagnosis.

Adenotonsillectomy is the treatment of choice for the vast majority of children with OSAS. When surgery is not an option, or if the resolution of symptoms is not achieved following surgery, nasal CPAP is usually effective.

Rattles

Parents tend to use "wheeze" as a generic term to describe a variety of abnormal respiratory sounds. One of the most common errors is the misuse of the word "wheeze" to name the coarse respiratory sounds known as rattles. These sounds are characterised by a much lower pitch than wheeze, they have a "rattling", discontinuous quality, they are usually accompanied by chest wall vibrations that are easily detectable by parents, and they can be heard during both inspiration and expiration. Rattles are present quite often in infants and toddlers and, although there is a paucity of data in the literature regarding the underlying mechanism, it is believed that they are created by the movement of (excessive) secretions in the large intrathoracic and extrathoracic airways during normal airflow. The mislabelling of a rattle as wheeze may result in overdiagnosing (and overtreating) asthma in children.

The most common cause of rattles is acute viral bronchitis and, in preschoolers, upper airway viral infections. The rattles can be heard for a few days or weeks and subside after the removal of secretions with cough and mucociliary clearance. A chronic rattling sound is often related to chronic aspiration in children with various neurological conditions.

Grunting

Grunting is a short, hoarse, moaning or crying-like expiratory sound that occurs when a partially closed glottis halts the expiratory flow of air. The mechanism may be considered as a self-administered form of positive end-expiratory pressure, since the slowing of expiratory flow increases the FRC and alveolar pressure and prevents alveolar collapse. However, the underlying pathophysiology is not yet fully elucidated. In neonates, the noise is commonly associated with respiratory distress syndrome. In older, previously healthy children, it is a sign of pneumonia.

Snuffles

The term "snuffles" (or "snorts") is used to describe noisy breathing coming from blocked nasal passages. It is also used to describe the common cold or simply a runny nose. The noise is audible throughout the respiratory cycle and is associated with visible secretions from the nares. Apart from upper respiratory tract infections, snuffles may also indicate allergic rhinitis or, on rare occasions, nasal polyps as in CF.

Hoarseness

The term "hoarseness" (or "dysphonia") is used to describe a change in the quality of the voice. It can be caused by any pathological or behavioural condition that affects the function or the structure of the larynx. The problem appears to be common in children, with the reported incidence ranging from 6% to 23%. However, these numbers are derived from small epidemiological studies that have used a variety of definitions for dysphonia/hoarseness or no definition at all.

Hoarseness usually evolves gradually, which may result in delayed diagnosis and treatment. Fortunately, in most children, it is due to benign or self-limited causes that require no intervention or can be managed with voice therapy techniques.

Assessment of hoarseness

A detailed history and clinical examination are essential for the evaluation of hoarseness. The persistence and evolution of hoarseness, *i.e.* if it is acute or chronic, intermittent or continuously progressive, is of pivotal importance. Acute hoarseness is usually due to injury of the mucosa overlying the vocal cords after vocal abuse but may also result from infectious or inflammatory processes. Chronic problems typically indicate structural abnormalities. If hoarseness is intermittent and worsens in the morning, then GOR is a distinct possibility. Conversely, if it is worse in the evening following prolonged use of the voice, it may be related to anatomical problems such as vocal nodules. Persistent, progressive dysphonia that fluctuates from day to day may suggest the presence of papillomatosis. The presence of stridor or any other form of noisy breathing and/or respiratory distress indicates a serious and potentially life-threatening condition that must be evaluated and treated promptly. The presence of dysphagia implies either a neurological problem affecting both the laryngeal and hypopharyngeal areas or a mass lesion affecting both swallowing and vocalisation. It is imperative to ask if there are potential iatrogenic causes, including previous endotracheal intubation or nasogastric tube insertion, that may have contributed to the emergence of the problem.

Vocal cord paralysis is rare in children and can be bilateral or unilateral. The former is mostly caused by central nervous system anomalies like Arnold–Chiari malformations, whereas the latter mainly results from damage to the left recurrent laryngeal nerve because of birth trauma, heart anomalies or cardiac surgery. However, bilateral and unilateral vocal cord palsy can be idiopathic without any identifiable cause. In bilateral palsy, there is almost always severe airways obstruction and stridor, whereas in unilateral palsy the stridor may be absent and the lesion may manifest by a husky weak cry. About half of these palsies recover spontaneously, largely irrespective of their cause.

In general, history and physical examination may help to distinguish among many of the pathological conditions causing hoarseness. However, direct inspection of the larynx with laryngoscopy is usually necessary for a definitive diagnosis. If the hoarseness is rapidly progressive and/or is accompanied by stridor or respiratory distress, laryngoscopy is mandatory.

Summary

Distinguishing the various respiratory noises can be at times quite challenging. The terminology is confusing and there is no gold standard for the definition of the different sounds. Things are more complicated when the clinician has to rely only on the parent's description and interpret their term for the breathing noise to which they refer. The clinical usefulness of respiratory noises could be improved by technology, such as video recording and sound analysis, but, although these techniques would clearly reduce uncertainty regarding the estimation of each specific noise, they are not suitable for everyday clinical practice and their use remains confined to research projects.

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Evaluation and management of dyspnoea, respiratory distress and respiratory insufficiency

Nilay Bas Ikizoglu, Sedat Oktem and Refika Ersu

The primary function of the respiratory system is to supply oxygen to the tissues and to remove carbon dioxide. Respiratory distress occurs when there is abnormality in gas exchange processes including ventilation, perfusion and diffusion. Respiratory distress may progress to respiratory insufficiency if oxygenation or elimination of carbon dioxide is not maintained.

The signs and symptoms of respiratory distress include dyspnoea and abnormal breathing rate and pattern. Dyspnoea is defined as subjective experience of breathing discomfort, which consists of qualitatively distinct sensations (notably work/effort, air hunger and chest tightness) that vary in intensity. It derives from interactions between multiple physiological and psychological factors, along with social and environmental inputs, and may lead to secondary physiological and behavioural changes. Interplay between afferent signals and higher cerebral functions leads to the sensation and impact of dyspnoea.

Key points

- Dyspnoea and respiratory distress are caused by various diseases of the airways, lung parenchyma, rib cage and diaphragm. Cardiac, metabolic, neuromuscular, haematological or psychogenic conditions may also present with respiratory distress.
- Respiratory distress must be promptly recognised and treatment should be started rapidly in order to prevent respiratory insufficiency. Delay may result in cardiopulmonary arrest and death.
- Careful observation, history taking and physical examination are key steps in determining the need for urgent intervention and in establishing underlying aetiology in patients with respiratory distress. Blood gas analysis remains the central investigation when assessing respiratory insufficiency.
- The initial treatment for hypoxaemia is to provide supplemental oxygen. High-flow nasal cannula and NIV are widely used to treat respiratory distress and may reduce the need for intubation and invasive ventilation in children.

Objective signs of respiratory distress include tachypnoea, chest wall retractions, nasal flaring, stridor, wheezing, accessory muscle use and a seesaw type of thoraco-abdominal movement.

Various diseases of the airways, lung parenchyma, rib cage and diaphragm, as well as of other organs, can cause dyspnoea and respiratory distress (table 1). Signs of respiratory distress and insufficiency may be subtle in patients with central nervous system abnormalities and neuromuscular disorders, or a child with other systemic diseases may present with respiratory distress even though the respiratory system is normal, *e.g.* patients with metabolic acidosis (diabetic ketoacidosis, inborn errors of metabolism).

Pathophysiology of respiratory distress and dyspnoea

The pathophysiology of respiratory diseases is influenced by age and growth. Airway size increases, lung parenchyma and respiratory control mechanisms mature over time and airway dynamics are influenced by these changes.

During normal respiration, intrathoracic airways expand in inspiration as intrapleural pressure becomes more negative, and narrow in expiration as they return to their baseline. In cases of obstruction or dynamic compression of the extrathoracic airways, the child increases the respiratory effort to overcome the narrowing. This leads to an increase of the negative intratracheal/intrabronchial pressure distal to the obstruction site during inspiration, which often results in airway collapse. At the same time, the intrapleural pressure becomes more negative (up to –40 cmH_2O), leading to retraction of the compliant parts of the chest wall and of suprasternal and substernal tissue. This can be seen particularly in infants with floppy airways and the more quadratic shape of the thorax with horizontally lined ribs. Nasal flaring may be present and helps to reduce upper airway resistance and to stabilise the upper airways

Table 1. Causes of dyspnoea and respiratory distress

Respiratory
Congenital or acquired extrathoracic airway obstruction (croup, epiglottitis, tracheitis, peritonsillary abscess, retropharyngeal abscess, laryngomalacia, extrathoracic tracheomalacia, subglottic stenosis, subglottic web or cyst, inducible laryngeal obstruction, laryngospasm, foreign body aspiration)
Intrathoracic airway and lung diseases (asthma, bronchiolitis, pneumonia, pleural effusion, atelectasis, pneumothorax, CF, pulmonary embolus, vascular ring, tracheo- or bronchomalacia, foreign body aspiration)
Pulmonary hypertension
Cardiac
Myocarditis, acute myocardial infarction, congestive heart failure, cardiac tamponade
Cardiac arrhythmias
Metabolic
Metabolic acidosis (diabetes mellitus, inborn errors of metabolism)
Metabolic alkalosis (hypertrophic stenosis of pylorus)
Neuromuscular and central
Defects or dysfunction of diaphragm
Myopathy and neuropathy (spinal muscular atrophy, Duchenne muscular dystrophy, Guillain–Barré syndrome, myasthenia gravis)
Central nervous system infections or tumours
Poisoning, drugs, trauma and anaemia
Psychogenic (anxiety and hyperventilation)

by reducing the negative pharyngeal pressure. In normal inspiration, the diaphragm contracts and moves downwards, leading to outward motion of the thorax and the abdomen. Paradoxical breathing refers to inward movement of the chest wall during inspiration. This breathing pattern with a seesaw type of thoraco-abdominal motion can normally be seen in preterm babies and newborns because their thoracic cage is more compliant compared to older children. This pattern is especially prominent during rapid eye movement (REM) sleep because the activity of intercostal muscles that stabilise the chest wall is supressed. However, in older children, the most likely cause of paradoxical breathing is respiratory muscle fatigue and impending respiratory failure. The more distal the obstruction, the more effort is needed to get the air out of the lung. The elastic "recoil pressure" of the lung tissue is no longer sufficient as a driving force in expiration and this usually passive process becomes an active one. In this situation, the usually negative intrapleural pressure becomes positive during expiration, leading to bulging of intercostal spaces.

Physiological triggers in the various causes of dyspnoea are changes in P_{aCO_2}, P_{aO_2} and blood pH, as well as irritation of pain receptors and thermoreceptors and direct damage of neuronal receptors of breathing. Particulate matter, noxious gases, chemical irritants and cold air are also important stimulants. The afferent receptors that function in regulation of respiration are central and peripheral chemoreceptors, pulmonary receptors such as stretch, irritant and J receptors, arterial baroreceptors, and muscle, skin, pain and temperature receptors. Voluntary and autonomic control mechanisms are located in the central nervous system. The stimulation of irritant receptors that are located between the epithelial cells in the airway mucous membrane induces bronchoconstriction and hyperpnoea and plays an important role in triggering dyspnoea.

Assessment of respiratory distress and dyspnoea and differential diagnosis

The initial approach to a patient with respiratory distress includes determining the severity of illness and evaluating the need for emergency intervention. After that, a more thorough work-up for determining the aetiology is performed. Usually, a careful history and physical examination is sufficient to determine the underlying cause. Further investigations can be performed to confirm the diagnosis and guide treatment.

History

Patient complaints (cough, dyspnoea, wheezing, stridor, choking, chest pain, *etc*.) and the onset and duration of the symptoms should be questioned. Choking and sudden onset of respiratory distress may be related to foreign body aspiration or angioedema. Inspiratory stridor and change in voice usually indicate upper airway diseases. Wheezing usually indicates lower airway obstruction. Sudden onset of chest pain may be related to spontaneous pneumothorax, while gradual onset may be a sign of pleural effusion. Fever suggests infectious aetiologies. Dyspnoea at peak exertion that improves with reduction of effort may be related to inducible laryngeal obstruction or laryngospasm or cardiac arrhythmias. Exercised-induced bronchospasm comes on with sustained effort of relatively high intensity and diminishes more slowly after exercise. Dyspnoea due to functional or psychological conditions usually disappears during sleep. In patients with long-lasting or recurrent episodes of dyspnoea, normal growth and normal physical fitness point towards a more benign course.

History of any previous respiratory problems, history of asthma and other respiratory diseases, prematurity, recent infections, trauma, exposures, allergies, drugs,

underlying medical problems including cardiovascular and neuromuscular diseases, sickle cell anaemia, coagulopathies, factors that exacerbate the symptoms, and response to previous treatments should also be obtained. Family history should be assessed for inheritable and infectious diseases.

Physical examination

Careful observation is one of the most important parts of the physical examination in a child with dyspnoea and respiratory distress. The patient's general appearance, presence of pallor or cyanosis, abnormal sounds, respiratory rate and pattern should be noted. In addition, the following signs should be evaluated on physical examination: notation of voice and phonation, use of accessory muscles or retractions and splinting, chest wall deformities including kyphoscoliosis, muscle strength, growth and development of the child, digital clubbing, and auscultation of both the neck and chest during both quiet and deep breathing. Heart rate and blood pressure should be noted, and cardiac auscultation performed with the patient in both in the sitting and lying positions.

Diagnostic tests

Noninvasive measurement of S_{pO_2} provides valuable information about the severity of respiratory distress and must be performed as soon as possible during the evaluation of the patient. A haemoglobin oxygen saturation <94% at or near sea level is abnormal and values ≤90% indicate significant hypoxaemia.

Laboratory tests

Usually, a history and physical examination are adequate in establishing the underlying aetiology of respiratory distress and the extent of laboratory testing depends on the need for further tests for making the diagnosis and guiding treatment. Patients who have findings of severe respiratory distress warrant measurement of arterial blood gases to assess oxygenation, ventilation and acid–base status more accurately, to determine whether further airway management or ventilatory support is needed.

Other studies may also be performed depending on clinical findings. Complete blood count can be performed in patients with suspected anaemia or infection; polycythaemia suggests chronic hypoxaemia. Serum glucose, electrolyte and blood gas tests can be performed in patients with suspected diabetic ketoacidosis, inborn errors of metabolism or electrolyte disturbances. Hypokalaemia, hypocalcaemia and hypophosphataemia can impair muscle contraction.

Imaging

A chest radiograph should be obtained in patients with respiratory distress if the aetiology has not been determined with clinical findings. Parenchymal infiltrates, pulmonary vascular markings, cardiac size, hyperaeration, air leaks and the position of the diaphragm may be evaluated with chest radiographs. Chest radiographs may reveal pneumonia, atelectasis, pneumothorax, radio-opaque foreign bodies and pleural effusion. In newborns with respiratory distress, a chest radiograph can confirm respiratory distress syndrome due to surfactant deficiency or suggest different pathologies, such as lobar emphysema or cysts, or other causes of congenital airway malformation or cardiac pathology. Chest radiographs are hardly ever useful in the assessment of dyspnoea due to upper respiratory tract pathology.

Ultrasonography is helpful in determining the amount and characteristics of pleural fluid and it is the method of choice in patients with pleural effusion. Thoracentesis and insertion of chest drains may be performed with the guidance of ultrasonography.

CT or MRI of the chest is necessary in the work-up of lung, mediastinal or rib cage tumours and vascular processes.

Lung function measurement

In most cases with acute respiratory distress, lung function measurement is not possible and/or necessary. However, in cases of repeated episodes of dyspnoea or limitations in physical activities and normal physical examination, lung function measurements may confirm or rule out obstructive or restrictive lung disease and show the degree of functional impairment.

In the diagnosis of obstruction, spirometry and flow–volume loops are essential, whereas in suspected restriction, vital capacity and TLC should be assessed. Carbon monoxide diffusion is measured when an impairment of the alveolar–capillary diffusion capacity is suspected as a cause for dyspnoea. In addition, gas exchange abnormalities and exercise-induced bronchoconstriction and dysfunctional breathing can be evaluated by cardiopulmonary exercise testing. A drop in FEV_1 of ≥10% after standardised physical activity suggests exercise-induced bronchoconstriction. In inducible laryngeal obstruction, the inspiratory part of the flow–volume loop is usually flattened. In functional or psychogenic dyspnoea, a normal lung function may be useful for reassuring patients and parents of the non-organic, and usually benign, course of the disease.

Laryngoscopy, bronchoscopy and BAL

In an acutely dyspnoeic child with unilateral diminished lung sounds, localised wheezing and a possible history of foreign body aspiration, rigid bronchoscopy should be performed.

In patients with stridor, dysphonia and upper airway anomalies, flexible laryngoscopy and direct visualisation of the extrathoracic airway can be performed, and laryngomalacia, congenital or acquired subglottic stenosis, subglottic haemangioma or vocal cord disorders can be diagnosed. Whenever possible, the entire airway should be examined as lower airway anomalies are often associated with upper airway pathologies.

Flexible bronchoscopy and BAL are warranted in children with recurrent or persistent pneumonia or atelectasis, suspected *Pneumocystis jirovecii*, *Aspergillus* species or *Cytomegalovirus* infections, unexplained or localised and persistent wheeze, haemoptysis, suspected congenital anomalies, or ILD.

Lung biopsy

Lung biopsy may be indicated if BAL does not reveal a pathogen, especially in immunocompromised hosts; it can identify *Aspergillus* species or *P. jirovecii*. Lung biopsy is also helpful in the diagnosis of ILD, sarcoidosis and other granulomatous conditions.

Evaluation of nonrespiratory causes of respiratory distress

Diseases in other organ systems may manifest with dyspnoea and respiratory distress without underlying respiratory disease. Cardiac diseases may decrease lung compliance by causing pulmonary congestion or oedema or may present with cardiogenic shock. Dyspnoea with chest discomfort or palpitations, light headedness, loss of consciousness during exercise and a family history of serious cardiac disease or sudden death warrants cardiac evaluation. Abnormalities in blood gases, blood glucose, lactate, pyruvate or ammonia suggest defects in metabolism. Central nervous system infections and intoxications can cause stimulation or inhibition of respiratory centres. In some cases, a detailed neurological or psychological evaluation will be necessary.

Management of respiratory distress

The initial step in management of respiratory distress is rapidly evaluating the patient for conditions that require immediate intervention. After initial stabilisation, evaluation for determining underlying aetiology must be initiated to guide the specific treatment. In a toxic, dyspnoeic child with typical symptoms of epiglottitis, rapid intubation and administration of antibiotics are necessary. Systemically applied steroids and, in selected cases, inhalation of adrenaline are cornerstones of the treatment of a child with inspiratory stridor and suspected croup. If airway obstruction due to a foreign body or mechanical narrowing is suspected, bronchoscopy and further evaluation or treatment is necessary. Appropriate antibiotics should be started if a bacterial infection is considered. Chest drain placement or needle aspiration can be performed in patients with pneumothorax or pleural effusion.

Respiratory insufficiency

Respiratory insufficiency in children is the inability of the respiratory system to support oxygenation, ventilation, or both. The most common reasons for respiratory insufficiency in the paediatric population can be divided by anatomical compartments (table 2).

The frequency of acute respiratory insufficiency is higher in infants and young children than in adults. This difference can be explained by defining anatomical compartments and their developmental differences in paediatric patients that influence susceptibility to acute respiratory insufficiency (table 3). Smaller airways, more compliant chest wall, and immaturity in respiratory control mechanisms make infants and younger children more vulnerable compared to older children and adults with similar severity of disease.

Signs and symptoms

Tachypnoea and retractions are hallmarks of respiratory distress. Abnormal respiratory sounds (*e.g.* stridor or wheezing), increased accessory muscle use and positioning to maximise airway opening are other indicators of respiratory compromise. Children with upper airway obstruction often assume a "sniffing" position (neck flexed, head extended), while those with lower airway obstruction may sit in the "tripod"

Table 2. Common reasons for respiratory insufficiency

Extrathoracic airway causes		Intrathoracic airway and lung causes	Respiratory pump causes	Central control causes
Congenital	Acquired			
Laryngomalacia Tracheomalacia Subglottic stenosis Subglottic web Subglottic cyst Craniofacial anomalies	Infections (*e.g.* croup, bacterial tracheitis) Foreign body aspiration Trauma	Bronchiolitis Pneumonia Asthma Aspiration Vascular ring Tracheomalacia Bronchomalacia Cardiovascular disease Pulmonary oedema Pulmonary embolus	Spinal muscular atrophy Duchenne muscular dystrophy Diaphragmatic hernia Guillain–Barré syndrome Myasthenia gravis Spinal cord trauma	Central nervous system infection Central sleep apnoea Congenital central hypoventilation syndrome Drug overdose Traumatic brain injury

Table 3. Differences in paediatric patients that influence susceptibility to acute respiratory insufficiency

Extrathoracic airway differences
Neonates and infants are obligate nasal breathers. The nose is responsible for 50% of total airway resistance at all ages.
The airway is small in infants and children compared with older patients.
Infants and young children have a large tongue that fills a small oropharynx.
The larynx is opposite vertebrae C3–4 in children *versus* C6–7 in adults.
The epiglottis is larger and more horizontal in children than in adults.
Infants and young children have a narrow subglottic area. A small amount of subglottic oedema can lead to clinically significant narrowing, increased airway resistance and increased work of breathing.
Intrathoracic airway differences
Infants and young children have fewer alveoli than adults, and therefore have a relatively small area for gas exchange.
The alveolus is small.
Collateral ventilation is not fully developed in infants and young children.
Smaller intrathoracic airways are more easily obstructed than larger ones. With age, the airways enlarge in diameter and length.
Infants and young children have relatively little cartilaginous support of the airways.
Respiratory pump differences
The respiratory centre is immature in infants and young children.
The ribs are horizontally oriented. During inspiration, the capacity to increase tidal volume is limited compared with older individuals.
The small surface area for the interaction between the diaphragm and thorax limits displacing volume in the vertical direction.
The musculature is not fully developed in infants and young children. The bulk of respiratory muscles is small in infants and increases with age. Also, the composition of muscle fibre types in the diaphragm and intercostals changes throughout infancy. The percentage of type I fibres (which are slow-twitch, high-oxidative and less prone to fatigue) is lower in premature babies and small infants, whereas the percentage of type II fibres (which are fast-twitch, low-oxidative and more prone to fatigue) is higher. The proportion of type I fibres in premature infants is only ~10%. This increases to ~25% in full-term newborns and ~50% in children aged >2 years. This allows young infants to tolerate higher respiratory rates; however, respiratory muscles of premature babies and young infants are more susceptible to fatigue.
The soft compliant chest wall provides little opposition to the deflating tendency of the lungs. This leads to a lower FRC in paediatric patients than in adults, a volume that approaches the paediatric alveolus critical closing volume.

position (upright and leaning forward on outstretched hands). Inability to handle secretions and/or swallow are signs of oropharyngeal or laryngotracheal obstruction. Restlessness, agitation and combativeness are early manifestations of hypoxia. As respiratory distress progresses, respiratory rate often decreases, and the pattern of respirations becomes irregular. These are ominous signs. Without intervention, respiratory arrest quickly ensues.

During evaluation, every reasonable effort must be made to keep children calm and comfortable, because anxiety and crying can substantially increase the work of breathing in young children by decreasing upper airway diameter and increasing metabolic demand for oxygen. Children should be positioned or allowed to maintain a position that best supports their respiratory effort.

Diagnosis of respiratory insufficiency

Respiratory insufficiency can be determined by clinical, laboratory (*e.g.* arterial blood gas) and pulmonary function parameters. Classically, the hallmark of respiratory failure is hypoxaemia and/or hypercapnia. Hypoxia is defined as decreased amount of oxygen supplied to or utilised by the body's tissues and cells, while hypoxaemia refers to a decreased amount of oxygen in the blood or less than the physiologically normal amount of oxygen in the blood. Common methods for evaluating oxygenation are:

- Arterial blood gas values: normal values are P_{aO_2} 80–100 mmHg, P_{aCO_2} 35–45 mmHg, pH 7.35–7.45 and S_{aO_2} 95–100%; hypoxaemia is any value less than normal for P_{aO_2} and/or S_{aO_2}
- Alveolar–arterial oxygen gradient: $P_{AO_2}-P_{aO_2}=P_{A\text{-}aO_2}$; the $P_{A\text{-}aO_2}$ is normally <15 mmHg in children
- Ratio of P_{aO_2} to inspiratory oxygen fraction (F_{IO_2}): the normal P_{aO_2}/F_{IO_2} ratio is 500–600

The generally accepted values of hypoxaemia that define acute respiratory insufficiency are P_{aO_2} <50–60 mmHg, S_{aO_2} <90%, P_{aO_2} <60 mmHg on F_{IO_2} of 40%, or P_{aO_2}/F_{IO_2} <300.

Hypercapnia or hypercarbia is an elevated level of carbon dioxide in the blood. Acute respiratory insufficiency is indicated by the following P_{aCO_2} values: P_{aCO_2} >50 mmHg with acidosis (pH <7.25) or P_{aCO_2} >40 mmHg with severe distress, or P_{aCO_2} >55 mmHg. End-tidal carbon dioxide tension (P_{ETCO_2}) may be used as a less invasive method for ongoing monitoring of ventilation.

Capillary blood gas samples may be used in place of arterial blood gas samples to estimate acid–base balance (pH) and adequacy of ventilation (carbon dioxide tension). However, capillary oxygen tension measurements are of little value in estimating arterial oxygenation.

Management of respiratory insufficiency

Management depends on the severity of respiratory insufficiency and the specific cause. Oxygen should be given to all children with respiratory distress to maintain an oxygen saturation >90–94%. The World Health Organization recommends an oxygen saturation target of 90% for supplementing oxygen in stable children. S_{pO_2} >90% corresponds to the flat part of the haemoglobin–oxygen dissociation curve and represents a safe margin of error where there are sufficient oxygen supplies. Small reductions in S_{pO_2} below 90% may represent a dangerous fall in P_{aO_2}. Oxygen therapy at higher thresholds than 90% S_{pO_2} is required in some conditions, such as serious impairment of oxygen delivery from the lungs to body tissues and when the vital organs are particularly susceptible to low oxygen levels, *e.g.* in severe heart failure, severe sepsis or brain injury or in critically ill children with emergency signs. In these conditions, oxygen should be given if the S_{pO_2} is <94%.

The appropriate device for oxygen supplementation depends on the age of the child, the amount of oxygen needed and the local circumstances. Low-flow (<6 L·min^{-1}) oxygen delivery systems include the nasal cannula and simple face mask. High-flow (>15 L·min^{-1}) oxygen delivery systems include a Venturi-type device that places an adjustable aperture lateral to the stream of oxygen. High-flow nasal cannula (HFNC), CPAP, NIV or conventional mechanical ventilation may be required in patients with severe respiratory distress or respiratory insufficiency.

High-flow nasal cannula

HFNC use has been demonstrated to be a safe and well tolerated treatment for children with respiratory distress. Before the introduction of HFNC, a maximum flow

of 2 L·min^{-1} of oxygen by nasal cannula was used for children, in order to prevent drying and discomfort of the nasal mucosa and other nasal mucosal complications. With HFNC, heated and humidified oxygen with an F_{IO_2} up to 100% and at a flow rate up to 60 L·min^{-1} can be delivered to the patients. As a result, oxygen can be supplied to match or exceed patients' inspiratory flow rates. The suggested mechanisms of action of HFNC are washout of nasopharyngeal dead space resulting in increased fraction of oxygen in inhaled air and removal of carbon dioxide, reduction of inspiratory resistance and work of breathing by providing adequate flow, improvement of airway conductance and pulmonary compliance by reducing the effect of cold air, reduction of the metabolic cost of gas conditions by providing air with 100% relative humidity and providing an end-distending pressure to the lungs. The exact distending pressure is not measured; however, recent studies have suggested limited pressure delivery ranging from 2 to 4 cmH_2O. HFNC has some advantages over a face mask as an oxygen delivery system. One study found HFNC to be more comfortable and better tolerated by patients. HFNC has been used in selected illnesses (*e.g.* bronchiolitis and pneumonia) and available data suggest that it may reduce the need for endotracheal intubation. Rates of complications with HFNC are very low in the paediatric population.

How to use HFNC

Circuit size must be large enough to minimise resistance to gas flow, and nasal cannulae must be small enough to fit but should not obstruct the patient's nostrils. Choice of circuit and cannula size should be patient specific and in full accordance with individual manufacturer specifications. When initiating HFNC therapy, set the start flow at 1 L·kg^{-1}·min^{-1} and escalate as needed to minimise work of breathing (*e.g.* retractions, tachypnoea, grunting, nasal flaring). The maximum flow rate should be 2 L·kg^{-1}·min^{-1}, with an upper limit of 50–60 L·min^{-1}. Commonly, oxygen concentration is started at F_{IO_2} 50% and titrated as needed to achieve a target oxygen saturation. As work of breathing improves, flow rate can be slowly titrated down. The F_{IO_2} for delivered gas should be reduced based on oxygen saturation and determined independently of the titrated flow rate. When patients can tolerate a lower gas flow rate and F_{IO_2}, they can be switched to low-flow oxygen support.

Continuous positive airway pressure

CPAP may be indicated if lung disease results in severe oxygenation abnormalities. CPAP is provided *via* a nasal prong or nasal or face mask and pressures of 3–10 cmH_2O are applied throughout the respiratory cycle. The primary goal for the use of CPAP is to improve oxygenation by restoring airway patency and by improving FRC and lung inflation in patients with an adequate respiratory drive. Applying continuous positive pressure to the ventilating lung units reduces the work of breathing by eliminating the need to overcome the opening pressure of the lung, and it prevents collapse and reopening of alveoli. Patients receiving CPAP alone must have adequate respiratory muscle strength and neurological drive to breathe. CPAP is indicated in paediatric patients for the treatment of acute or chronic respiratory insufficiency secondary to pulmonary disease, neuromuscular disease, airway obstruction or infectious processes, or post-extubation management or to avoid intubation or reintubation.

Noninvasive ventilation

NIV refers to assisted ventilation provided with a nasal, face or full-face mask instead of an endotracheal tube. It has been increasingly used in children with acute and chronic conditions associated with impaired respiratory drive, inadequate lung inflation and altered gas exchange resulting in respiratory insufficiency. It is commonly used in

children with acute respiratory failure in lower airway disease, asthma, acute lung injury/acute respiratory distress syndrome and upper airway obstruction. NIV is widely used to treat respiratory distress and reduces the need for intubation and invasive ventilation in children. NIV recruits the lung, increases FRC, improves respiratory dynamics, reduces respiratory work and optimises gas exchange. Skin injuries, eye irritation or injury, gastric distention, nasal obstruction, nasal bridge sores, possible pulmonary aspiration and pneumothorax are some of the complications associated with NIV.

In children with bronchiolitis, NIV reduces respiratory distress, and clinical scores and various outcomes improve. It is currently not possible to reach a definite conclusion regarding the effectiveness of NIV in the prevention of endotracheal intubation in infants with severe bronchiolitis. However, the safety of NIV makes it a useful treatment for bronchiolitis.

Adjusting the ventilation settings

Peak pressure, PEEP and F_{IO_2} can be adjusted for NIV. Suggestions are as follows:

- Peak pressure: start with 8–10 cmH_2O and gradually increase it in steps of 1–2 cmH_2O, until there is obvious clinical relief from dyspnoea and decrease in work of breathing
- PEEP: start with PEEP of 4 cmH_2O and gradually increase it in steps of 1–2 cmH_2O, until you reach your targeted pressure
- F_{IO_2}: this can be adjusted to reach the target oxygen saturation, often with a goal of >90–94%

Criteria for NIV failure

The following criteria should be observed when making the decision to use intubation and conventional mechanical ventilation:

- Clinical worsening or no improvement of dyspnoea
- Asynchrony between ventilator and patient
- Increasing apnoea severity
- Higher respiratory rate and greater work of breathing with the risk of exhaustion
- Increasing heart rate
- Increasing F_{IO_2} >60%
- Worsening of the blood gases (pH <7.2, carbon dioxide tension >60 mmHg)
- Complications (too much/too thick secretion, vomiting)
- Disorders of consciousness/confusion, coma
- Haemodynamic instability
- Refusal of NIV by patient or guardians

Conventional mechanical ventilation

Conventional mechanical ventilation is partial support or complete replacement of spontaneous breathing *via* endotracheal tube. Guidelines are provided; however, clinicians will need to individualise strategies based on the clinical scenario as well as provider preferences and institutional practice.

Pressure-controlled ventilation is commonly utilised in paediatrics, particularly in neonates and infants. Ventilator measurement of tidal volume may be less accurate in infants, potentially affecting volume-controlled ventilation. However, trials in paediatrics have not shown any mode to be superior to another in improving outcomes. Mechanical ventilation should provide sufficient V'_E and oxygen delivery to meet metabolic demands at the lowest pressures possible, to minimise risk of secondary lung injury. Mechanical ventilation should aim to optimise the patient's work of breathing and comfort. F_{IO_2} should be reduced as low as possible to reduce the

risk of oxygen toxicity. PEEP can be optimised to prevent alveolar collapse and improve oxygenation, provided haemodynamics (*e.g.* reduced preload) are not compromised.

Prognosis of respiratory insufficiency

The prognosis can be good when the respiratory insufficiency is an acute event that is not associated with prolonged hypoxaemia (*e.g.* in bronchiolitis, pneumonia or asthma). It may be fair to poor when a new process is associated with chronic respiratory failure secondary to a neuromuscular disease or thoracic deformity or in the case of hypoxia exceeding 10–20 min.

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Questionnaires in clinical assessment

John A. King and Louise J. Fleming

A wide range of questionnaires is available to aid clinical assessment of childhood respiratory health and disease. The purposes of these include:

- Screening for disease-specific symptoms to aid diagnosis
- Monitoring of disease severity and control
- Identifying exacerbations or those at risk of exacerbation of chronic disease
- Monitoring medication adherence
- Assessing the non-medical impacts of disease, including quality of life and psychological sequelae
- Providing standardised end-points for clinical trials

Some questionnaires are disease specific, whereas others are more generally applicable to chronic disease. Most questionnaires use a scoring system to provide a composite score. Occasionally questionnaires are divided into different domains, where domain-specific scores are interpretable as well as the composite score. Questionnaires and their resulting composite scores are important in the clinical assessment of respiratory conditions as they provide objective measures for monitoring chronic disease and can be useful for screening children to determine whether more invasive assessments are needed.

For all questionnaires, it is important to consider their reliability and validity. Reliability relates to the ability of the questionnaire to produce the same results if tested multiple times. The validity refers to whether the questionnaire measures what it intends to measure and is assessed by comparing with other measures of the same construct.

Key points

- In clinical practice, questionnaires aid diagnosis, are useful in monitoring disease progression and treatment response, and help in assessing the impact of chronic disease, in terms of quality of life and psychological sequelae.
- Some questionnaires are disease specific, but several are useful across a range of chronic diseases.
- Questionnaires need to be validated to help identify the most clinically useful items and provide a framework for interpretation. They should be validated for the population in which the clinician intends to use them, which includes patient age, language and disease.

Table 1. Clinical questionnaires used in paediatric respiratory medicine, by disease area

Asthma	Sleep	CF and chronic suppurative lung disease	Breathlessness	Other
ACT	ISQ	CFQ	Nijmegen	SNOT
C-ACT	TCSQ	SGRQ	PVCDI	PI-ED
ACQ	ASWS	PC-QOL	NLHQ	SDQ
TRACK	ESS Revised for Children	QOL-PCD	D-12	PedsQL
CASI	ASHS			
PAQLQ	BISQ			
MARS-A	CSHQ			
	PSQ			

Further details are given in the main text.

The utility of any assessment tool is the product of its validity and reliability. Validation may start with adult populations, which can then be extended to a paediatric population, often requiring changes to the wording of the questionnaire to make it age appropriate. However, some tools have not been validated for a paediatric population, and this should be considered when using and interpreting them. Questionnaires should also be re-validated in each language they are translated into.

Authors of questionnaires need to ensure design, wording and format are appropriate for the target audience (child or parent). Separate questionnaires are sometimes developed for different age categories. Attention should also be given to the way in which questionnaires are intended to be administered: some can be completed by the child or parent and others only by a trained interviewer.

In this chapter we will review clinical questionnaires that are used in specific areas of paediatric respiratory medicine, and those that are more generally applicable. A summary list of those discussed is given in table 1. While this chapter cannot provide an exhaustive list, these are the questionnaires most commonly used in practice. It should be noted that most are subject to copyright, although some will allow free use for clinical or scientific (nonprofit) purposes. Copyright should always be checked and, if necessary, the authors may need to be contacted for permission to use these questionnaires.

Asthma

Monitoring asthma control using questionnaires is well established. There are at least 15 validated tools, each attempting to gain a snapshot of asthma control based on symptom reporting from a specified time prior to assessment, by the child and/or parent. Some questionnaires also include an objective measure, such as FEV_1, to form part of the composite score. The final score indicates the degree of asthma control and this can be used to monitor control over time and response to treatment changes.

The most commonly used measures of control are the Asthma Control Test (ACT), the Childhood Asthma Control Test (C-ACT) and the Asthma Control Questionnaire (ACQ). The ACT is validated for children and adults aged >12 years and consists of five symptom-based items scored from 1 to 5, based on perception of symptoms over the previous 4 weeks. Higher scores indicate better control. A total score out of 25 is calculated, with scores of ≥20 indicating that asthma is controlled, scores of 15–19 indicating poorly controlled asthma and scores of ≤14 indicating uncontrolled asthma. The minimum score possible is 5. The C-ACT is adapted from the ACT and

validated for children aged 5–11 years. It consists of seven items: three questions for parents and four pictorial scaled items for the child. Scored out of 27, a score of ≤19 represents uncontrolled asthma. One study identified a C-ACT score of ≤12 as representing very poorly controlled asthma in this age group. The minimum score for the C-ACT is 0. The ACQ consists of seven items, six of which are questions based on symptom reporting and rescue bronchodilator use over the previous week. This is combined with a measurement of FEV_1 (percentage predicted). The scores for each item range from 0 (no impairment) to 6 (maximum impairment). The items are equally weighted and the ACQ score is the mean of the seven questions. Scored out of 6, scores of ≥1.0 represent uncontrolled asthma. An abbreviated version, without FEV_1 measurement (ACQ-6), is possible but is not as good at predicting uncontrolled asthma when compared to the 7-item score. The ACQ is validated for those aged >12 years. A single study validated the ACQ for children aged 6–12 years; however, it recommended trained interviewers for children aged 6–10 years.

The ACT and C-ACT have the benefit of reviewing control over a longer period, although recall for the shorter period required for the ACQ may be more accurate. The ACT and C-ACT do not require lung function measurement, making them easy to administer in any clinical setting, from primary to tertiary care or even remotely. None of these measures are valid for use during an acute exacerbation. Furthermore, they do not account for underlying disease severity and do not include asthma attacks as part of the assessment of asthma control.

The Test for Respiratory and Asthma Control in Kids (TRACK) is validated for children with asthma-type symptoms aged 0–5 years, and accounts for underlying severity by scoring exacerbation frequency as part of the 5-item questionnaire. The questionnaire is intended to be completed by parents. Scored out of 100, a score of >80 indicates controlled symptoms. The Composite Asthma Severity Index (CASI) also accounts for exacerbation frequency and includes information about current preventer therapy as a marker of severity. It is validated for children aged >6 years.

The Paediatric Asthma Quality of Life Questionnaire (PAQLQ) is validated for children aged >7 years. It assesses the physical, social and emotional impact of asthma in childhood. It consists of 23 questions, over three domains: physical impact of symptoms, activity limitation and emotional functioning over the preceding week. Each question is answered on a scale of 1 to 7 (1 being extremely bothered, 7 not bothered at all). The overall score is the mean of the 23 items and the individual domain scores are the means of the items in those domains. Responses are child led, and a trained interviewer is recommended for those aged <11 years. The mini-PAQLQ is reduced to 13 questions and is similarly validated.

Assessing medication adherence is an essential part of childhood asthma management. There are many medication adherence questionnaires available. The Medication Adherence Rating Scale (MARS) can be used for a range of conditions and the original 5-item questionnaire has been specifically adapted for asthma medication (MARS-A). Across 10 items, beliefs and barriers to medication adherence in asthma are evaluated. Validated in adults, studies have demonstrated a strong correlation between composite score and electronic inhaler monitoring devices. However, one study has suggested that the scale is too inaccurate to be a useful measure in children.

Sleep

Paediatric sleep medicine has many questionnaires available to help assessment of childhood sleep symptoms that may represent a primary sleep disorder or be

secondary to a respiratory issue. Most tools are designed to help diagnose sleep-related problems and identify those who require further investigation. Tools are available to look at specific problems relating to sleep, such as sleep initiation and maintenance, daytime sleepiness, sleep habits and hygiene, and attitudes towards sleep. Several questionnaires are multidimensional, covering some or all of these areas.

Sleep initiation and maintenance can be assessed in infancy with the Infant Sleep Questionnaire (ISQ). Validated for children aged 12–18 months, this 10-item questionnaire reviews parent-reported symptoms over the previous month. A composite score of ≥12 out of a total of 38 has been shown to screen positively, with good sensitivity and specificity, for difficulties falling and staying asleep in infancy. The 10-item Tayside Children's Sleep Questionnaire (TCSQ) screens for similar issues over the previous 3 months in children aged 1–5 years. The TCSQ authors have validated a scoring system, with a score of ≥8 (out of 36) indicative of difficulty initiating and maintaining sleep. The 28-item Adolescent Sleep Wake Scale (ASWS) has five subscales (going to bed, falling asleep, waking, returning to sleep and wakefulness) and is validated for children aged 12–18 years. Higher scores indicate worse sleep, but no specific cut-off scores are provided for interpretation.

Daytime sleepiness can be assessed with the Epworth Sleepiness Scale (ESS) Revised for Children. This consists of eight items, answered by parents and the child, and relates to the current timeframe. A score of 0–5 suggests less than normal sleepiness, 6–10 a normal amount of sleepiness, 11–12 mildly excessive symptoms, 13–15 moderately excessive symptoms and 16–24 severely excessive symptoms. The questionnaire is adapted from an adult tool and has not been validated in children; however, it is short, easy to use and has been shown to identify children with sleep disordered breathing.

Sleep habits and hygiene in children aged 12–18 years can be examined with the Adolescent Sleep Hygiene Scale (ASHS). This uses 28 items over eight domains, with children responding in relation to the previous month. A scoring system is established, from each domain and total score, with higher scores indicating better sleep habits, but again no specific cut-offs have been given for interpretation.

The Brief Infant Sleep Questionnaire (BISQ) for those aged 0–29 months, the Children's Sleep Habits Questionnaire (CSHQ) for age 4–10 years and the Paediatric Sleep Questionnaire (PSQ) for age 2–18 years all assess a broader range of sleep-related problems. The BISQ is a screening tool for infant and toddler sleep problems, including sleep duration and night waking. Parents respond to the 13 items in relation to the prior 2 weeks. The BISQ correlates well with actigraphy and daily sleep logs. A revised version (BISQ-R) is currently being validated to provide an interpretative framework for the composite score. The CSHQ screens for behaviourally and medically related sleep issues, including bedtime behaviour, parasomnias, night-time awakening and sleep disordered breathing. The 35-item scale provides a composite score, with scores of ≥41 distinguishing between children with medical or behavioural sleep problems and control groups with high sensitivity and specificity. The PSQ is a 69-item parent-reported questionnaire, with eight subscales. A score of ≥0.33 correctly identifies 86% of children with evidence of OSA on PSG.

CF and chronic suppurative lung disease

Advances in diagnosis and treatment of CF have seen an increase in life expectancy. However, it is well recognised that this comes with a significant treatment burden. As a result, assessment of health-related quality of life (HRQoL) has been the focus of development of questionnaires for CF. While many generic HRQoL questionnaires are

available, the purpose of a CF-specific tool is to account for the physical, emotional and social impact of CF. Assessment of HRQoL in CF also allows the impact of new therapies to be assessed beyond physiological parameters, such as lung function. A popular validated tool for HRQoL assessment in CF is the Cystic Fibrosis Questionnaire (CFQ), which was developed in 1997 and revised in 2000 (CFQ-R). The questionnaire has four versions: 1) adolescent/adult, 2) child interviewer-led, 3) child self-report, and 4) parent-reported for children and preschool children. The questionnaire covers nine quality of life domains as reported over the 2 weeks prior to assessment: physical functioning, vitality, treatment constraints, social limitations, role limitations/school performance, emotional state, embarrassment, body image, and eating disturbances. A score is calculated out of 100, with higher scores indicating better HRQoL. The tool is reliably reproducible and validated in respective age groups, demonstrating correlation with subscales in the Nottingham Health Profile (a validated tool used to measure patient perceptions of their own health) and with FEV_1 and BMI. Validation has occurred in several languages.

Measures of HRQoL in chronic suppurative lung disease are well established in adult populations; however, validity is often extended to older children without specific trials. The St George's Respiratory Questionnaire (SGRQ) has shown validity in assessment of HRQoL in adults with bronchiectasis. It covers three domains (symptoms, activity and impact of disease) and correlates well with subjective symptom reporting but poorly with objective measures like lung function. The SGRQ is self-administered and has been used in older children but is not validated for that use. The Parent Cough-Specific Quality of Life Questionnaire (PC-QOL) uses 27 items to assess parents' feelings towards their child's cough across three domains (physical, psychological and social). The PC-QOL is a validated measure of cough and has shown sensitivity to detect change in symptoms over time. As cough is a predominant symptom in chronic suppurative lung disease, it may be a useful tool for younger patients in this category. The Quality of Life – Primary Ciliary Dyskinesia (QOL-PCD) questionnaire, as the name suggests, assesses HRQoL in PCD. While a QOL-PCD tool for adults has been validated, validation for a child-focused questionnaire, for age 6–12 years, is ongoing. It covers a wide range of topics including symptoms, physical and emotional functioning, treatment burden and vitality.

Breathlessness

The Nijmegen questionnaire was developed over 30 years ago as a tool to screen for hyperventilation symptoms. The questions ask responders to score 16 symptoms on a scale of 0 to 4, with a total of ≥23 out of 64 strongly suggestive of hyperventilation symptoms. The questionnaire's use has changed over time and numerous studies have validated its ability to quantify subjective sensations that are common in people with disordered breathing patterns. However, it is recognised that higher scores can also represent panic disorder and uncontrolled asthma, so these need to be considered and ruled out simultaneously. Although frequently used in children, this questionnaire has not been validated for use in the paediatric population specifically.

The Pittsburgh Vocal Cord Dysfunction Index (PVCDI) is a useful tool to help differentiate symptoms of asthma and inducible laryngeal obstruction (ILO; previously referred to as vocal cord dysfunction). The presence or absence of symptoms of dysphonia, throat tightness, wheeze and triggers by odour lead to a weighted total score out of 11. A score of ≥4 is strongly suggestive of ILO in adults. Another useful tool to screen for laryngeal dysfunction is the Newcastle Laryngeal Hypersensitivity Questionnaire (NLHQ).

Respondents answer to 14 statements on a scale from 1 to 7. The statements are grouped into three domains: obstructive symptoms, pain and heat-related symptoms, and throat tickle sensation. Each domain can be totalled and means of each domain are totalled. A score of ≤17.1 is suggestive of abnormal laryngeal function. The PVCDI and NLHQ have not been specifically validated in children, but are still widely used.

Assessment of non-disease-specific breathlessness can be assisted with the use of the Dyspnoea-12 (D-12) questionnaire. D-12 consists of 12 items, each relating to breathlessness symptoms, which respondents rank on a 4-point scale from none to severe, based on current status (referred to as "these days"). This tool has been validated in a range of adult respiratory disease, including asthma, bronchiectasis and ILD.

Other useful questionnaires

Chronic rhinosinusitis and nasal polyps are a common comorbidity in paediatric respiratory disease, including asthma, CF and PCD. The Sino-Nasal Outcome Test (SNOT) comes in 20- and 22-item versions and is well validated in adults as a tool for monitoring symptoms and HRQoL relating to the nose and sinuses, in conjunction with various respiratory diseases. Scoring allows monitoring over time and the minimal clinically important difference has been assessed. However, the tool has not been validated for children and is designed for self-reporting. Parent-reported answers should therefore be interpreted with caution.

The Paediatric Index of Emotional Distress (PI-ED) was developed from the adult-based Hospital Anxiety and Depression Scale (HADS) and is a self-rating scale that screens children and young people for emotional distress. Validated for children aged 8–16 years, this 14-item questionnaire is easy to administer and provides clear cut-off scores to identify those in need of further psychological assessment, with higher scores indicating greater likelihood of significant emotional distress. The Strengths and Difficulties Questionnaire (SDQ) is a screening tool for emotional and behavioural issues in children. The parent responder version is validated for ages 2–17 years, while the child responder version is validated for 11–17 years. There are short and longer versions available, but both consist of five subscales, examining emotional symptoms, conduct issues, inattention and hyperactivity, peer-relationships and prosocial behaviour. The Pediatric Quality of Life Inventory (PedsQL) is a generic HRQoL questionnaire that can be useful for assessing the impact of respiratory disease where disease-specific questionnaires are not available. Consisting of 23 items with four subscales, examining physical, social, emotional and educational functioning, this tool is validated for children of all ages, with multiple age range and disease-specific versions produced. A composite score is converted to a total out of 100, with higher scores indicating better HRQoL. It has been shown to identify healthy children from children with acute and chronic disease and distinguishes disease severity within a chronic disease.

Summary

A wide range of questionnaires is available for use in clinical practice, which can help to standardise the assessment of a group of patients as well as monitor changes in the individual over time. Questionnaires should be carefully chosen to help address a specific issue and care must be taken not to overburden the child and their family. Used judiciously, questionnaires are an essential tool in paediatric respiratory practice across a range of conditions.

Further reading

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Static and dynamic lung volumes

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This chapter begins with a short review of static and dynamic lung volumes, and the principles of body plethysmography. Then, physiological principles underlying forced expiration and flow limitation are highlighted. Lastly, the reader is introduced to the field of lung function and relevant literature in relation to current guidelines for those measurements in children as well as normative data.

Static lung volumes

Lung volumes that are not affected by air flow are termed static lung volumes and consist of specific volumes and capacities (sums of specific volumes). All static volumes are age-dependent and increase with age during childhood. In contrast to a forced expiration, the following static lung volumes can be directly measured with "slow" breathing manoeuvres: tidal volume (V_T), inspiratory reserve volume (IRV), expiratory reserve volume (ERV), inspiratory capacity (IC) and vital capacity (VC), the latter being the volume exhaled from full inspiration to full expiration, or inhaled from full expiration to full inspiration. This explains the limitations especially of a VC manoeuvre in uncooperative subjects, particularly during early childhood and preschool age.

Using additional methods such as body plethysmography and gas dilution techniques, it is possible to measure the FRC, which is called FRC_{pleth} if measured by body plethysmography, and calculate the RV and the TLC.

Body plethysmography is a measure of compressibility of thoracic gas volume and consists of a sealed glass chamber with ambient air pressure (P_m) inside, in which

Key points

- Lung volumes that are not affected by air flow are termed static lung volumes and consist of volumes and capacities (sums of specific volumes).
- The FRC and the TLC include a volume of gas that cannot be exhaled (RV), which is important for maintaining continuous gas exchange during profound expiration. They can be measured and calculated using body plethysmography.
- Lung volumes that are affected by air flow are termed dynamic lung volumes and are measured during forced expiration.

the subject sits while breathing through a pneumotachograph to measure flow and volume. The device also consists of pressure transducers to measure pressure differences, *e.g*. between the pressure in the chamber and the pressure at the airway opening. In case of airflow cessation, the pressure at the airway opening equals the alveolar pressure (P_{alv}), which can be achieved by closing the mouthpiece with a shutter for two or three breath cycles.

The FRC_{pleth} is the volume of air in the lung after a normal expiration during tidal breathing and corresponds to the intrathoracic gas volume. It is dependent on standing height, age, posture, compliance and tone of the diaphragm and represents the volume at which the elastic recoil pressures of the lung and of the chest wall are in balance. In case of the presence of so-called "trapped gas" (representing trapped air in non- or poorly ventilated lung regions), FRC_{pleth} represents a good indicator for small airway obstruction and hyperinflation of the lung.

The measurement of FRC_{pleth} is based on Boyle's law, which states that the pressure (P) multiplied by the volume (V) of a gas is constant in a closed system and under isothermal conditions. By producing and measuring variations in pressure and volume (ΔP and ΔV, respectively), gas volume can be calculated by using the following simplified equation:

$$V = -\Delta V/\Delta P \times P \quad (1)$$

In body plethysmography, we consider two constant volumes, the lung volume represented by FRC_{pleth} and the volume in the body plethysmograph. We generate a change of alveolar pressure (ΔP_{alv}) corresponding to the pressure at the airway opening by closing a shutter at the mouthpiece, and an opposing change of the pressure in the body plethysmograph (ΔP_m) as a result of thoracic excursion against the obstructed mouthpiece. As we can measure the volume change in the body plethysmograph and the pressure change at the airway opening (corresponding to ΔP_{alv}), we can calculate the volume of FRC_{pleth} as follows:

$$FRC_{pleth} = -\Delta V/\Delta P_{alv} \times P_m \quad (2)$$

By measuring FRC_{pleth} and ERV, it is also possible to calculate the RV, which is the volume of air remaining in the lung after maximal expiration. The RV is important for maintaining continuous gas exchange during profound expiration. In cases of obstructive lung disease, RV is elevated and this elevation then represents the amount of trapped gas. The RV is calculated as:

$$RV = FRC_{pleth} - ERV \quad (3)$$

Static lung volumes (and their respective acronyms), measured directly or indirectly, as well as capacities, are displayed in table 1 and figure 1.

Dynamic lung volumes

Lung volumes affected by air flow are termed dynamic lung volumes and measured during spirometry with a forced expiration. Dynamic lung volumes and expiratory flows (and their respective acronyms) that can be measured during spirometry are displayed in table 2 and figures 2 and 3. Forced expiration rarely occurs under physiological conditions in everyday life; it requires collaboration with inhalation to TLC and then exhalation down to the RV, both as long and as quickly as possible, thus provoking flow limitation without any further effort dependence. This measurement displays limitations in uncooperative subjects, which is why a forced expiratory manoeuvre is usually possible only from late preschool age onward. In order to better understand the performance and results of such

Table 1. Static lung volumes

Parameter	Acronym	Explanation
Volumes		
Tidal volume	V_T	Normal volume of air moved between inspiration and expiration during quiet tidal breathing when no additional effort is applied
Inspiratory reserve volume	IRV	Volume of air that can additionally be inhaled in maximal inspiration
Expiratory reserve volume	ERV	Volume of air that can additionally be exhaled in maximal expiration
Residual volume	RV	Volume of air that remains in the lung after maximal expiration
Capacities (sums of volumes)		
Functional residual capacity	FRC	RV+ERV: volume of air that remains in the lung after normal expiration during quiet tidal breathing when no additional effort is applied
Inspiratory capacity	IC	V_T+IRV: volume of air that can be inhaled in maximal inspiration, starting from FRC
Vital capacity	VC	ERV+V_T+IRV: volume of air moved between combined maximal inspiration and expiration
Total lung capacity	TLC	RV+ERV+V_T+IRV: maximal total volume of air in the lung including volume of air moved between combined maximal inspiration and expiration and volume of air that remains in the lung after maximal expiration

a manoeuvre, it is important to be familiar with airway and respiratory mechanics as well as with the physiological principles underlying forced expiration in spirometry.

The airways are interconnected by surrounding lung tissue, leading to pulmonary tethering. During inspiration, the lung expands and the airway calibres increase due to this tissue network. During expiration, the lung deflates and the airway diameter decreases concurrently, reflecting breathing-dependent changes in airway resistance. Thus, the airways do not resemble a system of rigid tubes, but compliant and compressible tubes building up resistance to air flow (although this is still an oversimplification). As for electrical systems, different airway resistances of peripheral and central airways are connected in series. According to Ohm's law, the resulting airway resistance (R_{aw}) as well as the pressure difference between the alveoli (P_{alv}) and the airway opening (mouth), usually the barometric pressure (P_m), determine air flow during expiration. While P_{alv} drops below P_m during inspiration, it rises above P_m during expiration. Expiration during quiet tidal breathing usually happens passively due to static retraction forces (elastic recoil); however, during forced expiration it is additionally supported by active muscular contraction. Active expiration results in a reduced transversal and sagittal diameter of the thorax (due to activity of the internal intercostal muscles), elevation of the diaphragm and, as the main contributor of the expiratory driving force, increased intra-abdominal pressure (activity of rectus abdominis, transversus abdominis and external as well as internal oblique muscles). The consequent driving force of expiratory flow (the resulting pressure drop from the alveoli along the airways to the airway opening), the transairway pressure (P_{ta}) can be calculated as:

$$P_{ta} = P_{alv} - P_m \quad (4)$$

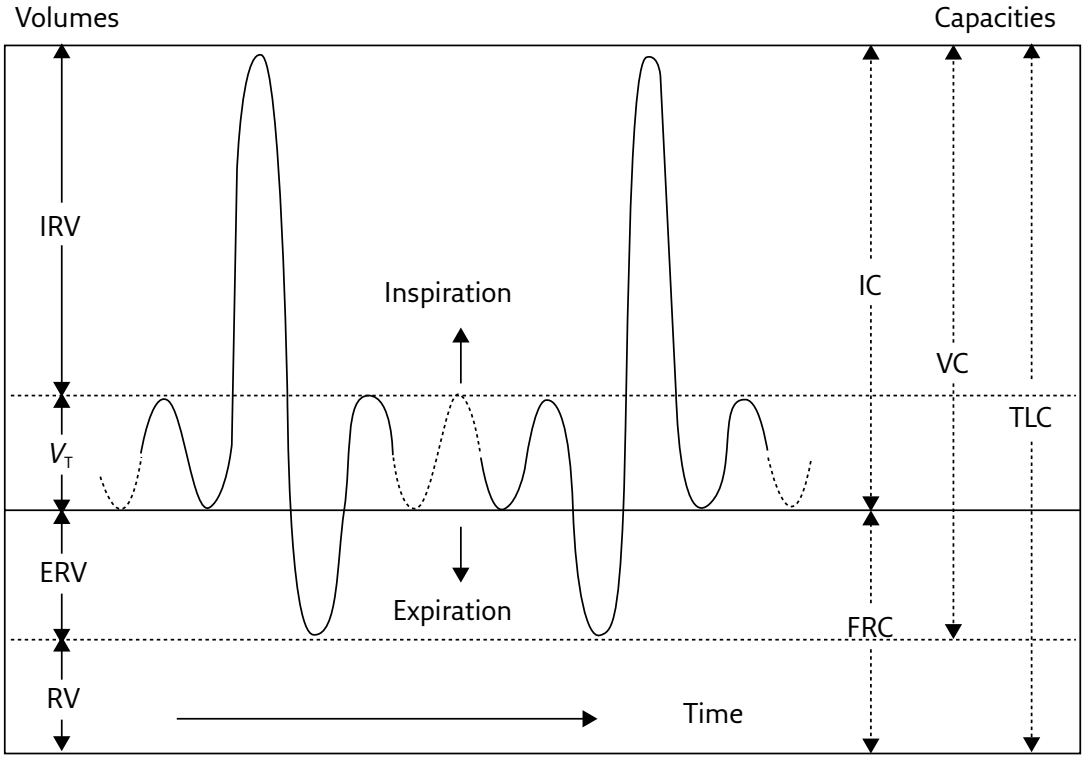

Figure 1. Spirogram with lung volumes and capacities and with expiratory and inspiratory vital capacity manoeuvres.

where P_{alv} is the sum of pure static (volume-dependent) pressure made up by elastic recoil (P_{st}) and of the additional positive pressure in the pleural space (P_{pl}):

$$P_{alv} = P_{st} + P_{pl} \quad (5)$$

This results in expiratory flow ($\dot{V}$) which can be calculated according to Ohm's law as:

$$\dot{V} = P_{ta} / R_{aw} = ((P_{st} + P_{pl}) - P_m) / R_{aw} \quad (6)$$

Hence, any change in $\dot{V}$ is dependent on both resulting pressure and resistance. By measuring flow during spirometry, one cannot know whether any change in flow is due to a change in pressure (*e.g.* neuromuscular disorders) or in resistance (*e.g.* intrathoracic obstruction). However, under the condition of flow limitation with maximal muscular activity flow is independent of any further increase in driving force, and thus representative of airway calibre. The following section depicts why this is the case during forced expiration.

Dynamic airway compression

As highlighted earlier, inhaling deeply and then exhaling with maximum effort increases P_{pl} and P_{alv} well above P_m, thus creating the driving force for airflow during forced expiration. The positive P_{pl} results in pressure on the whole lung tissue and airways. Accordingly, both P_{alv} and pressure in the airway lumen ($P_{intrabronch}$) increase as a result of P_{st} and positive P_{pl}.

$$P_{intrabronch} = P_{st} + P_{pl} \quad (7)$$

$P_{intrabronch}$ slowly decreases from the alveoli (where $P_{intrabronch} = P_{alv}$) towards the airway opening (where $P_{intrabronch} = P_m$). Under the condition of maximum forced expiration and flow limitation, there will be a point in the airway tree where intra- and extrabronchial

Table 2. Dynamic lung volumes and expiratory flows

Parameter	Acronym	Explanation
Volumes		
Forced vital capacity	FVC	Volume of air that can be exhaled during forced expiration after maximal inspiration to TLC
Forced expiratory volume in 1 s	FEV_1	Volume of air that can be exhaled during 1 s in forced expiration after maximal inspiration to TLC
Forced expiratory volume in x second(s)	FEV_x	Volume of air that can be exhaled during x second(s) in forced expiration after maximal inspiration to TLC Preschool children may not be able to expire for 1 s; here, $FEV_{0.5}$ or $FEV_{0.75}$ are useful parameters
Tiffeneau index	FEV_1/FVC	Ratio of volume of air that can be exhaled during 1 s in forced expiration after maximal inspiration to TLC over total volume of air that can be exhaled during forced expiration after maximal inspiration to TLC
Flows		
Peak expiratory flow	PEF	Maximal expiratory flow during forced expiration
Forced expiratory flow at x% of FVC (already exhaled)	FEF_x (FEF_{75}, FEF_{50}, FEF_{25})	Maximal expiratory flow at 75%, 50% or 25% of FVC already exhaled, primarily used in English language
Maximal expiratory flow at x% of FVC (to be exhaled)	MEF_x (MEF_{75}, MEF_{50}, MEF_{25})	Maximal expiratory flow at 75%, 50% or 25% of FVC to be exhaled, primarily used in German language
Maximal mid-expiratory flow	MMEF or FEF_{25-75} or MEF_{25-75}	Maximal mean expiratory flow between 25% and 75% of FVC expired (FEF_{25-75}) or, equally, 75% and 25% of FVC to be expired (MEF_{25-75}); is highly correlated with, but not equal to, FEF_{50} or MEF_{50}, respectively

pressures are equal (where $P_{intrabronch}=P_{pl}$), the so-called equal pressure point (EPP). Accordingly, airways can be divided into three segments: 1) inflated segments (where $P_{intrabronch}>P_{pl}$); 2) EPP (where $P_{intrabronch}=P_{pl}$); and 3) airflow limiting segments (where $P_{intrabronch}<P_{pl}$). According to equation (7) and taking into consideration that P_{pl} remains relatively constant around the lung, the pressure drop along the airway equals P_{st} at the site of EPP, with P_{st} being volume-dependent, as highlighted earlier. This has an important implication: during expiration, lung volume decreases and consequently so does P_{st}; hence, the EPP will be closer to the alveoli with small lung volumes (*e.g.* towards the end of expiration) as compared to the start of forced expiration, where it is located near the upper thoracic aperture. One can imagine the EPP entering the trachea during expiration and then splitting up into several EPPs in segmental, more compliant bronchi, making up an EPP wave front.

The movement of the EPP during forced expiration is the reason why this airway compression is described as dynamic. Upstream of the EPP, towards the alveoli,

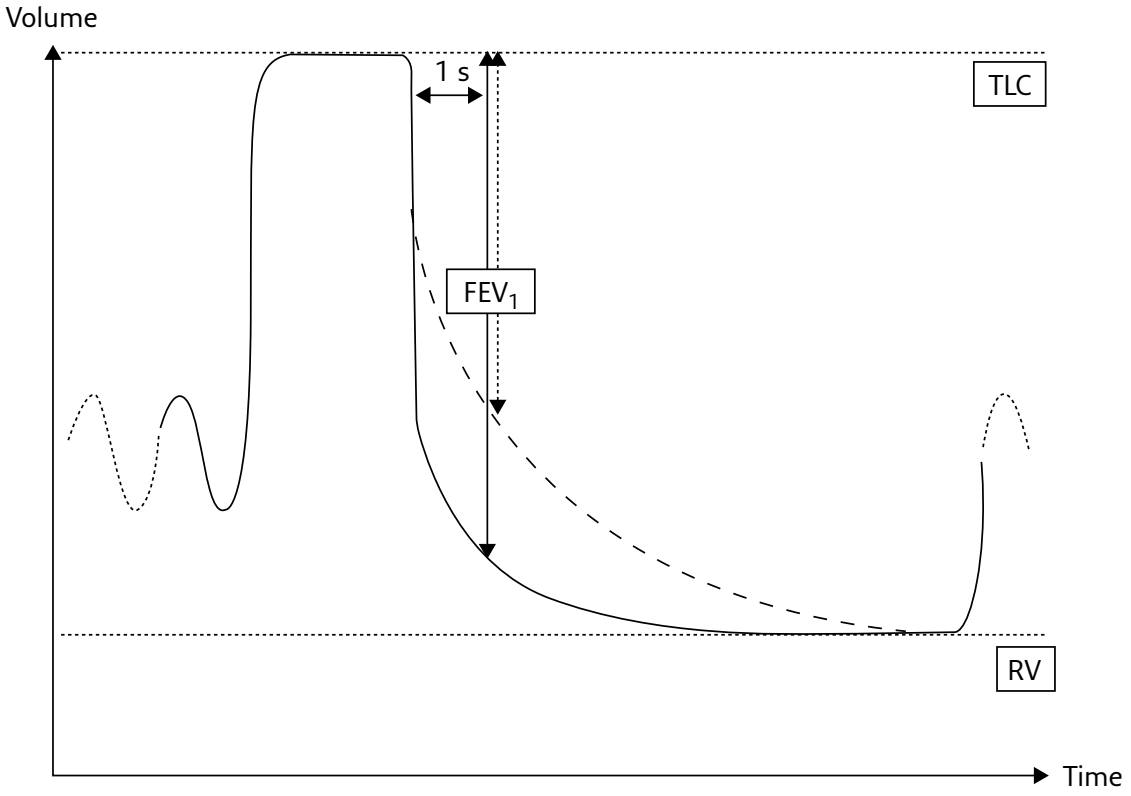

Figure 2. Volume–time relationship during forced expiration in a healthy subject (solid line) and in a subject with obstruction and a lower value of FEV_1 (dashed line).

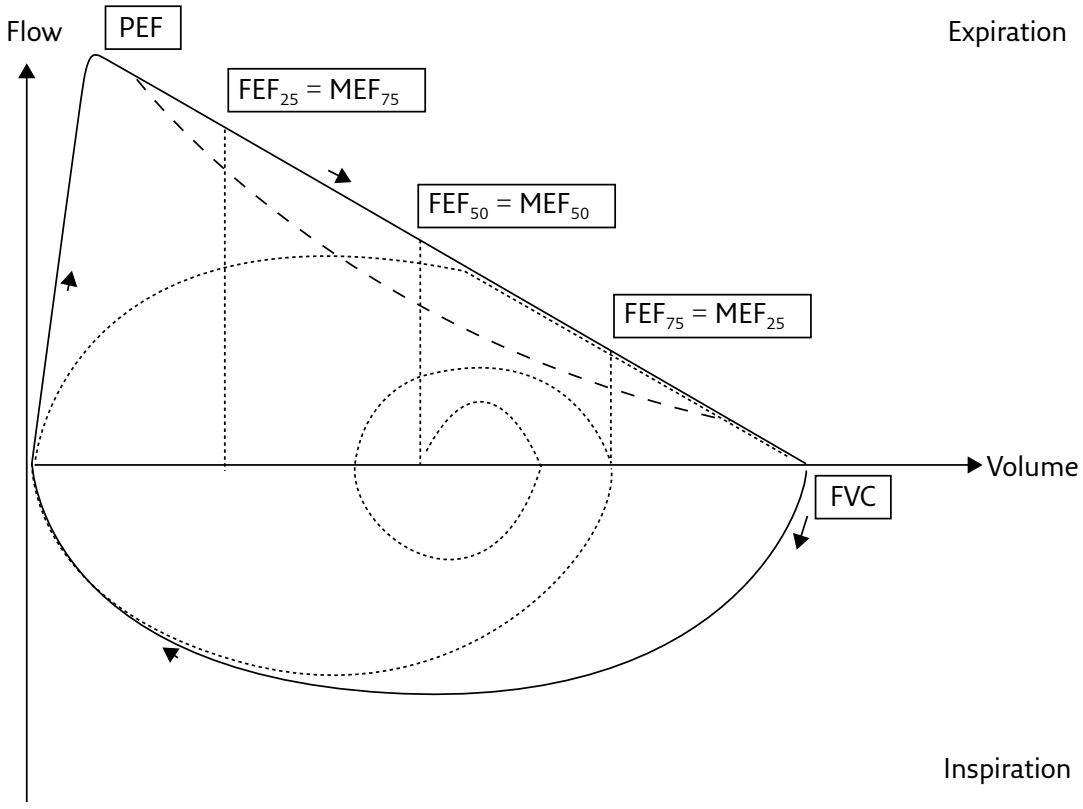

Figure 3. Flow–volume loops during inspiration and expiration before (dotted line) and during forced expiration. Measurements in a healthy subject (solid line) and in a subject with obstruction (dashed line) are displayed.

airways are not compressed as $P_{intrabronch} > P_{pl}$. However, downstream, there will be airway compression, creating a check valve, through which the flow is effort-independent. Why is this so? If we picture the airway as a compressible tube, airway compression results in an increased resistance to flow. Likewise, the intraluminal gas pressure upstream of the compressed airway is increased. Despite this, the speed of air through this airway segment can never exceed the velocity by which a pressure wave propagates through the wall of this airway segment (so-called wave-speed limitation). This is similar to a loud sound which cannot travel any faster than a quiet sound, the speed of both being limited to that of sound in air.

Limiting maximum expiratory flow (MEF) in addition to increased airway resistance, airway compression at the site of the check valve depends on airway wall thickness and tone of bronchial muscles. More compliant airways will give rise to lower flow rates than stiffer airways in the case of airway compression. Consequently, MEF is smaller at low lung volumes than at high volumes, explaining the descending portion of the flow–volume curve during forced expiration. In the case of both abnormally compliant airways (*e.g.* in bronchomalacia) and of airways with increased resistance (*e.g.* in asthmatic airway obstruction), the EPP and the site of airway compression will be located further downstream (towards the larger airways). In a healthy subject, all these EPPs can be pictured at the same relative position at the same time and the same airway generation, resulting in homogenous deflation, generating a straight downward line from peak expiratory flow (PEF) to FVC in the flow–volume curve during forced expiration. In cases of airway obstruction, the EPP front becomes inhomogeneous; the EPPs attain different relative positions and the flow–volume curve becomes concave (figure 3). The end of the forced expiratory manoeuvre results from the thoracic structure itself, which imposes an insurmountable impediment to any further expiration, resulting in the RV. In case of airway obstruction with a more upstream EPP (towards the alveoli, where airways are smaller and more compliant), $P_{intrabronch}$ will be smaller than P_{pl} at this position before reaching the above anatomical impediment, resulting in airway closure and increased RV resembling hyperinflation (figure 4).

Measurement of static and dynamic lung volumes

As highlighted earlier, the static lung volumes V_T, IRV, ERV, IC and VC can be measured directly during spirometry, while others (RV, FRC and TLC) require body plethysmography or gas-dilution techniques such as multiple-breath washout (MBW). Importantly, body plethysmography and MBW do not measure exactly the same thing. As mentioned, the measured volume FRC_{pleth} includes non- or poorly ventilated lung regions (trapped gas), in contrast to FRC_{MBW} reflecting a volume that communicates with larger airways. FRC_{MBW} can be computed by either mass spectrometry or devices based on ultrasonic flow meters which are also able to measure molar mass of gas. Here, FRC_{MBW} is calculated based on conservation of mass. This means that any amount of gas within the lung may be computed after measuring the concentration of this gas in expired air as well as the total volume of expired air if this gas is washed out of the lung, such as by inhaling pure oxygen to measure washout of nitrogen. Additionally, with MBW it is possible to calculate parameters that allow assessment of ventilation homogeneity, such as the LCI, which is important in small airway diseases such as CF, but also in asthma.

Clearly, detailing all the guidelines for lung function measurements in children would be beyond the scope of this chapter. Measurements during quiet tidal breathing are possible even in infants, and in toddlers if sedation is used. Due to lack of cooperation,

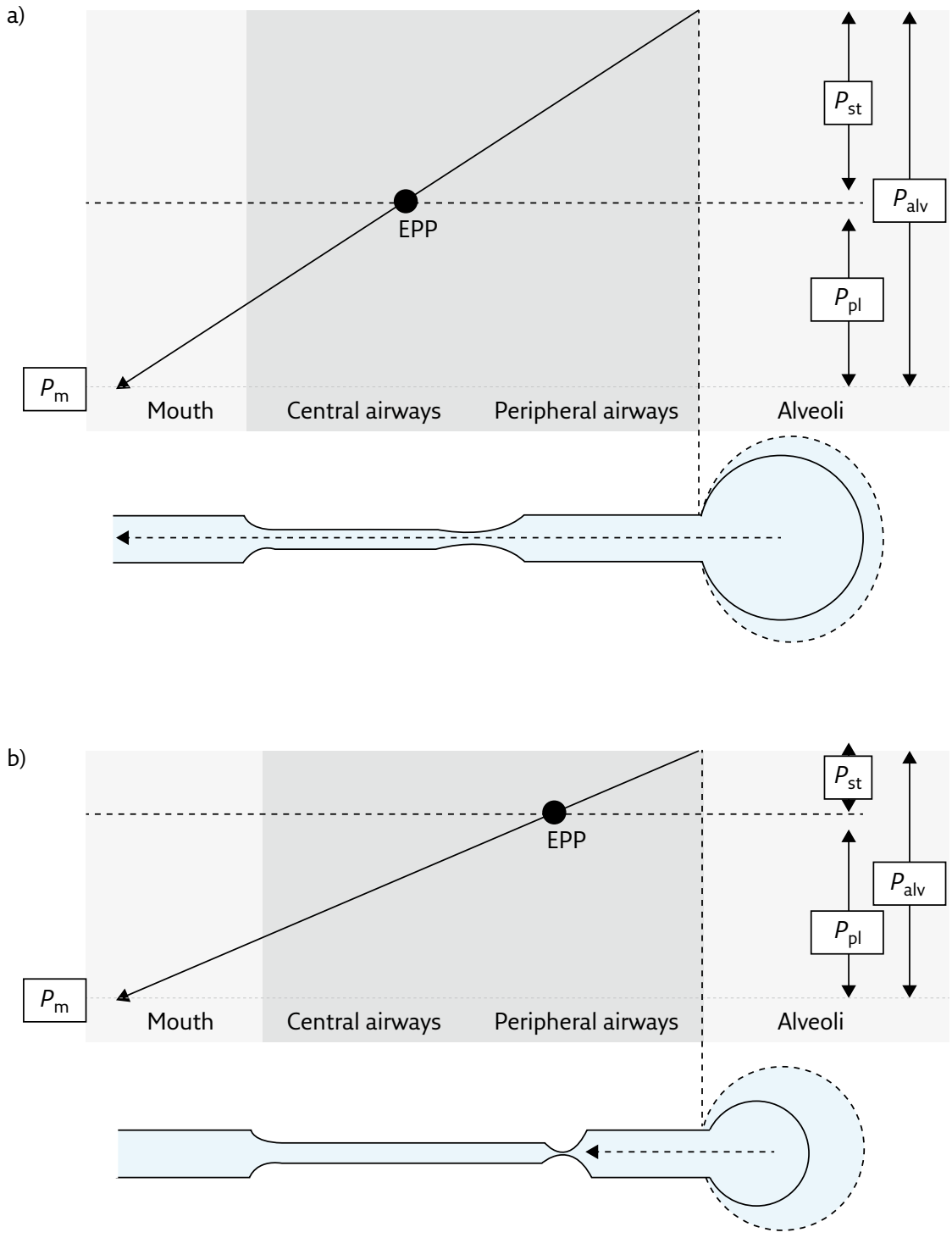

Figure 4. Respiratory mechanics during forced expiration in a simplified lung model in a) a healthy subject and b) a subject with obstruction.

early childhood may impose difficulties for any lung function measurements. From preschool age onward, measurements during tidal breathing and especially those requiring either forced expiration or a VC manoeuvre are once again feasible, especially in experienced paediatric centres. For normative data, readers are referred to the Global Lung Function Initiative (GLI; www.lungfunction.org), which has collected respiratory function outcomes covering large age ranges (including early childhood) and different ethnicities, and produced reference equations for spirometry; the generation of reference equations for lung volumes is ongoing.

Further reading

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Respiratory mechanics

Marc-Alexander Oestreich, Christoph Corin Willers and Oliver Fuchs

Breathing is the movement of air along pressure differences in the lung and airways. A simple model of the respiratory tract is that of a stiff tube (airways) connected in series to an elastic balloon (lung). The following formula describes how much pressure (P) is needed for a certain volume (V), dependent on the compliance (C), the resistance (R) related to a certain flow (V'), and the acceleration (V'') necessary to overcome the system's inertia to changes in flow (impedance; I):

$$P = V/C + RV' + IV''$$

Respiratory mechanics are determined by elastic properties of the respiratory system (C), reflecting changes in volume without any change in flow (static forces). Non-elastic forces (RV'), which are dynamic forces due to their dependency on flow, are another factor. The third factor, impedance (I), plays only a minor role. The major part of physical work is necessary to overcome elastic or static forces and is stored as potential energy. Any force necessary to overcome resistance is lost as heat due to friction; its contribution to physical work is very small.

In the healthy subject, expiration happens passively along elastic retraction forces. However, during inspiration, a negative intrapleural (P_{pleur}) and secondly intra-alveolar pressure (P_A) is created by respiratory muscles in relation to the surrounding atmospheric pressure (P_{atm}). P_A and P_{pleur} can be used to calculate the resulting transpulmonary pressure ($P_{transpulm}$):

$$P_{transpulm} = P_A - P_{pleur}$$

Key points

- Respiratory mechanics are helpful in understanding the cyclic changes in airflow due to pressure differences during breathing and the influence of elastic (compliance) and dynamic (resistance) properties of the respiratory system.
- Both compliance and resistance are volume dependent.
- Compliance displays a strong influence of age. It is higher in infancy and the elderly while being lower during late childhood and adulthood. In contrast, resistance is higher in case of denser or more viscous gases.

Airway mechanics can be altered by lung disease. For example, compliance (*C*) is increased in lung emphysema and decreased in lung fibrosis, *e.g*. due to interstitial lung disease. Resistance (*R*) is increased in obstructive lung disease, *e.g*. asthma, but also due to lung emphysema, given the tendency to airway collapse due to decreased tethering (see section "Resistance is volume dependent", later in this chapter). Moreover, the pressure driving airflow during breathing is affected by any disease affecting the driving forces, such as neuromuscular diseases. In order to understand the underlying pathophysiology of altered airway mechanics in lung disease, it is important to understand the basics of respiratory mechanics in the healthy individual. A complete description of altered airway mechanics in the whole variety of lung diseases including mechanical ventilation is beyond the scope of this chapter.

Importantly, strain and static properties of the respiratory system change constantly during pulmonary development. During breathing, P_A equals P_{atm} at the end of inspiration and expiration. For P_{pleur}, this is only the case during infancy. Even earlier, *i.e*. during the first breaths after birth and then again from childhood when elastic retraction forces increase during growth, P_{pleur} is always negative in relation to P_{atm}, both during inspiration and expiration.

Elastic properties of the respiratory system: compliance

Elastic properties of the thorax and lungs act in opposite directions. While the thorax is predisposed to expand due to its structure, lungs tend to collapse because of their content of elastic fibres and surface tension at the alveolar gas–water interface. Lung collapse is prevented by adhesion forces in the pleural space, which make the lung tissue follow changes in thoracic diameter during inspiration and expiration. Pulmonary tethering transmits these forces throughout the lung tissue; pressure differences (P_A–P_{atm}) are built up and enable airflow towards alveoli.

Law of Laplace, alveolar gas–water phases and surfactant

Alveolar physical properties can be compared to those of soap bubbles. Surface tension minimises the area between the gas–water phases. Resulting forces follow the law of Laplace, describing the pressure (*P*) in relation to surface tension (*T*) and radius (r):

$$P = 2 \times T/r$$

The higher the surface tension and the smaller the radius, the higher the resulting pressure and the more probable alveolar collapse is. Surfactant (surface active agent) reduces surface tension directly proportional to its alveolar concentration. Thus, reducing surface tension becomes more efficacious in case of smaller radii and concomitant increases in concentration, the opposite being the case during pulmonary hyperinflation. As a net effect, alveolar radius is stabilised and the coexistence of neighbouring smaller and larger alveoli is possible. Without surfactant, lung compliance would decrease, smaller alveoli would collapse (atelectasis) and empty into larger alveoli in direct contact, and alveoli would fill with transudate, resulting in pulmonary oedema.

Compliance measurement

Compliance is a measure for elastic properties of the respiratory system; it describes how much change in pressure (ΔP) is necessary for a specific change in volume (ΔV). Its reciprocal counterpart is the elastance (*E*), describing how much change in volume is necessary for a specific change in pressure.

$$C\ (L \cdot kPa^{-1} \text{ or } cmH_2O) = \Delta V/\Delta P = 1/E$$

The compliance of the whole respiratory system (C_{rs}) is made up by the compliance of the thoracic wall (C_{cw}) and that of the lung (C_L). These add up like electrical resistances connected in series; hence, by the addition of their reciprocal units (individual elastance values):

$$1/C_{rs}\ (\text{kPa or cmH}_2\text{O}\cdot\text{L}^{-1}) = 1/C_{cw} + 1/C_L$$

Depending on where pressure changes are measured at zero flow at the end of inspiration and expiration, it is possible to calculate C_{cw} (P_{pleur}–P_{atm}), C_L (P_A–P_{pleur}=$P_{transpulm}$) or C_{rs} (P_A–P_{atm}). P_{pleur} and its relative changes are measured using an oesophageal pressure probe.

Compliance is volume dependent

There is a direct relationship between compliance and the ratio of volume over pressure gradients. Accordingly, compliance is volume dependent, visualised in a pressure–volume curve (figure 1). The pressure–volume curve for C_{rs} has a

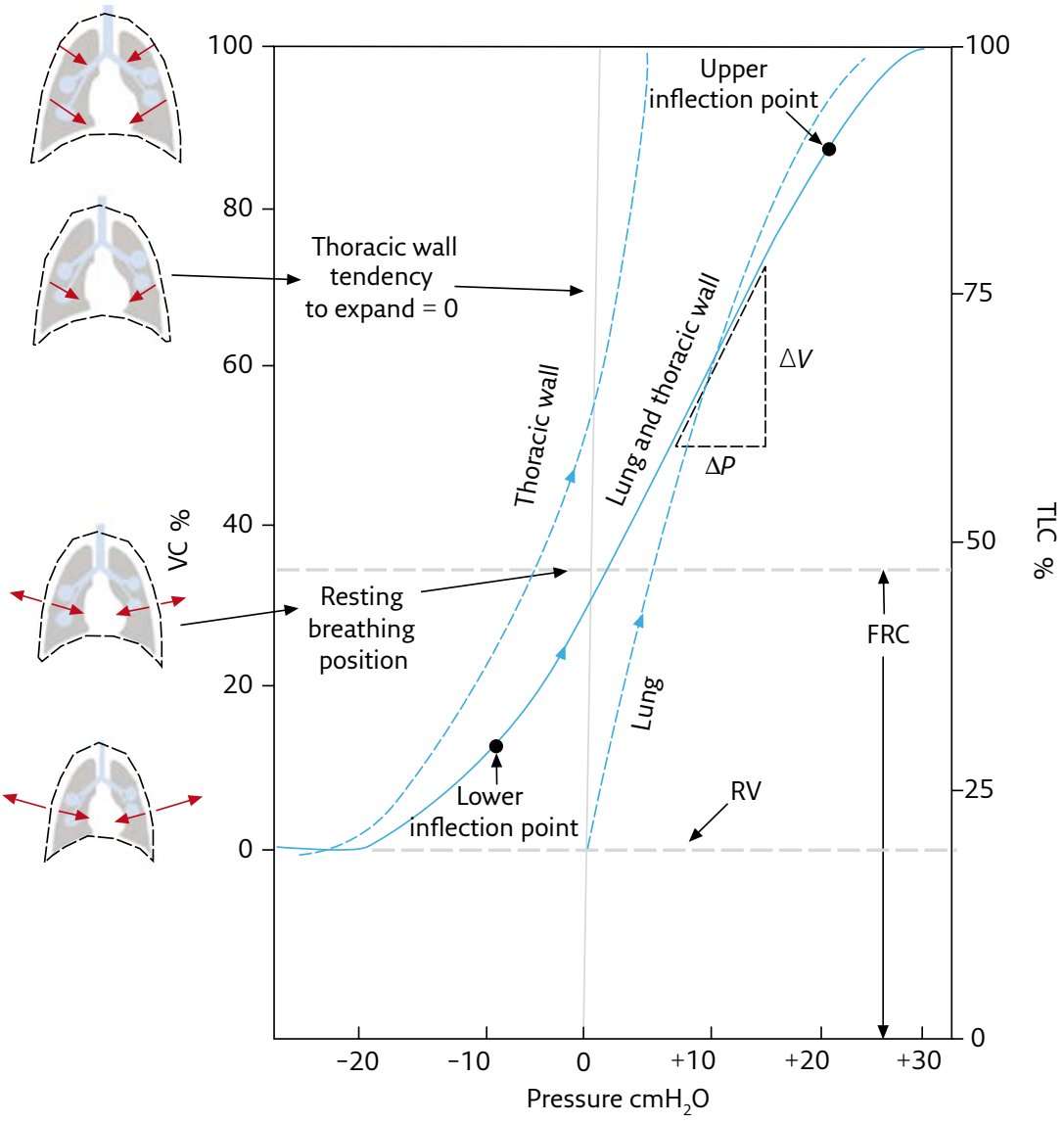

Figure 1. Inspiratory pressure–volume curves for C_{cw}, C_L and C_{rs}. The dashed lines represent C_{cw} (thoracic wall) and C_L (lung). The solid line represents C_{rs} (whole respiratory system, i.e. *lung and thoracic wall). The different states of the respiratory system and resulting forces are shown on the left of the graph (red arrows). VC: vital capacity; ΔP: pressure gradient; ΔV: volume gradient.*

characteristic S-shape with inflection points. The slope reflects C_{rs}, which is largest in the steep middle part of the curve and where physical work needed for inflation during inspiration is lowest. Beyond inflection points, high volumes stiffen the lung, which increases physical work. Thus, respiration becomes less efficacious. The lower part of the curve results from closure of smaller airways and alveoli below a specific lung volume, the so-called closing volume. The upper part results from exhaustion of elastic properties in the lung structure due to distension of elastic fibres, thorax and alveolar septa. Thus, mechanical ventilation beyond the upper inflection point may carry the risk of volutrauma or barotrauma. As the compliance is volume dependent, its value is standardised by relating it to a certain lung volume, usually the FRC, resulting in the specific compliance. Interestingly, volume decreases less in relation to pressure during expiration than inspiration, which is reflected in non-identical pressure–volume curves, known as hysteresis. This is possibly due to reorganisation of surfactant molecules during expiration, with complex folding processes, the creation of several surfactant layers and perhaps even partitioning into different surfactant subcompartments.

Influence of age on C_L, C_{cw} and C_{rs}

FRC reflects the intrapulmonary volume at which elastic properties of C_{cw} and C_L equal each other. Here, tendencies towards (thoracic) expansion and (lung) collapse are in balance. Generally, this is the case for a higher FRC in older children and in adults rather than newborns or toddlers. In addition to surfactant, elastic properties of the pulmonary system also depend on lung structure, especially elastic fibres. Owing to ageing, elastic retraction forces (P_{el}) increase from birth through adolescence, but then decrease again, resulting in considerably less negative intrapleural pressure at end-expiration.

Thus, in both newborns and in older people, FRC can be below the closing volume during tidal breathing. Accordingly, the newborn and the aged lung are very similar with regard to their tendency for airway collapse below the closing volume which is itself, therefore, age-dependent. This is also the reason for the higher amount of functional shunts early in life and the increasing incidence of shunts among older people. In order to circumvent airway collapse in dependent lung areas the newborn has several mechanisms available to dynamically upregulate FRC, leading to either a shorter duration of expiration or a decrease in expiratory flow (expiratory braking):

- Increasing the respiratory rate reduces the time for passive expiration (t_E) in comparison to the duration of active inspiration (t_I).
- During expiration, vocal cords are either actively moved towards each other (adduction) or there is a loss of laryngeal abductor activity; thus, resistance increases on the vocal cord level. Due to reduced expiratory flow, lung emptying is slowed down. While this is noiseless in the healthy newborn, it may become audible in the sick infant as expiratory grunting.
- During expiration, the activity of respiratory muscles is adapted in such a way that passive expiration is decelerated or even terminated through tonic muscular activity of the diaphragm. In addition, inspiration starts earlier than in older children or adults.

Dynamic upregulation of FRC lasts approximately until the end of the first year of life, when elastic retraction forces of the relatively more compliant thoracic skeleton increase due to progressing ossification, *i.e.* when C_{cw} slowly decreases.

At the end of the second year of life C_L equals C_{cw} in resting expiratory position without any necessary regulatory measures. C_{rs} changes predominantly due to increasing numbers of alveoli during childhood, further influenced by the development of upright walking.

Dynamic properties of the respiratory system: resistance

Respiratory mechanics are influenced not only by elastic properties of the respiratory system, but also by its dynamic properties, which are by definition dependent on flow. These non-elastic, viscous resistances are made up by airway resistance to flow, non-elastic tissue resistance and resistance due to inertia.

Resistance of the whole respiratory system

In analogy to Ohm's law, the resistance of the whole respiratory system (R_{rs}) is defined as the ratio of difference between pressure in alveoli (P_A) and pressure at airway opening (P_{ao}) over airflow (V'), which is itself measured at airway opening:

$$R_{rs}\ (\text{kPa}\cdot\text{s}\cdot\text{L}^{-1}) = (P_A - P_{ao})/V'$$

R_{rs} can be subdivided into the resistance of the airways (R_{aw}) and the resistance due to friction between chest and lung tissue. Resistance due to friction is only minor compared to R_{aw}, which itself accounts for ~90% of R_{rs}.

In general, R_{aw} is influenced both by airway diameter and fluid flow behaviour of air and can be determined by body plethysmography. It is important to note that R_{aw} is calculated and requires cooperation during the shutter manoeuvre (see chapter "Static and dynamic lung volumes" for measurement of FRC_{pleth}). The specific airway resistance (sR_{aw}) is directly measured during quiet tidal breathing without shutter, which is why it is less dependent on cooperation.

In a strict sense of the word, sR_{aw} is not a resistance, but rather represents the work that has to be performed to establish flow-standardised volume-related work. More specifically, while P_A is not measurable during quiet tidal breathing, relating V' to the small shift in volume (ΔV_{box}) due to the pressure changes (ΔP_{box}) induced by the subjects' breathing efforts in the currently used volume-constant body plethysmography boxes is a surrogate marker for that.

Therefore, sR_{aw} can be seen as the product of P_{box} and ΔV_{box} over V':

$$sR_{aw}\ (\text{kPa} \times \text{s}) = P_{box}\ (\text{kPa}) \times \Delta V_{box}\ (\text{L})/V'\ (\text{L}\cdot\text{s}^{-1})$$

This is visualised in the schematic representations of specific resistance loops, which represent plots of V' over ΔV_{box}. The reciprocal slope of such loops represent sR_{aw}. For further details on mathematics and physics underlying lung function measurements by body plethysmography boxes, readers are referred to relevant literature.

As mentioned earlier, besides R_{aw} being dependent on airway diameter, it is also a measure of fluid flow behaviour of air. Depending on airway generation and pathological conditions, such as airway obstruction, airways may demonstrate different shares of laminar and turbulent flow. The Hagen–Poiseuille equation describes laminar flow. According to this equation, airway resistance is proportional to airway length (l) and

dynamic gas viscosity (η) and inversely proportional to the fourth power of the airway radius (r) and π:

$$R\ (\text{kPa}\cdot\text{s}\cdot\text{L}^{-1}) = 8 \times l \times \eta/(r^4 \times \pi)$$

Under the condition of turbulent flow, movement of gas molecules seems more random and mathematically describing this state is more complex. In case of turbulent flow, resistance increases with flow rate and is proportional to gas density (ρ) and viscosity (η) but inversely related to the fifth power of the airway radius. Pressure differences are thus much higher than with laminar flow. The Reynolds number (Re) helps to predict when laminar flow changes into a turbulent one. This is again dependent on gas density (ρ) and dynamic gas viscosity (η), as well as airway length (l), but also flow (V').

$$\text{Re} = V' \times l \times \rho/\eta$$

Above a critical value of Re (~2300) laminar flow passes on to turbulent flow. Pure laminar flow can be found for smaller Re of <2300, usually in small peripheral airways, while flow in larger airways is predominantly turbulent. Airway branching and bending, as well as abrupt changes in airway diameter, as in the case of airway obstruction, play a role. Hence, peripheral airways only account for ~10–20% of R_{rs} despite their total share of airway diameter (~95%). The biggest portion of R_{rs} results from airway resistance secondary to turbulent flow in larger, more central airways.

Time constant of the whole respiratory system

Airways and lung tissue are considered separately in terms of their influence on respiratory mechanics. This is an oversimplification, as they are both interdependent on each other. The time constant (τ) of the respiratory system is a parameter taking both into consideration. In general, τ describes the duration during which an exponential process decreases to 1/e (Euler's constant; e), *i.e.* ~36.8% of the default value. In case of the respiratory tract, τ is defined by the product of C_{rs} and R_{rs} and represents the time in seconds that is needed for the respiratory system to expire 63.2% of the lung volume in air due to passive retraction forces. For a full expiration, the respiratory system will need approximately three to five time constants. Any decrease in R_{rs} is associated with an increase in C_{rs} and *vice versa.*

Resistance is volume dependent

Due to pulmonary tethering and the resulting elastic retraction forces that stabilise airway diameter, as well as concurrent bronchiolar distension during deep inspiration, resistance is volume dependent. In contrast, radial tension is decreased with lower lung volumes (figure 2). This volume dependency is taken into account when calculating the specific resistance and specific conductance (inverse of resistance) by relating both values to the FRC. Below FRC there is a steep increase in resistance. There is a hyperbolic relationship between resistance and lung volume, on one hand, and a linear relationship of the conductance (inverse of resistance) and lung volume, on the other (figure 2).

Resistance of the upper airways

In infants, the nasopharyngeal space can account for up to 40% of R_{rs}, and in adults as much as 60%. The larynx is the narrowest part of the upper airways; in infants and toddlers this is due to the anatomy of the cricoid, owing to growth it is the glottis in older children and in adults. Before it descends during growth, the larynx is initially

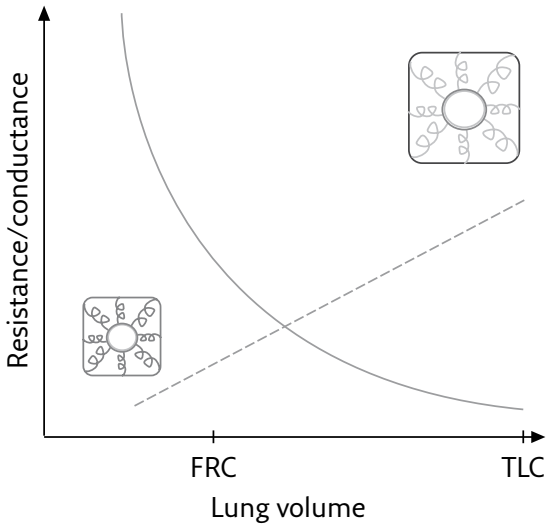

Figure 2. Volume dependency of resistance and conductance; pulmonary tethering. The boxes represent elastic fibres stabilising airway diameter in relation to lung volume (tethering). The solid line represents resistance, and the dashed line represents conductance in relation to lung volume.

located further forward and higher (C2–C3) in newborns and infants than in adults (C3–C6), favouring breathing through the nose and making simultaneous breathing and drinking possible. Accordingly, due to the laryngeal anatomy, breathing through the mouth is rather disadvantageous early in life. This explains the significant nuisance of infants and, to a lesser extent, of toddlers in case of upper airway infections with nasal obstruction.

Resistance of the lower airways

In contrast to their small individual diameter, the total share of the small peripheral airways is high in relation to that of other airways. Nevertheless, in older children and adults, the portion of R_{rs} formed by small airways is 10–20%. Consequently, measuring resistance is not very sensitive with regards to quantifying obstruction of small airways in these subjects. However, in infants, small peripheral airways may account for up to 50% of R_{rs}. Thus, as with nasal obstructions, even minor peripheral airway obstructions may be associated with significant impairment in this age group. Furthermore, in dyspnoeic infants, airways are more prone to collapse due to their relatively high compliance during forced inspiration and due to increased transmural pressure in the case of crying. This is the reason why measures of calming down agitated infants or even the use of sedatives may help to reduce resistance and thus to improve clinical status.

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Respiratory muscle function

Brigitte Fauroux, Alessandro Amaddeo and Sonia Khirani

Respiratory muscle tests are important to assess the strength and capacity of the respiratory muscles, not only in children with neuromuscular diseases (NMD), but also in those with other causes of respiratory muscle weakness or dysfunction, such as diaphragmatic paralysis or diaphragmatic hernia. Indeed, the accurate quantification of the performance, *i.e.* strength and endurance of the respiratory muscles will help to monitor and adapt the respiratory management of these patients. Most respiratory muscle tests are volitional tests, with the consequent limitations related to the patient's cooperation. Most are not specific to one type of muscle, underlying the need for a range of complementary tests for valid assessment.

Assessment of respiratory performance in children

Tests evaluating respiratory muscles can be "volitional" or "nonvolitional" and "noninvasive" or "invasive" tests (*i.e.* requiring the measurement of the oesophageal pressure (P_{oes}) and gastric pressure (P_{gas})) (figure 1 and table 1). Volitional noninvasive tests are the most commonly used in clinical practice because of their simplicity, availability and ease. In young children and those with poor cooperation or severe respiratory muscle weakness, other tests (mostly invasive), may be required for the evaluation of respiratory muscle performance.

Key points

- Respiratory muscle tests should be adapted to the child's age and cooperation.
- Respiratory muscle tests should privilege natural manoeuvres such as sniff and cough.
- Respiratory muscle function should be assessed on a combination of complementary tests.
- Respiratory muscle tests should be adapted to the patient's "respiratory muscle phenotype".

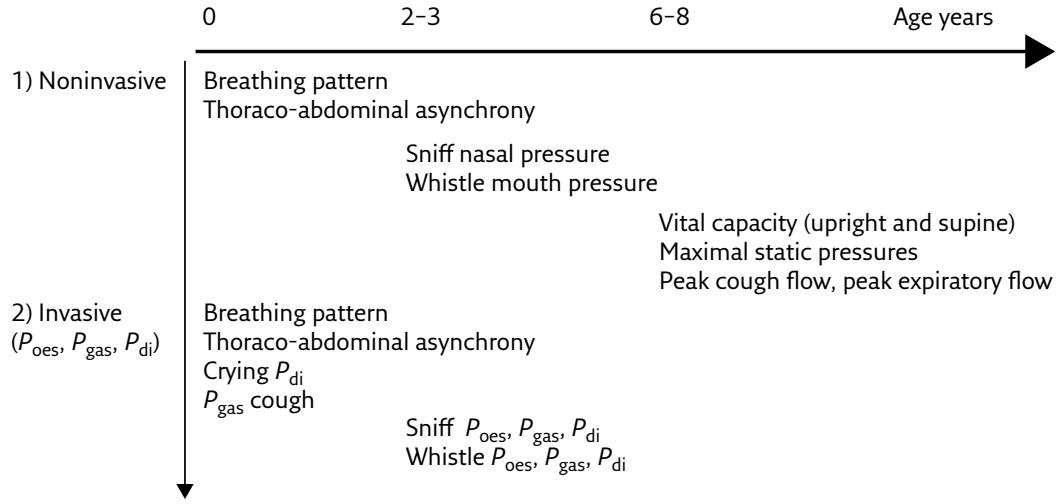

Figure 1. Algorithm of level of priority of respiratory muscle tests for clinicians according to the age of the patient. P_{oes}*: oesophageal pressure;* P_{gas}*: gastric pressure*; P_{di}*: transdiaphragmatic pressure. Reproduced from Fauroux* et al. *(2018) with permission.*

Noninvasive tests

Breathing pattern

The analysis of respiratory frequency (f_R), tidal volume (V_T) and V'_E (calculated as the product of $f_R \times V_T$) is easy and allows the calculation of the rapid shallow breathing index (f_R/V_T). However, this index represents a reflex response to an increase in the respiratory workload rather than a consequence of respiratory muscle fatigue or weakness *per se*.

Thoraco-abdominal asynchrony, defined as an abnormal, asynchronous movement of the thorax and the abdomen, may be observed in patients with diaphragmatic dysfunction or weakness of the expiratory intercostal muscles. A paradoxical inward motion of the ribcage during inspiration indicates intercostal muscle weakness, whereas paradoxical inward motion of the abdomen during inspiration indicates diaphragmatic weakness.

Lung volumes

The vital capacity (VC) manoeuvre consists of a maximal inspiration followed by a maximal expiration through a mouthpiece or a tight-fitting face mask. VC is a simple test and has excellent standardisation, high reproducibility and well-established reference values according to height and sex. In children with NMD and/or scoliosis, arm span or ulnar length can be used as a surrogate for height. In children with poor cooperation or intellectual disability, the inspiratory VC can be used as an alternative. A ⩾25% fall in VC between the prone and supine position reflects significant diaphragm weakness. Finally, a decrease in VC is not specific, and can be reduced by other factors than reduced muscle strength.

Maximal static pressures

Maximal static pressures consist of the maintenance of a maximal inspiratory (P_{Imax}) or expiratory (P_{Emax}) effort for ⩾1 s against an occluded airway. Pressures are measured through a cylindrical mouthpiece or a face mask with the child seated and wearing a nose clip. A small leak, created by placement of a needle in the mouthpiece, is necessary to eliminate glottis closure and artificially high P_{Imax}, and reduce the use of buccal muscles during P_{Emax}. P_{Imax} is generally measured from RV and P_{Emax} from TLC. Maximal pressures increase with age, and are greater in males than in females even

Table 1. Advantages and limitations of respiratory muscle tests in children

	Volitional/ nonvolitional	Specificity of the test for a specific (type of) muscle	Advantages (+)/limitations (–)
Noninvasive tests			
Breathing pattern	Nonvolitional	No	(+) Can be performed at any age (–) Requires quiet breathing (sleep in infants)
Lung volumes			
VC	Volitional	Inspiratory and expiratory	(+) Easy to perform, largely used in children aged >4–8 years; sensitive for assessing progress in moderate-to-severe respiratory muscle weakness (–) Requires cooperation; poor specificity for the diagnosis of respiratory muscle weakness
RV	Volitional	Expiratory	
TLC	Volitional	Inspiratory	
Maximal static pressures	Volitional	Inspiratory (P_{Imax}) Expiratory (P_{Emax})	(+) Easy to perform, largely used in children aged >6–8 years (–) Requires full cooperation
SNIP	Volitional	Inspiratory	(+) Natural manoeuvre, easy to perform, can be performed in very young children (aged >2 years) (–) Requires cooperation; glottic closure or airway characteristics may prevent adequate equilibration; not reliable in cases of nose obstruction
PEF/PCF	Volitional	Expiratory	(+) Easy to perform, largely used in children aged >4–8 years (–) Requires cooperation
Crying mouth pressure	Volitional	Inspiratory and expiratory	(+) Easy to perform in newborns (–) High variability; glottic closure should be prevented
P_{mW}	Volitional	Expiratory	(+) Easy to perform, natural manoeuvre, can be performed in young children (aged >3 years) (–) Requires cooperation; no reference values in children; only one study in children

(*Continued*)

Table 1. Continued

	Volitional/ nonvolitional	Specificity of the test for a specific (type of) muscle	Advantages (+)/limitations (–)
Invasive tests			
Breathing pattern with P_{oes} and P_{gas}	Nonvolitional	Diaphragm	(+) Can be performed at any age (–) Mildly uncomfortable, requires quiet breathing (sleep in infants)
P_{oes} and P_{di} during a maximal sniff	Volitional	Inspiratory and diaphragm	(+) Natural manoeuvre, easy to perform, can be performed in very young children (aged >2 years) (–) Mildly uncomfortable; requires cooperation; values may be less than maximal static values because of shortening of the inspiratory muscles
P_{gas} during a maximal cough	Volitional	Expiratory	(+) Natural manoeuvre, easy to perform, can be performed in very young children (aged >2 years) (–) Mildly uncomfortable; requires cooperation; no normal data exist from large studies
Crying P_{di}	Volitional	Diaphragm	(+) Can be performed in newborns (–) Mildly uncomfortable; high variability

VC: vital capacity; SNIP: sniff nasal inspiratory pressure; PEF: peak expiratory flow; PCF: peak cough flow; P_{mW}: mouth whistle pressure; P_{di}: transdiaphragmatic pressure; P_{Imax}: maximal static inspiratory pressure; P_{Emax}: maximal static expiratory pressure. Reproduced from Fauroux *et al.* (2018) with permission.

prior to puberty, with adult values being attained by 11–12 years of age. In cases of poor cooperation, peak inspiratory and expiratory pressures can be used.

In infants, peak mouth pressures generated during crying efforts may provide an index of the global respiratory muscle strength. Mean peak crying P_{Imax} is 118±21 cmH_2O in healthy infants aged <2 years with mean peak crying P_{Emax} being 125±35 cmH_2O.

Sniff nasal inspiratory pressure

Sniff nasal inspiratory pressure (SNIP) consists of measuring nasal pressure in an occluded nostril during a maximal sniff performed through the contralateral nostril from FRC. SNIP is based on the fact that the pressure measured in the mouth, nasopharynx and the nose during a sniff is closely related to the P_{oes}. Sniff is a natural manoeuvre that the majority of children aged 2–4 years are able to perform. Values in healthy children aged 6–17 years are 104±26 cmH_2O in males and 93±23 cmH_2O in females. SNIP underestimates inspiratory muscle strength in cases of nasal obstruction by adenoids or nasal polyps. As such, a normal SNIP value excludes inspiratory muscle weakness, but a low value requires the measurement of the P_{oes}. SNIP has been shown to decline at an earlier age than VC in males with Duchenne muscular dystrophy.

Peak expiratory flow and peak cough flow

Peak expiratory flow (PEF) and peak cough flow (PCF) involve generating a maximal expiratory flow or cough in a peak flow meter through a mouthpiece or a face mask and are used as a marker of expiratory muscle strength. Normal values of PEF and PCF are available for children.

Whistle mouth pressure

Whistle mouth pressure (P_{mW}) evaluates expiratory muscle strength by measuring mouth pressure during a short, sharp and maximal expiration through a whistle connected to a flanged mouthpiece without a nose clip. A reliable P_{mW} test may be obtained in children as young as 4 years. P_{mW} has been shown to be significantly correlated to other expiratory muscle tests.

For all volitional maximal tests, the best value is retained. The major limitation of volitional tests is that they depend on the patient's motivation, cooperation and ability. It is generally admitted that if three equal maximal efforts are obtained, then the subject is supposed to have realised a maximal effort, but reproducibility does not ensure maximality.

Invasive tests

These tests require the placement of balloons or pressure transducers in the oesophagus and stomach. Simultaneous measurements of P_{oes} and P_{gas} allows the calculation of transdiaphragmatic pressure (P_{di}) with $P_{di}=P_{gas}-P_{oes}$, which represents the pressure generated specifically by the diaphragm.

Spontaneous breathing

During normal quiet breathing, contraction of the diaphragm and inspiratory muscles produces a negative change in P_{oes} and a positive change in P_{gas}. As such, the $\Delta P_{gas}/\Delta P_{oes}$ ratio reflects the relative contribution of the diaphragm and the other respiratory muscles to quiet breathing. In healthy subjects, the $\Delta P_{gas}/\Delta P_{oes}$ is less than –1. A value ranging between –1 and 1 indicates an ever-increasing contribution of the ribcage and the expiratory muscles, as compared to the diaphragm, to tidal breathing. With total diaphragmatic paralysis, this ratio becomes equal to 1.

P_{oes} and P_{di} during a sniff manoeuvre

In clinical practice, sniff P_{oes} and sniff P_{di} are the most accurate and reproducible volitional tests available to assess global inspiratory and diaphragmatic strength, respectively, in cooperative children aged >2–4 years. Since the diaphragm is the most important muscle of inspiration, it is not surprising that sniff P_{oes} is closely related to sniff P_{di}. Interestingly, a negative P_{gas} deflection during a sniff can be seen in case of diaphragmatic dysfunction or paralysis.

P_{gas} during a maximal cough

The strength of the expiratory muscles can be easily measured by asking the patient to perform a maximal cough which is a natural manoeuvre than can be performed at any age.

Crying P_{di}

Crying P_{di} pressure measurements allow the assessment of diaphragm muscle strength during inspiratory crying efforts in awake infants. Crying P_{di} is ~60 cmH_2O at 1 month postnatal age, and increases rapidly with age to ~120 cmH_2O.

Respiratory muscle tests in practice

Respiratory muscle tests should be adapted to the child's age, cooperation and "respiratory muscle phenotype" (*i.e.* the type of respiratory muscle involvement). Tests reproducing natural, easy-to-understand manoeuvres such as a sniff or cough are privileged. Visual feedback, by the visualisation of the tracing by the child on a computer screen, is playful for the child and strongly recommended. As no test is ideal or sufficiently specific, practitioners should aim towards an agreement between several complementary tests for an optimal assessment of the inspiratory and expiratory muscles.

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Reversibility and bronchial provocation testing

Nicole Beydon and Monika Gappa

The variability in bronchial smooth muscle tone is an important, albeit nonspecific characteristic of bronchial asthma. It is probably related to the presence of airway inflammation, but also discloses bronchial remodelling. As early as 1859, Sir Henry Hyde Salter described "bronchial sensibility" in patients with asthma. This variability in bronchial smooth muscle tone may go in one of two directions:

- Towards exaggerated bronchodilation upon a bronchodilator stimulus, also called bronchodilator reversibility
- Towards increased bronchial constriction and obstruction after exposure to a bronchoconstrictor stimulus, often called bronchial hyperresponsiveness (BHR)

This variability in bronchial tone is assessed both in diagnosis and in monitoring of asthma. However, BHR may also be found in a number of other respiratory disorders such as CF, BPD or during acute respiratory tract infections.

Reversibility: bronchodilator responsiveness

Reversibility to bronchodilator drugs is usually measured in a standardised way by first measuring baseline lung function, usually FEV_1, then inhaling a bronchodilator drug before again measuring FEV_1 after a suitable time, enabling the bronchodilator drug to have an effect upon bronchial smooth muscle. In addition, other measures of lung function may be used. The procedure has been standardised by a joint task force of the European Respiratory Society (ERS) and the American Thoracic Society (ATS), and an increase in FEV_1 and/or FVC of ≥12% baseline and ≥200 mL after inhaled

Key points

- Bronchodilator reversibility demonstrates reversible bronchial obstruction and is a diagnostic marker of active asthma.
- Children with normal baseline spirometry rarely have a significant FEV_1 reversibility, whereas children with low baseline FEV_1 and no reversibility have a poor prognosis.
- The level of the pre-test probability of asthma determines the accuracy of bronchial provocative tests in diagnosing or excluding asthma. Direct bronchial provocative tests are more useful at excluding than at confirming asthma.

bronchodilator has been selected as a significant increase and as a criterion for a positive reversibility test. In young children with much lower vital capacity than adults, the absolute change of 200 mL represents a large volume, and no definitive threshold for a significant increase in FEV_1 and/or FVC is currently recommended in this age group. However, it has been shown that sensitivity and specificity of bronchodilator response are low in children with asthma. In fact, using a threshold of 12%, only 36% of children with asthma would have been positive in a *post hoc* analysis of the Childhood Asthma Management Program (CAMP) study.

Either salbutamol or another bronchodilator, such as ipratropium bromide, may be used. Most commonly, inhaled salbutamol at a dose of 400 µg (4×100 µg) given from a metered-dose inhaler through a suitable inhalation chamber with mouthpiece is the recommended dose in adults and in children/adolescents aged ⩾12 years. In younger children, the same dose of bronchodilator should be administered through a face mask adapted to an inhalation chamber if necessary. Alternatively, ipratropium bromide 160 µg (4×40 µg) may be used. If preferred, inhalation may be given by nebuliser or powder inhaler, but it is important to be sure of the delivery of drug from the device in order to ascertain that sufficient drug has reached the patient's lung. Lung function is measured 10–15 min after salbutamol inhalation or 30 min after ipratropium bromide inhalation. In order to assess the full reversibility, the patient should not be under influence of any other bronchodilator. The recommendations are to withhold short-acting inhaled drugs, such as the β_2-agonist salbutamol or the anticholinergic agent ipratropium bromide, for ≥4 h; long-acting β_2-agonists (salmeterol and formoterol) for 12 h; and tiotropium for ≥24 h. It is recommended that smoking should be avoided for ≥1 h before the procedure (which should not be relevant for the paediatric population).

In preschool children, assessment of bronchial reversibility has been performed using measures of the respiratory resistance. Techniques such as the interrupter technique (R_{int}) or forced oscillation technique (FOT) are performed during tidal breathing in seated (unsedated) children. The limit for a positive bronchodilator response has been set at 33–35% predicted decrease for R_{int}, or 32% baseline decrease for FOT. In these young children, specific airway resistance (sR_{aw}) measured by plethysmography has been shown to discriminate between healthy and asthmatic children. This technique does not involve any closure of the shutter, but requires that the child stays in a closed bodybox gently maintaining her/his cheeks while breathing at a determined rate. The significant decrease of sR_{aw} for a significant reversibility is not agreed; it has been reported from 25% to 50% of baseline. The tidal breathing parameters (time taken to achieve peak tidal expiratory flow (t_{PTEF})/expiratory time (t_E) ratio) was found to discriminate between children with asthma and healthy children. An increase in t_{PTEF}/t_E of at least two standard deviations of intra-subject variation was used as a criterion for a positive response to bronchodilator, and a highly significant correlation between reversibility and a marker of eosinophil inflammation, serum eosinophil cationic protein, was reported.

The advantage of all these techniques is the absence of sedation, as they are performed during tidal breathing. A disadvantage is the possible discrepancies between reversibility measured in asthmatic children using spirometry and tidal breathing techniques; there is usually a better sensitivity for the latter. This might be due to the fact that intra-individual variability is higher in tidal breathing techniques than for spirometry, or because in some subjects with asthma, deep inspiration during (repeated) spirometry may induce bronchoconstriction (spirometer asthma).

Clinical application of reversibility measurements

In the follow-up of children included in the CAMP study, the consistent presence of a positive bronchodilator response over a 4-year period was associated with persistently lower baseline FEV_1 values as well as a lack of use of inhaled steroids, thus demonstrating the usefulness of bronchodilator reversibility in the monitoring of childhood asthma when baseline lung function is impaired. However, this population of asthmatic children with consistent positive reversibility at each evaluation represented only 5% of the study population. In different studies, the proportion of asthmatic children with a positive reversibility varied up to 28%, depending on the use of controller and on the baseline lung function. Indeed, it has been shown that in children with a medical diagnosis of asthma and baseline spirometry within the normal range, a significant reversibility of FEV_1 was infrequent (5% of cases), challenging the relevance of systematically testing bronchial reversibility in these children if asthma symptom control is good.

In severe, steroid-resistant asthma, FEV_1 was persistently reduced, together with a reduced bronchodilator response despite therapeutic trials with prednisolone. The combination of a lack of bronchodilator response in the presence of persistent reduced FEV_1 may possibly indicate the presence of airway remodelling. The poor prognosis of asthmatic children with low baseline lung function and low reversibility has been further confirmed in prospective studies showing their impaired lung growth in early adulthood.

Finally, in studies looking at the relationships between significant reversibility and the presence of BHR in children, it was shown that positive reversibility was related to the presence of BHR. However, the presence of post-bronchodilator reversibility does not indicate the level of BHR, and its absence does not exclude BHR.

Classification of BHR

Bronchial responsiveness, which reflects the variability in bronchial tone in asthma, may be described as subjective, as demonstrated by the symptoms experienced by the asthmatic child and adolescent, or objective, as measured by procedures in the pulmonary physiological laboratory. BHR is defined as "an increase in the ease and degree of airflow limitations in response to bronchoconstrictor stimuli *in vivo*".

The specific bronchial responsiveness (the bronchial responsiveness to specific inhaled allergens) may be measured by the allergen bronchial provocation test (BPT); however, this is not a test used in children for clinical purposes, but is mainly restricted to assessing occupational disease.

The nonspecific BHR may be measured in several ways. According to the stimulus used to induce the bronchial response, the methods can be classified as direct or indirect. Direct bronchial responsiveness is measured by bronchial provocation with the transmitter methacholine or the mediator histamine, acting directly upon the bronchial and vascular smooth muscle. Indirect methods of measurement of the nonspecific BHR include exercise-induced bronchoconstriction (EIB) (standardised submaximal exercise on a treadmill or free running) and the reaction brought about by inhalation of cold and/or dry air or inhalation of other substances such as AMP or hyperosmolar agents such as mannitol and 4.5% hypertonic saline. In these indirect tests, the reaction, measured as a reduction in lung function, is brought about indirectly through an effect of mediator release. ERS guidelines on methacholine and indirect bronchial challenge testing were published in 2017 and 2018.

Methods of measuring bronchial responsiveness

The quantitative assessment of direct BHR is performed by doubling or quadrupling the concentration/dose of the test substance, usually methacholine.

FEV_1 is measured at baseline and 30 s and 90 s after each inhalation (diluent then increasing doses of bronchoconstrictive agent). The test is stopped when FEV_1 is reduced by ≥20% from baseline or from post-diluent value, and the provocative dose responsible for a 20% baseline (or post-diluent) decrease in FEV_1 (PD_{20}) is determined by interpolating on the semi-logarithmic dose–response curve (figure 1).

An inspiration-triggered nebuliser (dosimeter) is most often used as the delivery device. More recently, aerosol provocation systems connected to the spirometer enable inhalation by controlled tidal ventilation. With these methods, the number of inhalations determines the dose inhaled. Alternatively, a continuous 2-min nebulisation of solutions containing doubling/quadrupling concentrations of the bronchoconstrictive agent is inhaled. Whichever the method used (dosimeter or nebuliser) to deliver increasing doses of bronchoconstrictive agent every 5 min, it is recommended to calculate the cumulative dose inhaled at each step and to plot it against the decrease of FEV_1 to determine the PD_{20} (figure 1).

Another outcome for FEV_1 change during the BPT is the dose–response slope (DRS), which is the percentage fall in FEV_1 divided by the amount of bronchoconstrictive agent inhaled. It is thought that high DRS values truly reflect the intrinsic bronchial hyperreactivity of the subject, mostly determined by genetics, whereas the decrease in PD_{20} (leftward shift of the dose–response curve) reflects extrinsic bronchial hypersensitivity affected by environmental exposure for example, or respiratory infection.

The mannitol BPT is performed by inhaling cumulative doses of mannitol through a powder inhaler, with a 15% reduction in FEV_1 (PD_{15}) as the cut-off.

Exercise testing

Different types of exercise have been standardised for testing EIB: running is more provocative in children than cycling and a duration of 6–8 min gives a greater decrease in post-exercise FEV_1 than shorter or longer exercise periods. It is common to employ

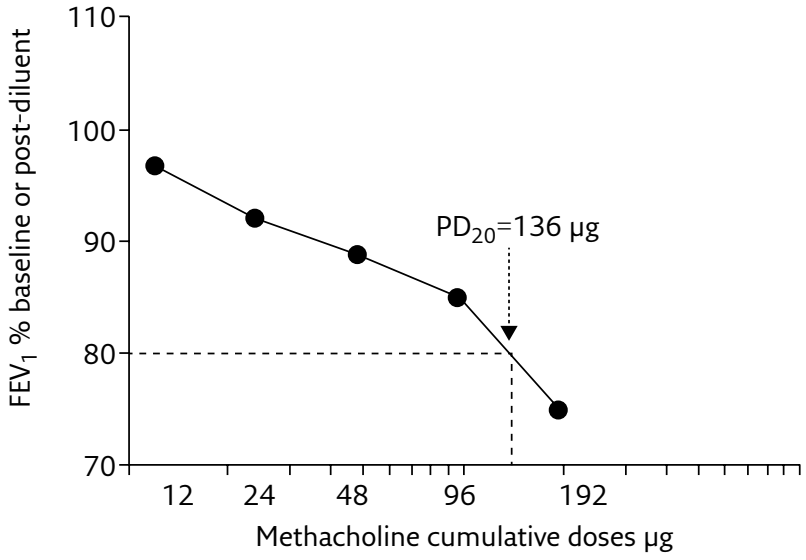

Figure 1. Determination of PD_{20} by interpolation on the logarithmic x-axis.

a treadmill incline of 5.5–10% with rapidly increasing speed until a steady heart rate of ~90–95% of the calculated maximum is reached (within the first 2 min of running) and then to maintain this level of exercise for 4–6 min. In children, heart rate should be followed electronically. The running test should preferably be performed at room temperature (20–22ºC) and a relative humidity of ~40%. Lung function is measured before, immediately after and 3, 6, 10, 15 and 20 min after running. FEV_1 is the most common lung function parameter employed, with a 10% fall in FEV_1 most frequently used for diagnosis of EIB.

Sensitivity of the test can be markedly increased while maintaining specificity by adding an extra stimulus to the exercise test, such as running on a treadmill with inhalation of cold (–20ºC) or dry air.

The exercise test may help to discriminate between EIB and exercise-induced laryngeal obstruction as a differential diagnosis to exercise-induced asthma. With EIB, the dyspnoea is expiratory and occurs after exercise with a simultaneous decrease in FEV_1, whereas for inducible laryngeal obstruction, the dyspnoea is inspiratory, usually audible and occurs at maximum exercise intensity.

Bronchial provocation testing in preschool children

In young children unable to perform reliable and repeated spirometry, other techniques have been proposed to assess bronchoconstriction. They are used in specialised centres with knowledge in these techniques. A 20% decrease in transcutaneous oxygen tension was correlated with a 20% decrease in FEV_1 in 8-year-olds. This threshold is also used in preschool children, whereas a –15% threshold is generally used in infants. The oximetry saturation (S_{pO_2}) is mostly used in infants with a –5-point threshold (or S_{pO_2} <91%) for a positive test. Techniques measuring the respiratory mechanics (R_{int}, FOT) or the sR_{aw} have been used with various thresholds for determining a significant bronchoconstriction (changes from +40% to +80%). In preschool children a –3-point cut-off for S_{pO_2} associated with R_{int} measurement improved the prediction of transcutaneous oxygen tension changes during methacholine challenge.

Safety precautions during bronchial challenges and patient preparation

Bronchial challenges with bronchoconstrictive agents, as well as those using indirect measures such as exercise testing require that the laboratory has the necessary competence and equipment for treating severe bronchoconstriction, including the treatment of anaphylaxis. A physician should be accessible for any emergency during testing and equipment for cardiopulmonary resuscitation should be immediately available. Whereas progressive pharmacological challenge testing with interval spirometry gradually builds up a bronchoconstriction, an exercise test represents a maximal or near-maximal stimulus for bronchoconstriction, requiring special awareness. Preferably, oxygen saturation should be monitored during exercise testing. FEV_1 should be at baseline ≥75% pred and oximetry saturation >94% before exercise testing, whereas FEV_1 should be >60% pred before graded inhalation testing (*e.g.* methacholine test).

The patient should be without the influence of bronchodilators during the BPT, unless the objective is to assess the bronchoprotection provided by the bronchodilator. When the BPT is designed as a diagnostic test, inhaled corticosteroids or anti-leukotriene drugs should not be used before the test. Vigorous exercise should be avoided for 6 h before testing, as there may be a refractory period of up to 4 h for EIB.

Effect of environmental conditions on BHR

Several environmental conditions influence BHR. Cockcroft and co-workers (Coates *et al.*, 2017) documented the link with atopy and allergen exposure by reporting that the late allergic response after allergen bronchial provocation increased direct BHR and that nonspecific BHR increased through exposure to seasonal allergens. Thus, a seasonal allergic sensitisation may contribute to a perennial asthma by increasing the nonspecific BHR through seasonal allergen exposure.

Respiratory viral infections, particularly rhinovirus infections, are the main environmental factor provoking acute asthma during childhood. In addition, respiratory viral infections increase bronchial responsiveness for as long as 3 weeks. Therefore, any child presenting within 3 weeks of a respiratory infection may have BHR due to this recent infection.

Air pollution has been reported to increase BHR, including exposure to diesel exhaust, and living in an industrially polluted area during the first 2 years of life was found to be related to BHR to methacholine at school age. Although not a consistent finding, assessment of BHR in relation to traffic air pollution has shown that children with BHR are particularly sensitive to traffic-related air pollution.

Second-hand smoke is among the most important air pollutants, and an effect upon BHR in children has been reported, although the results are not unequivocal.

Thus, several environmental factors may increase BHR in susceptible subjects and individuals with BHR may be particularly sensitive to environmental exposures. Conversely, for asthmatic subjects, staying in the mountains, with low allergen exposure and low air pollution, leads to improvement in both respiratory symptoms and bronchial responsiveness as measured by methacholine provocation. Measuring bronchial responsiveness, either by direct or indirect means, may thus assess the effect of environmental exposure upon respiratory health.

Epidemiological relationship of BHR to respiratory symptoms and variation with age

Tiffeneau (1955) suggested that BHR was the most important characteristic of asthma. Later studies have shown that BHR is not obligatory for asthma and that different ways of measuring BHR may relate differently to asthma severity.

BHR to direct provocation agents such as methacholine may be present in children without any respiratory symptoms. For example, in non-asthmatic school-aged children, the prevalence of a positive BPT to methacholine has been evaluated at 5–10%. Direct bronchial responsiveness varies throughout the lifespan, decreasing from infancy to early adulthood in population-based birth cohorts. BHR may develop before active asthma symptoms appear. Marked BHR to direct provocation agents during childhood has been related to both asthma and low baseline and post-bronchodilator FEV_1/FVC ratio at 18 years, whereas marked BHR to histamine in infants was not correlated to future BHR to histamine or asthma at 18 years. These results could be explained by the role of bronchial architecture in BHR to direct provocation agents in the first years of life followed by the influence of airway inflammation on direct BHR starting from childhood.

Diagnostic significance of BHR

As BHR may be found both in children with and without asthma, and asthmatic children may not demonstrate BHR, measurement of BHR cannot be a conclusive single tool for the diagnosis of asthma. Specificity of BPTs is generally good, whereas

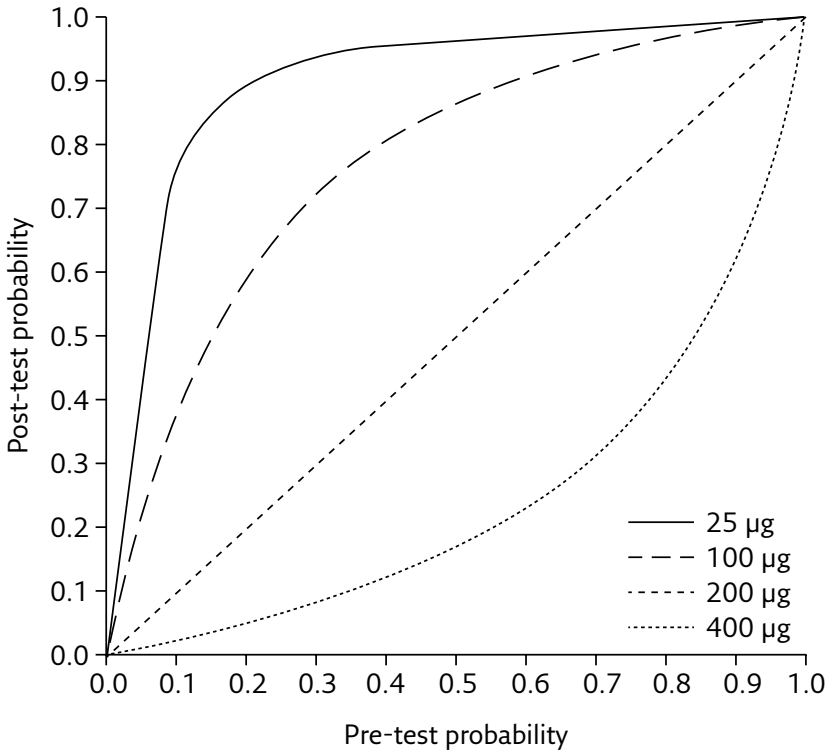

Figure 2. Curves illustrating approximate pre-test and post-test probability of asthma after a methacholine challenge test. The approximations are presented as examples to illustrate the relationships and principles of decision analysis. Reproduced and modified from Crapo et al. *(2000), with permission.*

sensitivity is poor, the latter being improved by using indirect tests in children with bronchial inflammation (atopic children). It is the clinical context (pre-test probability) that will determine the post-test probability of asthma diagnosis (figure 2). BPTs are more useful in children with an intermediate pre-test probability, especially when the test proves negative, allowing the exclusion of asthma diagnosis. In contrast, a positive test in a child with a very low pre-test asthma probability is questionable in terms of consequences.

BPTs are routinely performed for symptoms such as recurrent bronchitis or pulmonary infiltrates, chest tightness, dyspnoea, cough, phlegm production and symptoms during/after exertion. Good predictive factors of BHR in children reported in the literature are night-time or exercise-induced cough, hypereosinophilia and post-bronchodilator increase in FEV_1 of 7–11%, whereas exercise-induced dyspnoea is scarcely related to BHR.

The recent ERS recommendations on interpretation of methacholine challenges gave the following categories of PD_{20}: normal >2 µmol (>400 µg); borderline BHR 0.5–2.0 µmol (100–400 µg); mild BHR 0.13–0.5 µmol (25–100 µg); moderate BHR 0.03–0.13 µmol (6–25 µg); and marked BHR <0.03 µmol (<6 µg).

Effect of therapy on BHR

Anti-inflammatory therapy by inhaled steroids improves BHR in asthma. This may be assessed by repeated measurements of both direct and indirect BHR. However, it has been demonstrated that inhaled steroids improve direct and indirect BHR to different degrees and with different speeds. No effect on BHR was found from a single dose of inhaled steroid. Improvement in methacholine BHR did not occur until after 2–3 months of treatment with inhaled budesonide, but then continued throughout

a 22-month study, suggesting a slower effect of inhaled steroids on BHR than on clinical symptoms. Similarly, inhaled steroids improved outcomes of indirect tests of BHR (AMP, exercise) more quickly than of a direct test (methacholine), which may reflect different properties of nonspecific bronchial responsiveness in asthmatic children (bronchial inflammation for indirect tests and bronchial remodelling for direct tests).

Thus, BHR measurements may be used to monitor treatment effects in asthma, especially in research, as no recommendation on asthma treatment relies on the presence or the level of BHR.

Summary

BHR is a characteristic of asthma in children, but it is not a constant finding.

In children able to perform spirometry, bronchial reversibility is assessed as in adult subjects, but the cut-off of 12% to define a significant bronchodilator response is not sensitive, unless baseline lung function is reduced. In younger children, non-cooperative techniques performed during tidal breathing may help physicians in their diagnosis and therapeutic approaches.

Measurements of BHR are useful tools in routine to support the diagnosis of asthma in children with reasonable pre-test probability. BHR may be used to describe the severity of childhood asthma in research or in epidemiological studies. The two types of nonspecific BPT (direct and indirect) have given insight into the pathophysiological mechanisms of asthma. Indirect testing is most commonly performed using submaximal exercise challenge on a treadmill, and methacholine is the most commonly used direct challenge. The latter is more sensitive but less specific than the former; for example in the absence of BHR detected by methacholine test performed for nonspecific clinical symptoms, asthma can be ruled out, whereas many respiratory conditions (other than asthma) are associated with methacholine BHR. As for reversibility, non-cooperative techniques may be used to assess BHR in young children unable to perform spirometry, but in order to achieve this it is often necessary to send the child to a specialised centre.

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Cardiopulmonary exercise testing

Helge Hebestreit and Thomas Radtke

Dynamic muscular exercise raises metabolic demands over requirements at rest, thereby triggering an increase in $\dot{V}_E$, oxygen uptake ($\dot{V}_{O_2}$), carbon dioxide output ($\dot{V}_{CO_2}$), cardiac output, systolic blood pressure, *etc*. Thus, using physical exercise as "stressor", limitations of the respiratory, cardiovascular and muscular systems might be identified which are not evident at rest. In particular, the distinction between different pathophysiological causes of an abnormal response to exercise and/or a reduced exercise capacity and the demarcation from deconditioning is key information from cardiopulmonary exercise testing (CPET) which cannot be completely obtained during field testing or laboratory testing without gas exchange measurements.

Full CPET combines the assessment of ventilation, gas exchange and cardiovascular variables during a standardised incremental exercise challenge, usually performed on a cycle ergometer or a treadmill. CPET has become a valuable tool for clinical assessment and is used increasingly in paediatric respiratory research.

Paediatric health conditions and symptoms in which CPET is often performed include CF, PCD, premature birth with or without BPD, (suspected) restrictive lung disease, scoliosis, and dyspnoea with exercise.

Key points

- Cardiopulmonary exercise testing (CPET) is a valuable diagnostic tool in the paediatric population.
- CPET can detect adverse reactions to exercise and distinguish between respiratory, cardiovascular and peripheral (muscular, metabolic) limitations.
- A standardised CPET protocol has been established for assessing children, adolescents and adults with chronic respiratory diseases.
- Large normative data sets for CPET outcome variables covering different ethnicities are still needed.

Indications for CPET

There are many potential reasons to perform CPET in children. Very often, CPET is used to answer more than one question. Some typical indications for CPET are:

- To assess unclear symptoms associated with exercise/detect exercise-related adverse reactions
- To determine exercise capacity and compare to normal values
- To identify causes for exercise limitations (*i.e.* ventilatory, cardiovascular, muscular, deconditioning)
- To plan a physical training programme
- To monitor the effects of an (exercise) intervention
- To convince the child, parents/caregivers and/or physician that exercise is safe
- To motivate the child to be physically active
- To obtain prognostic information

Contraindications to CPET

When ordering CPET, the expected information from the test needs to be balanced with perceived risks. In general, CPET should not be scheduled when the patient's health is temporarily compromised or a very severe health condition exists. Table 1 summarises the most common contraindications for CPET in children. A more comprehensive overview on contraindications in the paediatric age group is available elsewhere.

Testing modalities: cycle ergometer or treadmill

A cycle ergometer or a treadmill are typically used for CPET. Each has advantages and disadvantages and the "optimal" testing modality depends on the purpose of the test and the child's anthropometric characteristics. The cycle ergometer is cheaper to purchase, requires less space and staff, and tests are usually associated with fewer motion artifacts and better quality recordings of ECG, blood pressure and pulse oximetry compared with treadmill tests. Furthermore, some children feel more comfortable to give a maximal effort on the cycle ergometer. However,

Table 1. Common contraindications to CPET

Respiratory disease	Cardiovascular disease	Other conditions
Uncontrolled asthma	Acute or chronic cardiac inflammatory or infectious disease	Acute non-cardiopulmonary disease that may increase the risk of exercise (*e.g.* infections, thyrotoxicosis, renal failure)
Massive haemoptysis	Uncontrolled heart failure	Uncontrolled metabolic disease (*e.g.* diabetes mellitus)
Large pneumothorax	Symptomatic or haemodynamically uncontrolled cardiac arrhythmias	Mental impairment with inability to cooperate
Pulmonary oedema	Symptomatic severe aortic or mitral valve stenosis	(Electrolyte abnormalities)
Pulmonary arterial obstructive disease	Hypertrophic cardiomyopathy with syncope	(Orthopaedic conditions that compromise exercise performance)
(Significant pulmonary hypertension)	Thrombosis of lower extremities	
	(Severe arterial hypertension)	

Relative contraindications are presented in parentheses.

a certain body height (usually ~120 cm) is required for testing children on a cycle ergometer, and performance is often limited by quadriceps muscle strength, which is a further disadvantage for testing small children. Walking and running are more natural modes of exercise compared to cycling for many children. A treadmill can accommodate even small children and walking/running on a treadmill involves more muscle groups during exercise, thereby often inducing a higher $\dot{V}_E$, $\dot{V}_{O_2}$ and heart rate (HR) at peak exercise. Successful CPET testing on a treadmill has been reported in children as young as 3 years, provided that the treadmill allows for very low speeds.

Ideally, CPET is performed on ergometers that are specifically designed for testing children. Alternatively, special equipment such as shorter crank arms can be used (see later section of this chapter "Preparation for CPET").

Face mask or mouthpiece plus nose clip

For CPET in children, both devices (face mask and mouthpiece plus nose clip) have been used successfully in both clinical and research settings. In comparison to using a face mask, the mouthpiece plus nose clip assembly usually has a smaller dead space and air leaks can be detected easily. Even if equipment-related dead space has only a negligible impact on respiratory measurements in larger children and adolescents, it may affect ventilatory responses in small children. When using a mouthpiece plus nose clip, swallowing is more difficult, and discomfort may arise from a dry mouth. Furthermore, in children with a small nose, the nose clip may not remain in place reliably during the test. In contrast, the face mask allows swallowing during the test and even verbal communication (although this is not recommended), but is more difficult to fit tightly, even if several different small sizes are available. Finally, children may be afraid of one or the other of the devices, so individual preferences need to be taken into account. In any case, the dead space of the device used must be entered correctly in the metabolic cart's software.

Infection control issues

As in pulmonary function testing, infection control is essential in CPET. Proper disinfection and cleaning of the exercise laboratory and all equipment must follow local guidelines and manufacturer's recommendations. If disposable bacterial filters are used, as in spirometry, the "dead space" entry in the software of the metabolic cart must be adjusted.

Preparation for CPET

Exercise testing in the paediatric age group presents its own unique challenges. The examiner should plan sufficient time for instructions and explanations and to create a child-friendly environment.

Subject

The child should come to the exercise laboratory in light exercise clothing and flat closed shoes (no platform shoes, no high heels, no slippers). Girls may wear a bikini top. The last meal should have been ~2 h prior to the test and the last intense exercise ⩾24 h ago. The reason(s) for the test and testing-related procedures are explained to the child and the parents/caregivers in detail. In many children, familiarisation with the equipment during a prior visit or some time before the test starts is very helpful (*e.g.* practice cycling at steady cadence).

Equipment

If a cycle ergometer is used, the seat height is adjusted so that the child's knee is bent not more than 90º at maximal flexion and not fully stretched at maximal extension. When testing small children, the seat needs to be adjusted in the horizontal position in addition to the vertical axis and the crank arms should be shortened. For many commercial cycle ergometers, accessories for paediatric testing are available.

Quality control

Regular quality control is indispensable to obtain accurate and reliable testing results. Different levels of quality control procedures have been suggested and include 1) the manufacturer's recommended calibration of the flow and gas analysers and ergometer; 2) the use of a metabolic simulator for troubleshooting and system checks; and 3) the biological and physiological validation of gas-exchange systems by healthy laboratory personnel. Details on quality control procedures are summarised in Porszasz *et al.* (2018).

CPET protocols

Numerous testing protocols are available both for cycle ergometry (*e.g.* Godfrey, James and McMaster protocols) and treadmill (*e.g.* Bruce, Balke and Naughton protocols) exercise testing. In general, a ramp protocol or an incremental protocol with stages of maximal 1-min duration has been recommended by the European Respiratory Society (ERS). Figure 1 provides a schematic representation of a test protocol including a resting phase, unloaded phase, incremental phase and recovery phase. The target duration of the incremental exercise phase is ~10±2 min. A frequently used cycle ergometer protocol in paediatric respiratory diseases is the Godfrey cycle protocol, a continuous incremental protocol with increments of 10–20 W·min^{-1}, depending on patient's height and pulmonary function.

The most commonly used treadmill protocol in the paediatric population is the (modified) Bruce protocol, a 2- or 3-min stepwise protocol. The major disadvantages of this protocol are the large between-stage increments that often lead to early test termination and the difficulties of analysing submaximal exercise responses

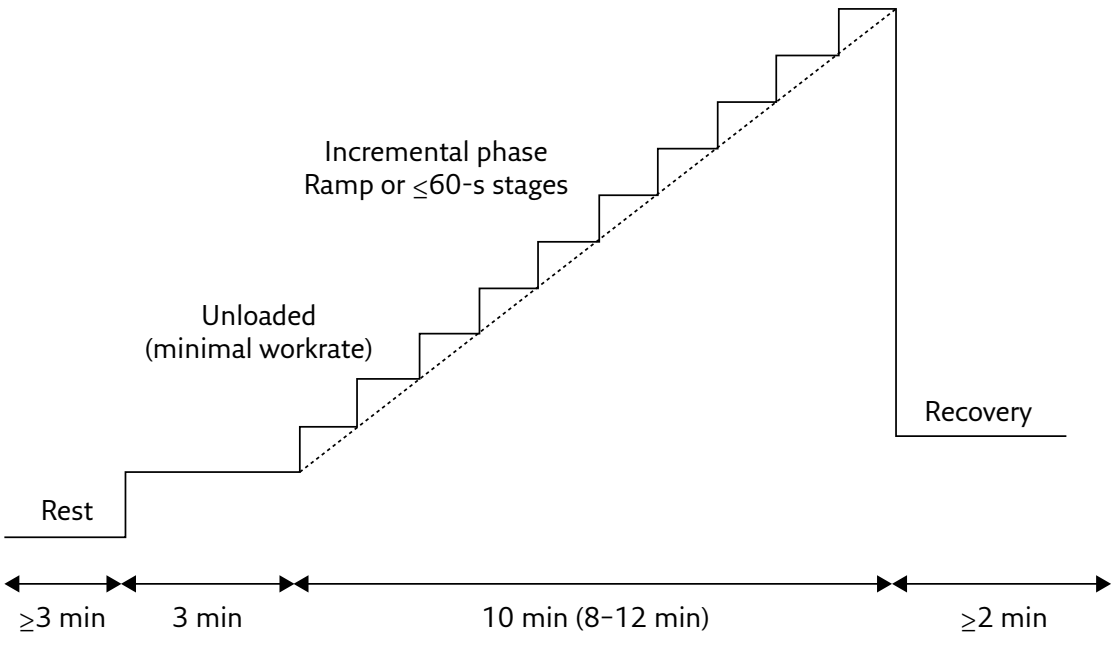

Figure 1. Schematic exercise protocol for CPET.

(*e.g.* non-even changes in respiratory data over time complicate determination of anaerobic threshold).

Interpretation of CPET data

Interpretation of CPET is based on an integrative analysis of several outcomes and both graphical and tabular presentations. Typical CPET variables and their explanations are given in table 2. Usually, data are first assessed by reviewing a so-called nine-panel plot (figure 2). Nowadays, different versions of the nine-panel plot are available and can be further customised in modern metabolic carts, allowing the panels to be replaced according to the examiner's preferences. In addition to data collected during CPET, normal values and pulmonary function data can be visualised within the corresponding plots. While each panel tells a different view of the same story, panel c (and panel e) are relevant to assess performance. To determine causes of exercise limitations, ventilatory limitations/ventilation–perfusion mismatch are detected best in panels a, d, f, g and i; cardiovascular limitations in panels b and e; and metabolic abnormalities in panel h.

Peak exercise data can only be assessed if a maximal effort was reached. Peak exercise data are calculated as average over 30 s at the time of the highest $\dot{V}'_{O_2}$ during the test and related to reference data. However, some important outcomes are based on submaximal data and do not require a maximal effort.

Outcomes assessable even if no maximal effort was reached (such as anaerobic threshold)

The relationship between $\dot{V}'_E$ and $\dot{V}'_{CO_2}$ is linear during incremental exercise up to the "respiratory compensation point" (RCP) at which $\dot{V}'_E$ increases out of proportion of $\dot{V}'_{CO_2}$ (figure 2d, last data points). The slope of the $\dot{V}'_E/\dot{V}'_{CO_2}$ relationship below the

Table 2. Alphabetic list of variables typically assessed during CPET and reported

Abbreviated variables	Commonly used units	Explanation
etP_{O_2} or P_{ETO_2} [#]	mmHg or kPa	End-tidal oxygen tension
etP_{CO_2} or P_{ETCO_2} [#]	mmHg or kPa	End-tidal carbon dioxide tension
HR	beats·min^{-1}	Heart rate
RER		Respiratory exchange ratio (quotient of carbon dioxide output over oxygen uptake)
S_{pO_2}	%	Oxygen saturation measured by pulse oximetry
VAT	%$\dot{V}'_{O_2peak}$	Ventilatory anaerobic threshold
$\dot{V}'_E$	L·min^{-1}	Minute ventilation
$\dot{V}'_{O_2}$	L·min^{-1}	Oxygen uptake
$\dot{V}'_{CO_2}$	L·min^{-1}	Carbon dioxide output
$\dot{V}'_E/\dot{V}'_{O_2}$		Ventilatory equivalent for oxygen, a measure of ventilatory efficiency
$\dot{V}'_E/\dot{V}'_{CO_2}$		Ventilatory equivalent for carbon dioxide, a measure of ventilatory efficiency
W_{peak}		Peak work rate

[#]: both abbreviations are frequently used.

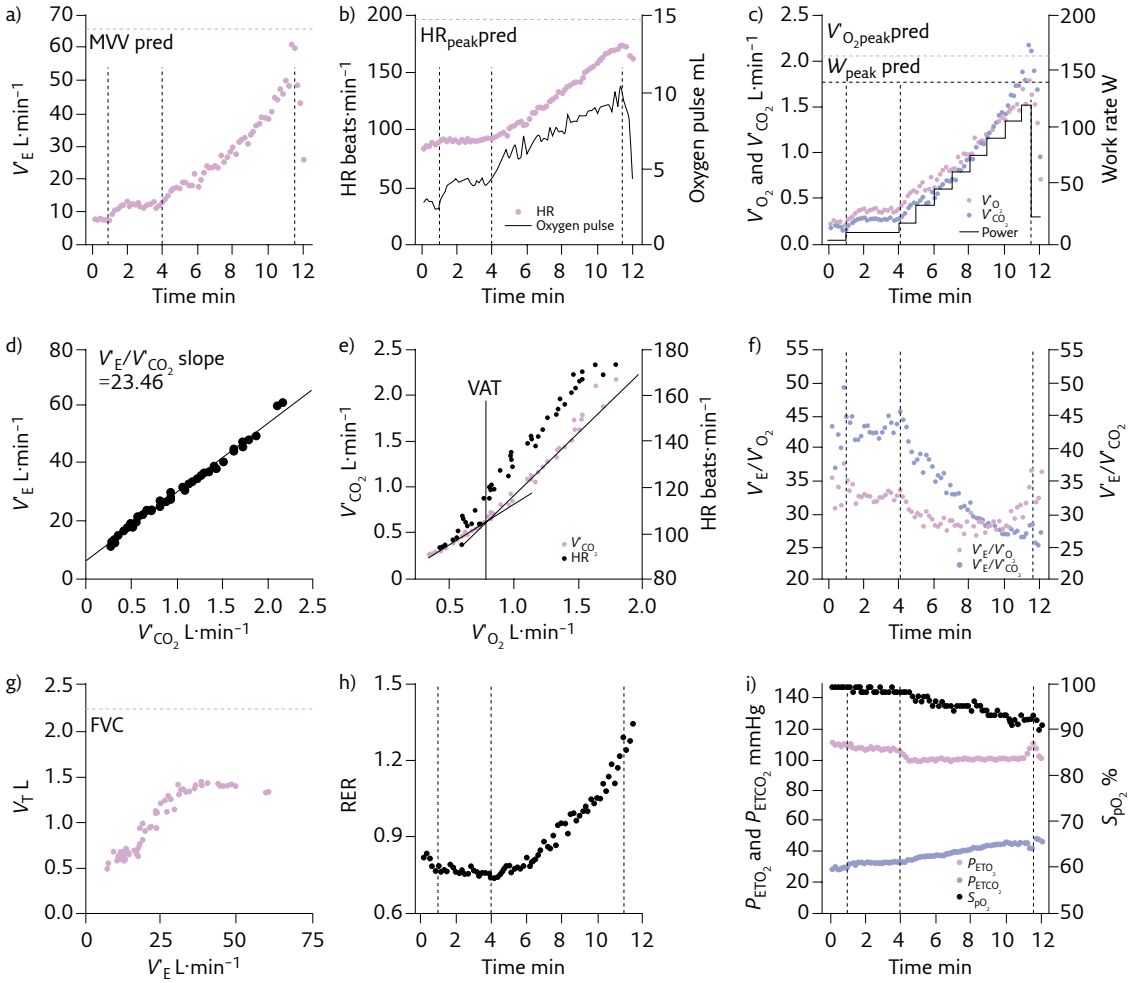

Figure 2. Nine-panel plot of CPET data in a 17-year-old female with CF and an FEV_1 of 39% predicted. a) Increase in V'_E with increasing work rate (estimated maximal voluntary ventilation (MVV) is indicated by a dotted line); b) increase in heart rate and oxygen pulse; c) increase in work rate and oxygen uptake (predicted peak values are shown by dotted lines); d) relationship between carbon dioxide output and V'_E; e) relationship between oxygen uptake and carbon dioxide output (the ventilatory anaerobic threshold is indicated); f) changes in the ventilator equivalents for oxygen uptake and carbon dioxide output during the test; g) relationship between V'_E and tidal volume (VT) (the FVC is indicated by a dotted line); h) changes of respiratory exchange ratio (RER) during the test; i) changes of oxygen saturation, and end tidal pressures of oxygen and carbon dioxide (P_{ETO_2} and P_{ETCO_2}, respectively). Where time is depicted, the time points indicated by dotted lines are start of unloaded (minimal work rate) exercise, incremental phase and start of recovery phase. Details of which panels (a–i) are useful for which assessments are given in the main text. There was a good effort during the test: RER at peak exercise was 1.22 (panel h); rating of perceived exertion at the end of exercise was 9 on a 0–10 scale; dyspnoea was rated 10. There is evidence for respiratory limitation with peak V'_E reaching 91% of predicted MVV (panel a) and S_{pO_2} dropping by >4% from 99% at rest to 92% at peak exercise (panel i). Peak HR was lower than expected (panel b) and exercise capacity was slightly reduced, with a peak V'_{O_2} of 81% pred and a peak work rate of 78% pred (panel c).

RCP holds important information when testing adults (*e.g.* elevated slope in cardiac insufficiency, low slope in some patients with hypercapnia). In children, a low slope may indicate respiratory limitations or dysfunctional regulation of breathing (high carbon dioxide tension set-point).

The term "anaerobic threshold" describes the point during incremental exercise when lactate starts to accumulate. Anaerobic threshold is often also referred to

as "first threshold" or "onset of blood lactate accumulation (OBLA)". At anaerobic threshold, a disproportional increase in ventilation occurs to compensate for the developing metabolic acidosis. These adjustments can be detected in gas exchange measurements (figure 2e) and allow the reliable assessment of anaerobic threshold determined from lactate measurements. If gas exchange data are plotted over $\dot{V}'_{O_2}$, a reliable detection of the anaerobic threshold is possible in >70% of relatively small children. For detection of anaerobic threshold from gas exchange measurements, data collected beyond the RCP are discarded from analysis. Then, the change in slope of the $\dot{V}'_{CO_2}/\dot{V}'_{O_2}$ relationship is usually assessed first for the detection of anaerobic threshold (V-slope method) and the anaerobic threshold detected is confirmed by simultaneous changes in RER and $\dot{V}'_E/\dot{V}'_{O_2}$ trajectory without a concurrent change in $\dot{V}'_E/\dot{V}'_{CO_2}$. $\dot{V}'_{O_2}$ at anaerobic threshold relative to $\dot{V}'_{O_2peak}$ is typically somewhat higher in children than in adults and averages ~65–70% before the age of 14 years.

Defining a maximal effort

Different criteria have been proposed to determine a maximal effort in children in the past. The ERS Working Group on Standardisation of Exercise Testing in Chronic Lung Diseases has agreed on the following indicators for children (at least one criterion must be met): 1) levelling off of $\dot{V}'_{O_2}$ despite a further increase in work rate; 2) a RER >1.05; 3) a peak HR ≥195 beats·min^{-1} for cycle ergometry and 200 beats·min^{-1} for treadmill ergometry; 4) $\dot{V}'_{Epeak}$/MVV ≥85% predicted; 5) a decrease in inspiratory capacity >150 mL during exercise; or 6) $\dot{V}'_{O_2peak}$ ≥100% pred. To verify whether "true" $\dot{V}'_{O_2max}$ has been achieved, supramaximal verification testing has been used in research settings in paediatrics. However, there is ongoing debate about the usefulness and practicability of such a testing procedure in clinical populations.

Outcomes determined at peak exercise

Numerous outcomes for the interpretation of normal (or abnormal) exercise responses are available from a CPET report. $\dot{V}'_{O_2peak}$ is considered the single best parameter of aerobic fitness and is used in addition to peak work rate achieved (cycle ergometry only) to interpret a person's exercise capacity. Reduced exercise capacity can be of multifactorial origin and the consequence of either ventilatory, cardiovascular, peripheral (muscular) limitation or deconditioning, or a combination thereof. Deconditioning is typically reflected by reduced $\dot{V}'_{O_2peak}$ and an early anaerobic threshold, with a normal peak HR, peak S_{pO_2} and sufficient breathing reserve. Ventilatory limitation to exercise is characterised by a reduced breathing reserve (*i.e.* $\dot{V}'_{Epeak}$/MVV >85% pred). In lung disease, ventilatory constraints to exercise are typically associated with reduced $\dot{V}'_{O_2peak}$ and peak HR, while S_{pO_2} at peak exercise can be normal or may be reduced indicative of gas exchange limitation and ventilation/perfusion mismatch. Cardiovascular limitations are associated with a low peak HR and oxygen pulse ($\dot{V}'_{O_2}$/HR), the latter being used as a surrogate marker for stroke volume. Children with mild-to-moderate lung disease are usually not limited by cardiovascular factors. Predominant reasons for exercise limitation in children with chronic respiratory diseases are of ventilatory origin and/or deconditioning due to lack of physical activity.

Reference values

Numerous different reference equations are available for the interpretation of the normality of submaximal and maximal exercise responses and maximal aerobic exercise capacity. A recent systematic review on CPET reference values in the paediatric population including 34 studies reveals substantial heterogeneity across

studies with respect to exercise testing protocols and methods to adjust for body size. To date, there is no single best reference equation to interpret a person's aerobic exercise capacity (*e.g.* $\dot{V}'_{O_2peak}$). The choice of reference equation depends on several factors such as the population under study, equipment and testing protocols used to collect CPET data. Importantly, growth and maturation largely impact on $\dot{V}'_{O_2peak}$, which shows a nonlinear dependence with age. In the paediatric population, the use of z-scores, a standardised value that is independent of age, body composition and pubertal status, *etc.*, may be optimal. Frequently used equations to predict $\dot{V}'_{O_2peak}$ and other CPET variables are summarised elsewhere or have recently been published. Reference values for submaximal data such as the $\dot{V}'_E/\dot{V}'_{CO_2}$ slope, $\dot{V}'_{O_2}$ at the anaerobic threshold or the $\dot{V}'_{O_2}$/work rate slope are also available.

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Blood gas assessment and oximetry

Paola Papoff, Corrado Moretti and Raffaella Nenna

A blood specimen for analysis of arterial blood gases helps to assess the following:

- Oxygenation
- Acid–base equilibrium
- Ventilatory function
- Metabolic function
- Electrolyte and metabolite balance (because pH changes affect electrolyte blood levels, their evaluation should be part of the acid–base equilibrium assessment)

The principles underlying traditional arterial blood gas measurement are based on the electrochemical interaction between respiratory gases and selected metals within electrodes. Whereas P_{aO_2}, P_{aCO_2} and pH are measured directly, other variables, such as bicarbonate (HCO_3^-), base excess and S_{aO_2} are computed using well-defined equations.

Assessing oxygenation

The oxygenation status of the patient is judged by the P_{aO_2}. The P_{aO_2} depends on inspired oxygen concentration (fraction of inspired oxygen (F_{IO_2})), alveolar oxygen tension (P_{AO_2}), alveolar gas exchange, pulmonary and systemic circulation, cardiac output, local perfusion and, to a lesser extent, the uptake and utilisation of oxygen by tissues. Therefore, assessing oxygenation should include all these parameters.

P_{aO_2} and S_{aO_2}

Oxygen in the arterial blood is present as dissolved oxygen (P_{aO_2}, expressed in mmHg or kPa (1 mmHg=0.13 kPa)) and oxygen bound to haemoglobin (S_{aO_2}, expressed

Key points

- Acid–base disturbances can be classified using a three-step systematic approach (pH/P_{aCO_2}/HCO_3^-).
- If pH is abnormal, determine if acidaemia or alkalaemia.
- If the measured pH and P_{aCO_2} are both abnormal, assess the direction of change (if they change in opposite directions, the primary acid–base abnormality is respiratory; otherwise, it is metabolic).
- When an acid–base imbalance is diagnosed look for compensation or mixed disorders.

in %). Although P_{aO_2} represents a very small proportion of oxygen availability, P_{aO_2} is a very sensitive, but nonspecific (*e.g.* pulmonary embolism) indicator of alveolar gas exchange impairment. Estimated normal P_{aO_2} is between 90 and 100 mmHg (12–13 kPa). P_{aO_2} declines progressively with age; the P_{aO_2} of many individuals aged >80 years is ~70–75 mmHg (9.3–10 kPa). Overall, a P_{aO_2} <80 mmHg (10.7 kPa) is considered to be mild hypoxaemia and a P_{aO_2} ≤60 mmHg (8 kPa) is the cut-off for the institution of oxygen therapy. P_{aO_2} is a major determinant of S_{aO_2}, and their relationship is the well-known sigmoid-shaped oxygen dissociation curve. The oxygen dissociation curve, and hence, the S_{aO_2} for a given P_{aO_2}, is affected by P_{aCO_2}, body temperature, pH and other factors. As long as the P_{aO_2} is >60 mmHg (8 kPa), S_{aO_2} remains >90%, in the plateau region, and thus, there is little change in of S_{aO_2} at P_{aO_2} variations. If P_{aO_2} is <60 mmHg (8 kPa), the oxyhaemoglobin dissociation curve becomes very steep (P_{aO_2} 60–20 mmHg, or 8–2.7 kPa), and this may lead to a significant reduction in S_{aO_2} and impaired oxygen delivery to tissues.

S_{aO_2} is more often assessed peripherally, as S_{pO_2}. S_{pO_2} is a good indicator of S_{aO_2}, although erroneous readings may occur in cases of patient motion, bright light on the probe or malposition, poor perfusion, high carboxyhaemoglobin, high methaemoglobin and severe anaemia.

Rule of five ($5\times F_{IO_2}\times 100$)

In a patient with normal lungs, breathing room air, the measured P_{aO_2} (mmHg) should equal $5\times F_{IO_2}\times 100$ ($5\times 21=105$). If the F_{IO_2} is 0.40 the patient will have a P_{aO_2} of $5\times 40=200$ mmHg (26.7 kPa). This rule is especially useful in the operating theatre, in patients with normal lungs, in whom a certain degree of hypoxaemia is present if the P_{aO_2} is less than $5\times F_{IO_2}\times 100$.

Alveolar–arterial oxygen gradient

The alveolar–arterial oxygen gradient (A–aD_{O_2} or $P_{A\text{-}aO_2}$) (*i.e.* difference between P_{AO_2} and P_{aO_2}) is one way to investigate significant intrapulmonary shunt. P_{aO_2} is dependent on alveolar oxygen pressure (P_{AO_2}). At atmospheric pressure ($P_{atm}=760$ mmHg, 101.3 kPa) the P_{AO_2} is lower than the partial pressure of oxygen in the atmosphere. In fact, the inspired air is humidified (P_{H_2O}=water vapour pressure at 37ºC=47 mmHg) and, so, $P_{AO_2}=(760–47)\times F_{IO_2}=713$ mmHg$\times 0.21=150$ mmHg (20 kPa). In addition, when humidified inspired air mixes with the carbon dioxide (CO_2) in the alveoli, the P_{AO_2} further decreases to 100 mmHg (13.3 kPa). The P_{AO_2} is a little higher than the P_{aO_2}, because R (the respiratory quotient) is 0.8 (more oxygen is consumed compared to CO_2 production, *i.e.* for every 10 molecules of O_2 leaving the alveoli, eight molecules of CO_2 enter the alveoli from blood). Thus, at sea level, on room air, $P_{AO_2}–P_{aO_2}=(F_{IO_2}(P_{atm}–P_{H_2O})–P_{aCO_2}/R)–P_{aO_2}=((0.21\times 713)–(40/0.8))–95=(150–50)–95=5$ mmHg.

In normal lungs, the A–aD_{O_2} is <12–15 mmHg (<1.6–2 kPa) in room air and <70 mmHg (<9.3 kPa) in 100% oxygen. A high A–aD_{O_2} implies a defect in oxygen diffusion across the alveolar–capillary membrane or a defect in ventilation–perfusion ratio or right-to-left shunting. Conversely, if the A–aD_{O_2} is not increased, and the P_{aO_2} is low, lack of oxygenation is due to hypoventilation.

Rule of 120

The "120 rule" is a simpler version of the A–aD_{O_2} gradient. In a normal patient, the sum of P_{aO_2} and P_{aCO_2} should be 140 mmHg±10. If it is <120 mmHg (<16 kPa), the patient has venous admixture (lower values being worse).

P_{aO_2}/F_{IO_2} ratio

The ratio between the P_{aO_2} and the F_{IO_2} (P_{aO_2}/F_{IO_2} ratio or *P/F* ratio) is a useful index for determining the presence and severity of impaired alveolar gas exchange. A patient who has a normal P_{aO_2} of ~100 mmHg (~13.3 kPa) while breathing room air should have a P_{aO_2}/F_{IO_2} ratio of 100/0.21≈480 mmHg (64 kPa). Patients with acute lung injury or acute respiratory distress syndrome have values <300 mmHg (<40 kPa) and <200 mmHg (<26.6 kPa), respectively, in addition to other required diagnostic criteria. The ratio has been also used to quantify pulmonary gas exchange during oxygen treatment. For this calculation the percentage of oxygen being administered must be entered in the blood gas analyser.

P_{aO_2}/P_{AO_2} ratio

The P_{aO_2}/P_{AO_2} ratio offers better accuracy in determining pulmonary shunting, diffusion defects and ventilation–perfusion mismatching than the P_{aO_2}/F_{IO_2} ratio. In fact, it is less influenced by F_{IO_2} and P_{aCO_2}.

Assessing acid–base equilibrium

A systematic approach for interpretation of acid–base equilibrium is necessary. This is usually assessed using a systematic sequence of questions, as follows.

- Is pH normal? (compare with normal range)
  - No: determine if acidaemia, alkalaemia
  - Yes: normal state or compensated or mixed disorders
- Is P_{aCO_2} normal? (compare with normal range)
  - No: if the measured pH and P_{aCO_2} are both abnormal, assess the direction of change (if they change in opposite directions, the primary acid–base abnormality is respiratory; otherwise, it is metabolic)
  - Yes: check with pH (normal state or lack of compensation for a metabolic disorder)
- Are bicarbonate and base excess normal?
  - No: if the measured pH and HCO_3^- are both abnormal, assess the direction of change (if they change in the same direction, the primary acid–base abnormality is metabolic; otherwise, it is respiratory)
  - Yes: check with pH (normal state or lack of compensation for a respiratory disorder)
- Is compensation occurring?
  - Calculate the degree of compensation; if compensation fails to reach the predicted level within the expected time, look for an additional underlying disorder (mixed acid–base disorders)
- Is there a mixed disorder?
  - Look for an excessive change in pH for a single type of disorder (respiratory or metabolic)

Assessing pH

pH is a scale for measuring acidity or alkalinity ranging from 0 to 10. Normally, blood is slightly alkaline (pH 7.4) with an acceptable range of 7.35–7.45. If the pH is <7.35, the patient is acidaemic; if it is >7.45, the patient is alkalaemic. Acidosis and alkalosis, the processes leading to these states, are either respiratory or metabolic. Significant deviations in pH from normal ranges rapidly become life-threatening; Marieb *et al.* (2007) suggested that "absolute blood pH limits for life" are 7.0–7.8, although patients may survive if isolated samples exceed this range. Both CO_2 and HCO_3^- affect

the pH. To quantify better the relationship between pH, CO_2 and HCO_3^-, Henderson and Hasselbalch developed the following formula demonstrating that the ratio of HCO_3^- and CO_2, rather than the absolute values, determines pH:

$$pH = 6.1 + \log([HCO_3^-] / (0.03 \times P_{aCO_2}))$$

"Normal" pH can be found under normal conditions or in a compensated state or in mixed acid–base abnormalities.

Assessing ventilation

Air normally contains CO_2 (0.04%); blood CO_2 is a normal metabolic waste product. CO_2 in the arterial blood is present as CO_2 physically dissolved (5%), CO_2 dissolved as bicarbonate ion (90%) and CO_2 combined with haemoglobin as carbamino compound (5%). Normal P_{aCO_2} ranges from 35 to 45 mmHg (4.7 to 6 kPa). Blood level depends on clearance, which in turn depends on ventilation. Small tidal volumes, low frequencies or obstructed airways lead to reduced CO_2 clearance and therefore high blood CO_2 ("acute respiratory acidosis"). The body's initial compensatory response is limited (table 1). It is estimated that, in the acute phase, the $[HCO_3^-]$ rises by 1 mmol·L^{-1} for every 10-mmHg increase in P_{aCO_2} above its reference value of 40 mmHg (5.3 kPa). For example, if P_{aCO_2} has risen acutely from 40 mmHg (5.3 kPa) to 70 mmHg (9.3 kPa), this increase of 3×10 mmHg (*i.e.* 70–40=30 mmHg rise) results in an increase of plasma bicarbonate by 1×3 from its reference value of 25 mmol·L^{-1} (*i.e.* 28 mmol·L^{-1}). Consequently, we would predict that if the plasma level is below this value there is a concomitant metabolic acidosis. In addition, for every increase in P_{aCO_2} of 20 mmHg (2.7 kPa) above normal value, the pH falls by 0.1. When respiratory acidosis persists beyond 6–12 h (usually 36–72 h), the kidneys generate bicarbonate by excreting ammonium (NH_4^+) with chloride ions in the urine and, in this process, HCO_3^- is added to the plasma, leading to the hypochloraemic alkalosis. As the renal compensatory response ensues (for every 10-mmHg increase in P_{aCO_2}, $[HCO_3^-]$ increases by 4 mmol·L^{-1}), the pH returns towards the normal value, and

Table 1. Compensatory response to a metabolic or respiratory disorder

	Expected compensation
Metabolic acidosis	P_{aCO_2} mmHg=1.5 $[HCO_3^-]$+8±2 (Winter's formula)
Metabolic alkalosis	P_{aCO_2} mmHg=0.7 $[HCO_3^-]$+20±1.5
Acute respiratory acidosis	HCO_3^- will increase by 1 mmol·L^{-1} for each 10-mmHg (1.3-kPa) rise in P_{aCO_2} above 40 mmHg or HCO_3^- will increase by ≈1 mmol·L^{-1} for each 1-kPa increase in P_{aCO_2}
Chronic respiratory acidosis	HCO_3^- will increase by 4 mmol·L^{-1} for each 10-mmHg (1.3-kPa) rise in P_{aCO_2} above 40 mmHg or HCO_3^- will increase by 3 mmol·L^{-1} for each 1-kPa increase in P_{aCO_2}
Acute respiratory alkalosis	HCO_3^- will decrease by 2 mmol·L^{-1} for each 10-mmHg (1.3-kPa) decrease in P_{aCO_2} below 40 mmHg
Chronic respiratory alkalosis	HCO_3^- will decrease by 5 mmol·L^{-1} for each 10-mmHg (1.3-kPa) decrease in P_{aCO_2} below 40 mmHg

Data from Dzierba *et al.* (2011).

the condition is now a "chronic respiratory acidosis". For example, if P_{aCO_2} has risen from 40 mmHg to 50 mmHg, this increase of 1×10 mmHg (*i.e.* 50–40=10 mmHg rise) results in a rise of plasma bicarbonate by 1×4 from its reference value of 25 mmol·L^{-1} (*i.e.* 29 mmol·L^{-1}). Metabolic compensation of respiratory acidosis takes time to reverse. Therefore, rapidly correcting chronic respiratory acidosis will result in a transitory metabolic alkalosis.

P_{aCO_2} may also be elevated in "compensated metabolic alkalosis", as a consequence of hypoventilation.

In contrast, hyperventilation (*e.g.* with pain, anxiety, central nervous system lesions) leads to increased CO_2 removal and then to a decreased P_{aCO_2} and an elevated pH ("respiratory alkalosis"). Uncompensated respiratory alkalosis is associated with an increased blood pH, and a modestly decreased HCO_3^- concentration. Renal compensation for respiratory alkalosis involves a decrease in HCO_3^- reabsorption. In the acute phase, the [HCO_3^-] drops by 2.5 mmol·L^{-1} for every 10-mmHg decrease in P_{aCO_2} above its reference value of 40 mmHg (5.3 kPa), whereas over the next few days for every 10-mmHg (1.3 kPa) decrease in P_{aCO_2}, [HCO_3^-] decreases by 3–4 mmol·L^{-1} ("compensated respiratory alkalosis"). Low P_{aCO_2} levels can be also found in "compensated metabolic acidosis" (table 1) consequent to hyperventilation. The minimum level of P_{aCO_2} that can usually be attained is ~10 mmHg (~1.3 kPa).

Compensation for respiratory or metabolic disorders

Because the body attempts to maintain blood pH at 7.40, respiratory or metabolic disorders normally trigger an equal counterbalancing effect in the other systems (table 1 lists formulae used for estimating the compensation level). Under these circumstances, the respiratory and metabolic components are both abnormal, but pH is almost normal (figure 1). The body never overcompensates, and may even fail to reach complete compensation. Failure to reach the predicted compensation level should lead the clinician to suspect a mixed disorder.

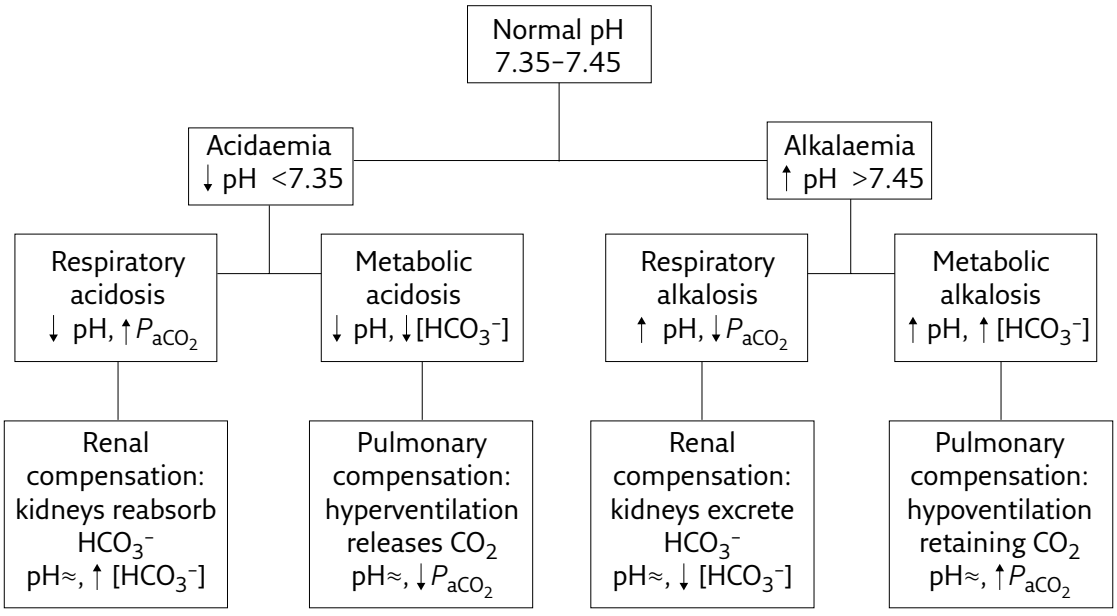

Figure 1. Diagnostic approach to acid–base disorders. Reproduced and modified from Ayers et al. *(2012) with permission.*

Mixed disorders

Mixed acid–base disorders can be defined simply as a condition in which two or more acid–base imbalances exist. Some of the more common mixed acid–base imbalances include those that have an additive effect on the change in pH (respiratory acidosis and metabolic acidosis or metabolic alkalosis and respiratory alkalosis). The other set of imbalances will have opposite effects on pH, resulting in apparent overcompensation (metabolic acidosis and respiratory alkalosis or metabolic alkalosis and respiratory acidosis).

Specific issues

Type of blood sample for blood gas analysis

Although blood gas has been historically analysed in arterial blood, obtaining arterial samples may be difficult and lead to complications. Capillary blood is routinely used in neonates or other patients when an arterial sample is not easy to collect. Capillary blood is a mix of arteriolar, capillary and venular blood with a small contribution of interstitial and intracellular fluid. Although the relative higher pressure on the arterial side of the circulation increases the proportion of arterial blood in the capillary sample, only pH and P_{aCO_2} are acceptable, because of their low arteriovenous gradient; in contrast, P_{aO_2}, which exhibits a relatively high arteriovenous difference, is less likely to show good agreement between capillary and arterial blood. Increasing local blood flow by the so-called "arterialisation" of capillary blood (warming) does not demonstrate a significant difference of pH and blood gas compared to the non-warmed capillary blood. Another acceptable alternative for the initial assessment of a patient with mild respiratory problems is peripheral venous sampling (table 2). Arterial and venous pH, HCO_3^- and base excess yield acceptable agreement in patients with normal peripheral circulation. The mean arteriovenous difference is ~0.035 pH units, 5.7 mmHg for P_{aCO_2} and –1.41 mmol·L^{-1} for HCO_3^-. Owing to the wide variations in venous P_{aCO_2}, a venous sample can be used only to screen for arterial hypercarbia or to monitor trends in P_{aCO_2} for selected patients, but not to establish the diagnosis of respiratory failure.

Storing of samples for blood gas analysis

Arterial blood gas samples must be collected, handled and analysed properly for accurate results. Every sample must be obtained anaerobically and anticoagulated. After collection, the sample should be immediately capped and analysed. Delays in measurement can decrease sample oxygen content and increase P_{aCO_2} due to

Table 2. Reference values for arterial, venous and "arterialised" capillary blood

	Arterial blood	Venous blood	Capillary blood
pH	7.35–7.45	7.33–7.43	7.40[#]
P_{aCO_2} mmHg	35–45	41–51	36–45
P_{aCO_2} kPa	4.7–6	5.5–6.8	4.8–6
P_{aO_2} mmHg	80–100	35–40	84–109
P_{aO_2} kPa	10.7–13.3	4.7–5.3	11.2–14.5
HCO_3^- mEq·L^{-1}	22–26	24–28	
Base excess mEq·L^{-1}	–2 to +2	0 to +4	
Oxygen saturation %	≥95	70–75	

Data are presented as ranges unless otherwise indicated. [#]: mean. Data from Sacks (2004) and Dong *et al*. (1985).

metabolism by blood cells (at room temperature, P_{aO_2} shows significant changes within 12 min and acid–base level is significantly different after 30 min). If properly stored (not in ice, due to possible haemolysis), the sample can be analysed within 30 min. Supplemental oxygen should be entered in the blood gas machine to obtain oxygenation indices. Factors influencing the results of arterial blood gas analysis include the type of syringe used for collection (unless the sample is analysed within 15 min), the presence of air bubbles (causing an artificially high P_{aO_2} and underestimating the true P_{aCO_2}), using too much heparin as an anticoagulant (decreased P_{aCO_2}), inadequate removal of flush solution in arterial lines prior to blood collection, mixture of venous and arterial blood during puncturing, haemolysis of blood cells and presence of clots.

Arterial blood gas values during systemic hypothermia

Physical laws determine that gas solubility within a liquid increases when the temperature diminishes, and the higher the solubility, the lower the partial pressure. Therefore, during therapeutic hypothermia, P_{aCO_2} decreases and pH increases. Each degree below 37ºC will result in a 2-mmHg (0.27-kPa) reduction in P_{aCO_2} and a 5-mmHg (0.67-kPa) reduction in P_{aO_2}. Accordingly, when blood gases of a cooled patient are measured at 37ºC, P_{aO_2} and P_{aCO_2} will be higher than the actual values. All blood gas machines have the option of analysing the blood at "actual" temperature (pH-stat approach) or the "core body temperature" (α-stat approach). For example, in a neonate cooled at 33ºC after birth asphyxia, the pH will be 7.55 and P_{aCO_2} 22 mmHg (2.9 kPa) if analysed at 33ºC, or pH 7.45, P_{aCO_2} 32 mmHg (4.3 kPa) if analysed at 37ºC. The American Association for Respiratory Care recommends against the routine correction of blood gas samples for actual temperature. Therefore, no measure will be taken to correct apparent respiratory alkalosis.

Obtain a relevant clinical history

While making an interpretation of an arterial blood gas analysis, never comment on the arterial blood gas without obtaining a relevant clinical history of the patient, which gives a clue to the aetiology of the given acid–base disorder.

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Single- and multiple-breath washout techniques

Bettina Sarah Frauchiger, Sophie Yammine and Florian Singer

Inert-gas washout (IGW) is a sensitive lung function test to measure ventilation inhomogeneity that is attributed to mainly peripheral airways function. IGW can be performed over a single breath, termed single-breath washout (SBW), or over a series of breaths, termed multiple-breath washout (MBW).

Anatomical and physiological background

The dichotomous branching structure of the lung has evolved to facilitate gas exchange by efficient ventilation distribution and a large surface area. Gas transport occurs mainly by convection in the conducting airways (approximate generations 0–16) (bulk flow), and mainly by diffusion in the intra-acinar airways (approximate generations 17–23). In the transition zone at the entry to the acinus, both mechanisms contribute to ventilation distribution, *i.e.* the convection–diffusion front. Gas transport dynamics in central and peripheral airways differ in children and adults. The definition of small airways is derived from *post mortem* adult data and includes all airways with a luminal diameter of <2 mm (corresponding to airway generations 8–23). There is currently no consensus on how to define small airways in the growing lungs of children. Airway obstruction, hyperinflation and bronchiectasis affect convective and diffusive gas transport and lead to inefficient gas mixing, *i.e.* increased ventilation inhomogeneity, which can be estimated using IGW.

Key points

- Inert-gas washout is a sensitive lung function test to measure ventilation inhomogeneity, a biomarker of mainly peripheral airways function.
- Inert-gas washout measurement recommendations exist, equipment is available and measurement is feasible across most age groups.
- The currently most recognised ventilation inhomogeneity index is the multiple-breath washout-derived LCI; it is repeatable, sensitive for structural airway pathology and responsive to treatment effects such as disease modifiers, hypertonic saline and dornase-α in CF.
- More studies on normative data and prediction of future disease outcomes aiding clinical decision-making are required.

Evolution of IGW

IGW techniques were introduced in the 1950s. Most recent data were obtained in patients with chronic suppurative lung diseases such as CF using nitrogen (N_2), sulfur hexafluoride (SF_6) or helium as an inert tracer gas. Increasingly, customised and expensive mass spectrometers for IGW are being replaced by available and user-friendly hardware and software that automatically align and integrate multiple signals. These systems measure airflow and tracer gas either directly or indirectly by oxygen, carbon dioxide or molar mass from sensors such as pneumotachographs, ultrasonic flowmeters, infrared and laser sensors and photoacoustic spectrophotometers. As MBW is currently the most established technique in the clinical setting, especially for preschool and school-aged children, in this chapter we focus on MBW.

SBW technique and parameters

Classically, SBW is performed using a vital capacity manoeuvre (figure 1), but can also be done during tidal breathing. The SBW expirogram shows the tracer gas concentration over expired volume, where phase III represents the expired gas from the alveolar zone (figure 1). The traditional index of SBW is the slope of phase III (SIII). Inhomogeneity of ventilation distribution delays inert tracer gas clearance and gives rise to SIII.

MBW technique and parameters

MBW is a tidal-breathing, gas-dilution technique and therefore relatively easy to perform. It requires a regular breathing pattern and tight mouthpiece/face mask seal ensuring a leak-free system.

For MBW using exogenous inert tracer gases, for example SF_6, the inert gas is washed-in until equilibration, then the inert gas is switched off and the washout is started

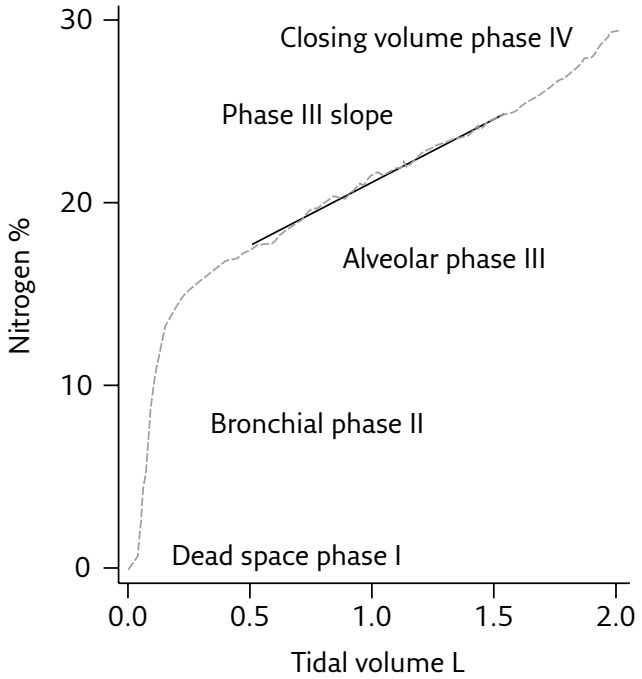

Figure 1. Classical vital capacity nitrogen SBW in a healthy subject. The four sequential phases of the expirogram are phase I (dead space); phase II (bronchial phase); phase III (alveolar phase); and phase IV (closing volume). (In tidal-breath SBW, phase IV is missing.) The slope of phase III is calculated by linear regression over phase III (%·L^{-1}) between 25% and 75% of expired volume, i.e. *vital capacity.*

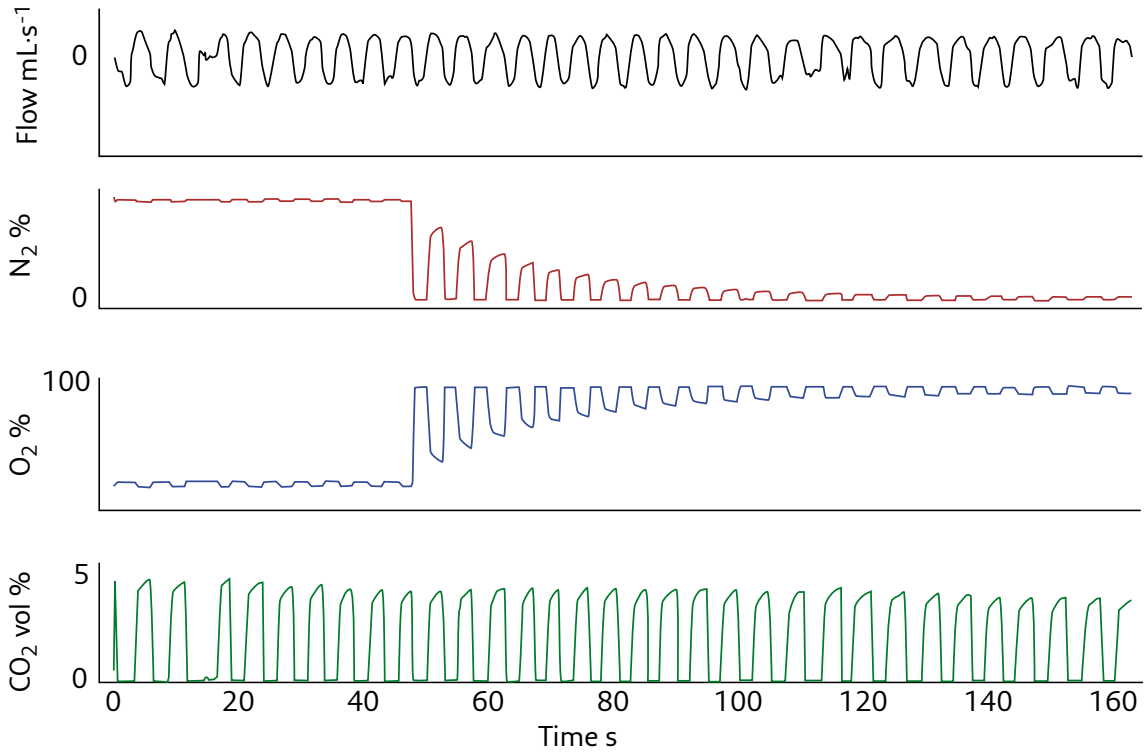

Figure 2. A nitrogen MBW test in a healthy adolescent. The raw signals flow (black), oxygen (O_2; blue) and carbon dioxide (CO_2; green) are plotted against time. In this example, the N_2 concentration (brown) is calculated indirectly as 100 – ([O_2]+[CO_2]+[argon set constant]).

usually with room air. Pure oxygen is standard to wash out lung-resident N_2 (figure 2). Between N_2-MBW trials, N_2 is washed-in back from tissue and mainly room air. The end of a washout is historically set when at least three tidal breaths reach an end-tidal tracer gas concentration C_{ET} <1/40th of the starting concentration, irrespective of the inert tracer gas in use.

The most frequently reported MBW index, LCI, reflects overall ventilation inhomogeneity. LCI is calculated as the cumulative expired volume (CEV) needed to clear the lungs of the tracer gas divided by the FRC determined at the end of MBW (see earlier). LCI units are lung turnovers (CEV/FRC). Lung disease may increase the ventilatory effort required to clear the lungs of the tracer gas, and therefore CEV increases. Analysis of SIII as performed in SBW can be applied to the first (S_{acin}) and consecutive washout-breaths (S_{cond}) across MBW. These indices reflect diffusion–convection-dependent (S_{acin}) and convection-dependent (S_{cond}) ventilation inhomogeneity.

$$LCI = \frac{CEV}{FRC}$$

$$FRC = \frac{\text{Net volume of exhaled } N_2}{C_{ETN_2 start} - C_{ETN_2 end}}$$

MBW testing procedure

A relaxed and uniform breathing pattern is essential to maintain a stable end-tidal lung volume to which ventilation inhomogeneity indices are related. In younger children, adequate distraction may improve test success. A leak-free system is crucial;

therefore, correct seal at the mouthpiece or face mask must be checked, as well as the device.

For one test occasion, the aim is to collect three trials. For outcome reporting, at least two technically acceptable trials are needed. In school-aged children, current recommendations suggest FRC variability ≤10% and rejection of tests if variability of FRC exceeds 25%. In preschool children, quality control relies on inspection of MBW signals and breathing pattern. Studies to better identify the quality of single MBW trials are underway.

Clinimetric properties of MBW

Reference values

FRC, LCI and other ventilation inhomogeneity indices variably depend on age, equipment and tracer gas used. Studies on equipment-specific reference equations exist. For most setups, the upper limit of normal LCI ranges from 7.5 to 8.5 lung turnovers in children.

Reliability

Data on variability of lung function indices are essential to depict physiologically meaningful changes, *i.e.* changes exceeding natural and technical variability. Variability of FRC and LCI depend on the setup, age and lung disease. Within tests, LCI varies by ~5% on average and ranges by approximately ±25% between tests (table 1). Between-test variability of LCI is comparable to between-test variability of FEV_1 at preschool age. CF lung disease management based on LCI requires further study, and the so-called minimal clinically important difference (MCID) has not yet been defined.

Table 1. Natural variability of LCI in CF

	First author, year	Subjects n	Age range years	Intra-test variability[#] %	Inter-test variability[¶] %
Preschool age					
Healthy	Oude Engberink, 2017; Stanojevic, 2017	71	2.5–6	3.9 (0.3–12.3)[+]	4.3 (–15–15)
CF	Oude Engberink, 2017; Stanojevic, 2017	77	2.5–6	4.9 (0.2–17.6)[+]	7.7 (–25–27)[§]
School age					
Healthy	Poncin, 2017	50	4–16	6.8 (3.4–10.5)[ƒ]	
CF	Poncin, 2017	47	4–16	6.6 (3.0–10.6)[ƒ]	
CF	Svedberg, 2018	25	6–17	5 (1.4–16)[+]	6.3 (1.1–18.3)[+]
CF	Green, 2018	14	5–18	8.2 (7.4–9.3)[##]	–22–23[¶¶]

Data were derived from similar setups using nitrogen MBW. Children with CF were considered clinically stable. [#]: variation of LCI measurements within one test occasion; [¶]: variation of LCI measurements between test occasions 3 months apart. Variability estimates are the coefficient of variation (CoV); values in brackets give the range of variability as reported in original publications, as follows. [+]: median CoV (range); [§]: mean CoV (95% limits of agreement of percentage change); [ƒ]: median CoV (interquartile range); [##]: mean CoV (95% CI); [¶¶]: limits of agreement of percentage change.

Practicability, validity and responsiveness of LCI

MBW is feasible in children, and European Respiratory Society/American Thoracic Society consensus recommendations for preschool and school-aged children exist. The majority of paediatric MBW studies have focused on CF.

Functional and structural airway impairment despite lack of symptoms (clinical silence) is prevalent in infants and preschool children with CF. Correlation of LCI with the extent of structural disease in preschool and school-aged children with CF is good, yet less established in infants. LCI correlates with lower airway infection and inflammation. Overall, LCI sensitively tracks early lung disease progression in CF. During pulmonary exacerbations, LCI deteriorates (increases) and is responsive (declines) upon antibiotic treatment in preschool children, but less so in older children. In clinical trials, LCI is increasingly used as an outcome. In several trials on disease modifiers targeted on CFTR, LCI improved markedly (11–25% average effect size), indicating good responsiveness of LCI. Reports on short-term effects from chest physiotherapy are heterogeneous in children with CF.

Few paediatric studies exist in other disease groups, such as PCD, asthma, BPD or post-lung transplantation. Discriminatory capacity, *i.e.* the ability of LCI to discriminate between health and disease, is good in CF and PCD. It is less established in other disease groups such as asthma or BPD. Alternate ventilation inhomogeneity indices such as S_{cond} and S_{acin} seem more promising in these diseases with different pathophysiology.

Clinimetric properties of SBW

Feasibility of tidal SBW has been demonstrated in school-aged children. Standardised protocols exist; however, hardware and software are often customised and normative data based on large population samples do not yet exist. Tidal SBW based on a double tracer gas mixture, *i.e.* the SIII index, may discriminate healthy children from children with CF or asthma with normal spirometry. Carbon dioxide (capnography) analysis seems promising in children with BPD. Compared to LCI, natural variability of SBW indices is larger, and its responsiveness requires further study in children.

Future directions and open questions

In chronic suppurative lung diseases such as CF, PCD and non-CF non-PCD bronchiectasis, MBW holds promise to become standard in clinical routine care. The role of LCI in chronic lung disease with variable airways obstruction such as asthma is less clear. Future studies should address 1) prediction equations for a broad age range; 2) the MCID; 3) prediction of future disease outcomes; and 4) clinical benefit of adding IGW tests to routine disease management. In addition, studies on lung models, functional imaging and possibly machine learning will aid interpretation and disentangle the complex association between reversible and irreversible airway changes and ventilation distribution efficiency.

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Pulmonary function testing in infants and preschool children

Enrico Lombardi, Claudia Calogero and Graham L. Hall

Measuring lung function in infants (first 2 years of life) and preschool children (2–6 years) represents a major challenge in paediatric respiratory medicine. Infants cannot voluntarily perform the manoeuvres required for PFTs used in older children and adults. The majority of lung function tests in infants require sedation to ensure acceptable and repeatable results. The most commonly used sedative is chloral hydrate (80–100 mg·kg^{-1}, maximum 1 g); however, this sedative is no longer available in the USA. Infant lung function tests performed during tidal breathing (such as tidal breathing measurements and the multiple-breath washout) are more readily used without sedation, although test success rates decrease with increasing age. While PFTs in this age group are possible and commercially equipment is available, infant PFTs are less suitable for routine clinical testing. A recent survey cited the "need for sedation" and the "uncertainty about how data actually impacts patient care" as limitations for the use of infant PFTs. Infant PFTs have been standardised by the American Thoracic Society (ATS) and European Respiratory Society (ERS).

Preschool children can be more challenging than infants as far as lung function testing is concerned. They are too old to sedate, have a very short attention span and the success of lung function testing in this age group depends on the capability of the operator of initiating a good relationship with the child. Several techniques are now available that are performed during tidal breathing, and therefore are suitable for use in preschool children. International recommendations have been published for most PFTs in preschool children and the evidence for the clinical utility of the tests has been reviewed.

Key points

- Measuring lung function in infants and preschool children is possible because of standardised techniques that require minimal cooperation from the child.
- Sedation is usually required in infants and young children up to 2 years of age (generally chloral hydrate 80–100 mg·kg^{-1}, maximum 1 g) for most PFTs, limiting the use of infant PFTs in routine clinical care.
- In preschool children, the feasibility of the interrupter technique and plethysmographic specific airway resistance, which are performed during tidal breathing, is usually >80%.
- Spirometry is feasible in preschool children when appropriate criteria are used.

This chapter describes the most frequently used PFTs in infants and preschool children. Other fundamental PFTs for infants and preschool children, such as washout techniques and the forced oscillation technique, are described in detail separately (see chapters "Single- and multiple-breath washout techniques" and "Forced oscillation techniques").

PFTs in infants

Raised-volume rapid thoracic compression

The measurement of forced expiratory flows and volumes (FEF and FEV) in infants is obtained using the raised-volume rapid thoracic compression (RVRTC) technique and international testing guidelines are available. The RVRTC technique is demanding in terms of staffing and equipment resources, as well as the training required to ensure that high-quality measurements are obtained. Briefly, the technique involves applying repeated inflation breaths to the sedated infant, *via* a face mask, to a pressure of 30 cmH_2O. An inflatable jacket is used to rapidly compress the infant's thorax and abdomen to produce the forced expiratory flow–volume curves. The jacket inflation pressure is increased progressively until there are no further increases in FEF, suggesting that flow limitation has been achieved. The reported RVRTC outcomes are FVC, FEV in 0.5 s ($FEV_{0.5}$) and FEF at a defined proportion of FVC. Technically acceptable and repeatable outcomes are influenced by laboratory experience. The reference equations are equipment specific and great care is needed in selecting the most appropriate equations. It remains unclear what change in RVRTC outcomes constitute a clinically meaningful difference, primarily due to the difficulties associated with repeated sedation and changes with lung growth over time. These place further limitations on the use of RVRTC for the management of lung disease in individual patients.

The RVRTC technique has been applied in a range of patient populations including CF, recurrent wheezing, infants born preterm and in infants with chest wall and parenchymal lung disorders. The majority of studies reported in the literature are in infants with CF and infants with recurrent wheeze. In infants and young children with CF diagnosed following newborn screening, $FEV_{0.5}$ is normal or near normal in the first months of life, declines over the first 12–24 months of life and is reduced in infants with pulmonary infection. The recent Infant Study of Inhaled Saline in Cystic Fibrosis (ISIS) demonstrated a significant adjusted treatment effect in $FEV_{0.5}$ of 38 mL, suggesting that RVRTC outcomes may be a valid choice for clinical trials in early CF lung disease. In infants with recurrent wheeze/infantile asthma, evidence of airway obstruction and improvements following treatment with bronchodilators, montelukast or inhaled corticosteroids have been reported. The RVRTC technique has been combined with inhaled challenge tests for the assessment of airway hyperresponsiveness (AHR), although these are limited to highly experienced centres.

In summary, the RVRTC technique has a role in research studies with emerging evidence of its utility in clinical trials. The role of the technique in the clinical management of infants and young children with lung disease is less clear, and further studies defining normal reference ranges and clinically meaningful differences are required.

Infant plethysmography

The use of body plethysmography in infants to measure functional residual capacity (FRC_{pleth}) operates on the same principles as plethysmography in older children and adults. The primary difference is that the infant or young child is sedated, lying supine

and breathing through a face mask that is sealed over the nose and mouth using silicon putty. Infant plethysmography measurement guidelines have been published. Success in obtaining FRC_{pleth} is generally high and is influenced by sedation success and the experience of the personnel. Reference data in healthy infants are available; however, the validity of these data in using currently available equipment has been questioned. There are very few data on the repeatability of FRC_{pleth} over time and a clinically meaningful change in response to treatments (such as bronchodilators) or deterioration in clinical status is not known. Considered together, these limit the ability of infant plethysmography to be used in a meaningful way in individual infants with chronic lung diseases.

The use of infant plethysmography in infants with CF, BPD and recurrent wheeze has been reviewed recently. Considering that equipment has been commercially available for a number of years there are relatively few published studies with sample sizes that allow for meaningful conclusions to be drawn. In general, studies in infants with CF have demonstrated an elevated FRC_{pleth} and this has been reported recently to be associated with pulmonary infections. In contrast to $FEV_{0.5}$, there was no change in FRC_{pleth} in the ISIS trial. The few studies in infants with recurrent wheeze suggest the presence of air trapping, probably secondary to airway obstruction, which improves following bronchodilation. In infants born preterm (with or without BPD), the majority of studies have reported reduced FRC obtained with gas-dilution techniques related to the decreased alveolar complexity occurring as a result of altered lung development. FRC using infant plethysmography is reported to be elevated in infants with BPD and may suggest the presence of trapped gas.

In summary, the limited information on healthy reference ranges for both the infant RVRTC and plethysmography techniques, and a limited understanding of a clinically meaningful change have impacted on the ability of these lung function tests to contribute to the clinical management of infants with respiratory disease. The application of lung function testing in sedated infants and young children is likely to require a combination of tests, and careful consideration of pathophysiological changes and the most appropriate PFT is required.

PFTs in preschool children

Preschool spirometry

In individuals aged >5–6 years, spirometry is the most commonly used lung function technique. Traditionally, it has been thought that preschool children are not able to perform acceptable spirometry manoeuvres. However, recent studies have highlighted that spirometry in preschool children is feasible (47–92%), especially when incentive software is used. A lower feasibility (as low as 21%) has been found in children aged ≤4 years and in those with neurodevelopmental disabilities (such as children with BPD).

Several studies have shown that preschool children have difficulty in meeting the acceptability criteria for spirometry recommended for adults and children aged ≥6 years. It is critical that those performing spirometry in young children are familiar with the relevant differences as advocated in international guidelines. Preschool children are physiologically different from older children and adults: they have smaller lung volumes and larger airways with respect to lung volume when compared with older children. Therefore, spirometric manoeuvres in preschool children are completed more quickly than in older children, sometimes even in <1 s. As a result, FEV_1 is not always measurable and indices such as $FEV_{0.75}$ or $FEV_{0.5}$ are more reasonable in this

age group. It has been shown that extrapolated volume is lower and extrapolated volume/FVC is higher in preschool children than in older children and adults. For these reasons, the ATS/ERS statement for lung function testing in preschool children has provided appropriate recommendations for spirometry in this age group, which can be summarised as follows:

- Children should have time to familiarise themselves with the equipment and operator
- Incentive software may be used, although this is not mandatory
- The child's posture (seating or standing) and the use of a nose clip should be reported
- If the extrapolated volume is >80 mL or 12.5% of FVC, the curve should be inspected again, but not necessarily rejected
- In case of early termination of expiration, it may be possible to record $FEV_{0.5}$, $FEV_{0.75}$ and FEV_1, but not FVC
- Ideally, a minimum of two acceptable manoeuvres should be obtained, where the second largest FVC and FEV values are within 0.1 L or 10% of the highest value; however, poor repeatability should not be a reason for automatic rejection of data

Several reference values for spirometry in preschool children have been reported and these data are now included in the recently published reference values of the ERS Global Lung Function Initiative (www.lungfunction.org). In addition, clinical data on the usefulness of spirometry in preschool children have been published. Although doubts on the clinical usefulness of the spirometry bronchodilator response (BDR) in preschool children have been raised, recent studies suggest that a positive BDR may be more sensitive than baseline spirometry in detecting asthma, while a negative BDR in a child suspected of having asthma makes a diagnosis of asthma less likely.

Interrupter technique

The interrupter technique is a suitable method to measure lung function in preschool children. It requires little collaboration and can be performed in children as young as 2 years. The interrupter resistance (R_{int}) reflects the resistance of the respiratory system (airways, lung tissue and chest wall) and equipment is commercially available. It is assumed that during a sudden flow interruption at the mouth:

- Mouth pressure will rapidly equilibrate with alveolar pressure
- The valve closure time will minimise leak
- Compliance of the upper airway is negligible

The interruption time is usually <100 ms. R_{int} can be calculated by dividing the change in mouth pressure at the beginning of the interruption by the flow measured immediately before the interruption (classical technique) or dividing the change in mouth pressure at the end of the interruption by flow measured immediately after the interruption (opening technique). The results obtained with the two different techniques cannot be used interchangeably.

The test procedure, technical aspects and data analysis for the classical interrupter technique have been fully described previously. The child should be seated, breathing quietly through a mouthpiece and bacterial filter, wearing a nose clip and with the cheeks supported. Each occlusion should be triggered during expiration by a flow set to coincide with peak expiratory flow and 10 interruptions should be recorded, with the aim of obtaining a minimum of five acceptable manoeuvres. At the end of the test, the median value of all technically acceptable interruptions should be reported.

International reference equations for males and females have been published. Measurements of R_{int} have been shown to have a good intra-measurement and between-test repeatability, with a coefficient of repeatability (2 SD of the difference between two sets of measurements) in the order of 0.25 $kPa \cdot s^{-1} \cdot L^{-1}$.

The feasibility of R_{int} in preschool children is >80% in most studies. The sensitivity and specificity for different BDR cut-off levels to discriminate between healthy and asthmatic children are available.

In the clinical setting, R_{int} can be used to measure lung function in children with different respiratory conditions such as wheezing, CF, history of prematurity or BPD. BDR assessed using R_{int} is probably more useful for asthma diagnosis than for excluding asthma. However, as the definitions of different phenotypes of preschool wheezing are complex, recent recommendations suggest that in the individual patient, measuring lung function, including BDR can help to differentiate common wheezing disorders from other diseases.

Plethysmographic specific airway resistance

In cooperating children, airway resistance (R_{aw}) can be measured with whole-body plethysmography, where the subject is asked to breathe against a closed shutter to obtain thoracic gas volume. In preschool children, the measurement of specific R_{aw} (sR_{aw}), only requiring minimal collaboration during tidal breathing, has been proposed. sR_{aw} is defined as the product of R_{aw} multiplied by FRC_{pleth} and its calculation avoids the need to perform breathing manoeuvres against a closed shutter.

Several indices for sR_{aw} have been proposed; it was recommended recently that sR_{eff} (which is the least-squared regression of pressure and flow throughout the breathing cycle) should be calculated, since it measures sR_{aw} over the entire breathing cycle. Being a product of a volume and a resistance, an abnormal value can indicate changes in both components.

Preliminary reference equations for sR_{aw} have been published recently; however, the authors highlight that those reference values can only be used when similar measurement conditions are applied. In a study conducted in the UK, statistically significant differences were reported for sR_{aw} measured in three different centres, suggesting that even after a methodological standardisation, reference values cannot be used interchangeably between different laboratories. Finally, a recent study highlights the need for standardisation of plethysmographic sR_{aw} measurements, despite their widespread use.

The repeatability of measuring sR_{aw} in preschool children has shown intra-subject coefficients of variation of ~9–13%. Feasibility is also good, being ~80% in 3–6-year-olds.

In preschool children, sR_{aw} has been shown to be able to detect airway calibre changes after bronchodilation. Preschool children with asthma were found to have higher sR_{aw} than healthy children and, in a longitudinal cohort study, high sR_{aw} at age 3 years was found to predict the persistence of recurrent wheezing at 5 years. In preschool children with CF, sR_{aw} was found to be higher than in healthy children and was shown to be more sensitive than spirometry in detecting early lung disease, although less sensitive than the LCI from multiple-breath washout.

Summary

The optimal lung function test to be used in infants and preschool children depends on the clinical or research questions that need to be answered. In preschool children with

wheezing, the interrupter technique, plethysmographic sR_{aw} and forced oscillation technique appear to be the most suitable to provide information on the change in airway calibre. However, techniques that are able to detect more peripheral changes (such as the washout techniques and, potentially, forced oscillation technique) appear to be more suitable for studying diseases such as CF or BPD.

In conclusion, measuring lung function in infants and preschool children is possible thanks to standardised techniques that require minimal cooperation from the child. Further studies will need to highlight the role of single tests in the clinical management of infants and preschool children with respiratory illness.

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Forced oscillation techniques

Shannon J. Simpson, Sherlynn Ang and Graham L. Hall

The forced oscillation technique (FOT) was first introduced by Arthur Du Bois in 1956. In short, time-varying pressures (or flows) of one or more frequencies are generated from a loudspeaker, which in the modern-day environment is generally several sinusoidal wave forms (pseudorandom noise) or a rectangular wave, as with the impulse oscillation system (IOS). This signal is applied at the airway opening and the resulting flow (or pressure) response of the respiratory system is measured in addition to the phase shift between these signals. This pressure-to-flow ratio is defined as the mechanical input respiratory system impedance (Z_{rs}). As Z_{rs} is a complex function of frequency, it is comprised of a real part, resistance of the respiratory system (R_{rs}), and an imaginary part, respiratory system reactance (X_{rs}).

The majority of FOT studies in humans have been conducted using medium-frequency ranges (4–50 Hz), with oscillations superimposed over spontaneous breathing. However, low-frequency oscillations applied during apnoea, particularly during infancy, allow the assessment of airway and tissue contributions to impedance *via* mathematical partitioning. In the medium-frequency range, X_{rs} is dominated by the tissue elastic properties at frequencies below the resonant frequency (f_{res}; where $X_{rs}=0$) and the inertial properties of the gas in the airways at higher frequencies. In younger children, R_{rs} also exhibits some frequency dependence in the medium-frequency range, which decreases in older children and adults. There is now an increasing availability of forced oscillation systems utilising a single frequency that are used to track R_{rs} and X_{rs} within each breath. Typical impedance spectra across the medium frequency range in young children are shown in figure 1.

Key points

- The forced oscillation technique can be used to measure respiratory mechanics with oscillatory signals superimposed over tidal breathing in awake children as young as 2 years of age.
- Alterations in respiratory mechanics have been evaluated in several commonly encountered paediatric lung diseases, including asthma; however, further work is required to cement a place for the forced oscillation technique in the routine clinical management of such diseases.

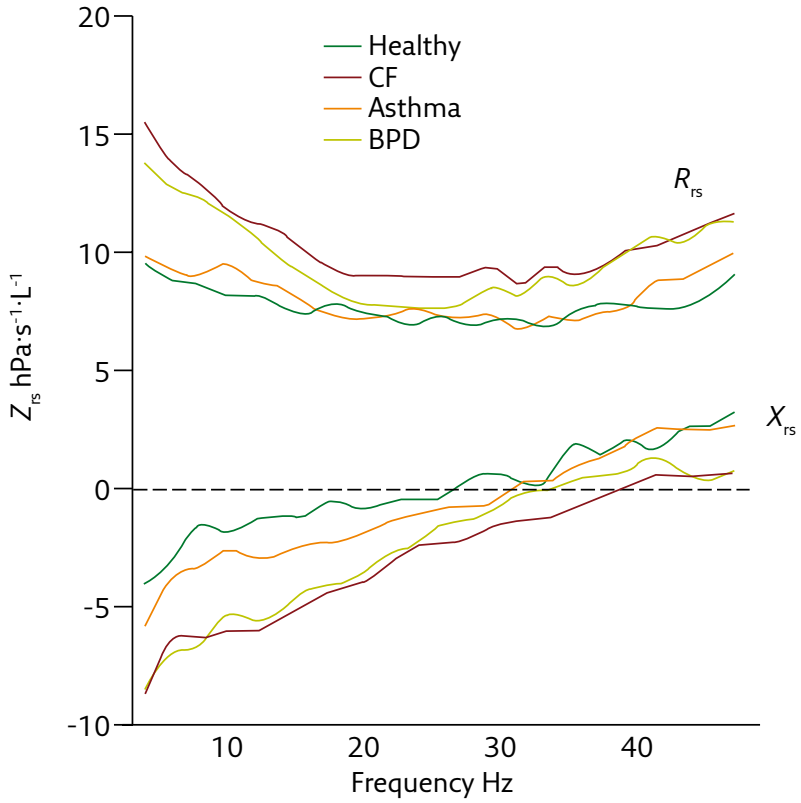

Figure 1. Impedance spectra in healthy children and in respiratory disease during early childhood. The components of respiratory system impedance, resistance and reactance are shown across the medium-frequency range. An average of three impedance measurements were obtained for a boy aged 4.4 years and 105 cm tall for comparison between disease states. Differences in R_{rs}, X_{rs}, *reactance area (AX),* f_{res} *and frequency dependence* (f_{dep}) *are evident, to varying extents, in commonly encountered paediatric diseases when compared to a typical healthy child.*

Use of the FOT in young children

The FOT is ideal for use in children unable to cooperate during traditional lung function tests, as it is effort independent. The FOT has been applied in children as young as 2 years of age with success rates >80% in young children. A number of commercially available FOT devices and guidelines have been established for the use of FOT in young children.

Data collection and repeatability

Instruction should be given to the child prior to the measurement, including how the test will feel. The child should be seated in the upright position with a neutral head position, a nose clip in place and a good seal around the mouthpiece. The cheeks and floor of mouth must be firmly supported to minimise upper airway shunting. Measurements should be obtained over several breathing cycles with no artefacts such as leak, vocalisation, swallowing, glottic closure, tongue obstruction or movement, and the average of three to five acceptable measurements should be reported.

Within a testing session, the coefficient of variation for R_{rs} has generally been reported up to 15%, while the coefficient of repeatability (twice the standard deviation of the difference between two measurements taken 15 min apart) ranges between 1.1 and 2.6 hPa·s^{-1}·L^{-1} for R_{rs} and equates to a relative change of 12–30% with similar repeatability reported over a 2-week period. The repeatability of X_{rs} is reported as absolute values and ranges from 1.2 to 2.0 hPa·s^{-1}·L^{-1}.

Reporting of outcomes and normative data

The upper and lower limits of normal are defined, although differences in oscillatory signal and the frequencies of reported outcomes can make comparisons difficult. In addition, much of the available reference data has been collected in Caucasian populations. Studies suggest that FOT outcomes are influenced by race and ethnicity and caution should be applied in the interpretation of FOT from non-Caucasian patients if Caucasian reference equations are used. The majority of reference equations use height as the only predictor of FOT outcomes, although sex was shown to contribute to R_{rs}, X_{rs} and the area under the X_{rs} curve (integrated area of low-frequency reactance (AX)) in some studies.

Generally, R_{rs} is reported at frequencies of 5–10 Hz, which is believed to approximate values of airway resistance. However, resistances at higher frequencies are also valuable, at least theoretically, and therefore the resistance and reactance curves should be considered as a function of the whole frequency range in clinical applications of the FOT. For example, the frequency dependence (f_{dep}; defined as the slope of the resistance–frequency curve or the AX), which has been proposed as an index of respiratory system elastance, may be particularly appropriate. Recently published normative data for these FOT outcomes will facilitate further information on their clinical utility.

Clinical utility

Alterations in respiratory mechanics have been evaluated in respiratory diseases commonly encountered in the paediatric setting using the FOT. However, it is reasonable to speculate that the FOT would be most clinically useful in paediatric diseases with pathophysiology in the distal lung. Although the FOT is able to detect changes in airway calibre after therapeutic interventions, to date, its role in the management of individual patients remains unclear. Examples of impedance measurements in children with commonly encountered respiratory diseases in the paediatric clinic are given in figure 1.

Asthma and wheeze

The ability of the FOT to sensitively distinguish between healthy and wheezy preschool children before or after the administration of bronchodilator remains unclear. There are statistical differences in FOT outcomes between children with uncontrolled asthma and controlled asthma. Some studies have shown no difference in baseline lung function and bronchodilator responsiveness between healthy and asthmatic children, while others have shown significant differences, even between different wheezing phenotypes. Several studies have defined the response to bronchodilators in healthy populations with relative cut-off values (derived from the 5th to 95th centiles) in the range of –33––42% for R_{rs}, 61–70% for X_{rs} and 81% for AX, regardless of the salbutamol dose, although most studies administered 200 µg of salbutamol.

The FOT has been used to assess bronchial hyperresponsiveness in young children, with significant increases in R_{rs} and decreases in X_{rs} reported during both direct and indirect bronchial challenge tests. The FOT outcome most useful for monitoring bronchoconstriction during bronchial provocation is yet to be defined. The respiratory system admittance, the reciprocal of Z_{rs}, is more sensitive to bronchoconstriction than the commonly used R_{rs} due to the elimination of the upper airway artefact. Previous studies have used various changes in R_{rs} to define a positive response to bronchial provocation and the most appropriate cut-off for a positive response is yet to be validated. The development of shortened protocols for challenge tests using the

FOT, such as for AMP and methacholine may help to overcome the shorter attention span of young children.

Cystic fibrosis

Lung function tests sensitive to small airway dysfunction are likely to be best at monitoring early CF lung disease. The role of the FOT in monitoring CF lung disease is unclear, with some studies reporting that the FOT fails to adequately identify airway obstruction in young children with CF. In contrast, increased R_{rs} and decreased X_{rs} have been reported in young children with CF, particularly in the presence of respiratory symptoms. The diagnostic ability of FOT to identify children with CF with more severe lung disease in comparison to children with mild lung disease is low, with many FOT measurements similar between the two groups, indicating that FOT may not be a useful surveillance tool in the progression of the disease.

Prematurity and BPD

The use of FOT in preterm-born children with and without BPD has revealed that R_{rs}, X_{rs}, f_{res} and f_{dep} are frequently abnormal among these groups. A longitudinal study identified poor lung function trajectories together with structural changes in a preterm population compared to healthy children, providing evidence of altered FOT measurements. Some clinically significant outcomes have been identified in preliminary studies, but further studies to examine the changes to FOT outcomes during development following preterm birth would be particularly beneficial.

Other/potential clinical utility

The FOT has also been used to examine the temporal changes in respiratory mechanics, although primarily as a research tool rather than in clinical practice. Such studies have examined temporal changes over the normal breathing cycle as a method of detecting expiratory flow limitation, the effect of deep inspiration on respiratory mechanics and the monitoring of upper airway patency during sleep. Additionally, this approach has potential for the non-invasive assessment of respiratory mechanics in patients receiving mechanical ventilation. While perhaps underutilised in this area, the FOT is useful at detecting and quantifying upper or central airway diseases including tracheal stenosis, tracheo-oesophageal fistula, laryngeal obstruction and inducible laryngeal obstruction, although separation of inspiratory and expiratory impedances to examine the flow dependence during each phase of the respiratory cycle would probably yield most information in this group of patients. Another underutilised area is neuromuscular disease, where, due to the nature of the condition, the FOT may provide better means of assessing lung function than conventional techniques.

Future directions

The measurement of respiratory system impedance has the potential to provide a great deal of information on a variety of conditions during the early years of life; however, further work is required if the FOT is to reach its full clinical potential. In the short term it is important to explore other FOT outcomes in addition to the traditionally reported R_{rs} at a single frequency with the knowledge that the pathophysiological mechanisms of many respiratory diseases exhibit strong peripheral lung involvement during early life. For example, measures of X_{rs} or AX may be more sensitive at monitoring the course of those respiratory disorders. Furthermore, we must work towards understanding which FOT outcomes are most relevant for particular pathologies, as a "one outcome for all disease" approach may not be appropriate. FOT outcomes

should be validated prospectively together with improved analysis techniques to help advance the detection, monitoring and management of respiratory diseases in a paediatric cohort. In the longer term, it is important to gain an understanding of how respiratory mechanics alter longitudinally during development and what kind of deviation from this path requires intervention.

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Exhaled nitric oxide, induced sputum and exhaled breath analysis

Mariëlle Pijnenburg, Valentina Ferraro and Silvia Carraro

Noninvasive tests to assess the presence and nature of airway inflammation in children are particularly relevant for the diagnosis and treatment of asthma, and may also be valuable for other inflammatory conditions of the airways. Other applications include the diagnosis and monitoring of respiratory infections and of certain non-respiratory metabolic conditions. This chapter focuses on the use of noninvasive markers of airway inflammation in childhood asthma.

The exhaled nitric oxide fraction

The exhaled nitric oxide fraction (F_{ENO}) is the best studied and validated noninvasive marker of airway inflammation, and is the only inflammation marker that has widely gained acceptance in routine patient care. Nitric oxide is a free-radical gas that is produced from L-arginine, involving constitutively expressed and inducible nitric oxide synthases (NOS). One of the isoforms of NOS, inducible NOS, also called type 2 NOS or iNOS, is present in airway epithelial cells, where it is upregulated by pro-inflammatory cytokines and then produces relatively high amounts of nitric oxide into the airway lumen. This nitric oxide can be measured at the mouth during exhalation, and with appropriately standardised methodology F_{ENO} is highly reproducible. F_{ENO} levels are

Key points

- Increased exhaled nitric oxide fraction is suggestive of eosinophilic airway inflammation and has a modest role in the diagnosis and management of asthma after preschool age.
- In a meta-analysis, dose titration of inhaled steroids on the basis of exhaled nitric oxide fraction was shown to reduce exacerbations in children with asthma.
- Sputum induction is a relatively safe, noninvasive procedure and several data support its possible role for assessing airway inflammation in children. Nonetheless, for now, there is no evidence of a clear benefit from this inflammation measurement in routine clinical asthma management.
- Exhaled breath and exhaled breath condensate have been studied through both a targeted (measurement of single analytes) and an untargeted approach (-omic techniques). These techniques have potential, but further standardisation is needed before application in clinical practice.

Figure 1. Measurement of F_{ENO} in a child using a hand-held device with an electrochemical sensor. Maintaining a low, constant expiratory flow is facilitated by optical, auditory and visual feedback signals. The result is immediately available.

measured in parts per billion, and hence extremely sensitive analysers are needed. F_{ENO} analysers for clinical purposes are commercially available, and have evolved from bulky, expensive, delicate chemoluminescence analysers into hand-held, user-friendly devices using a more robust electrochemical cell-based technology (figure 1). Unfortunately, the different devices do not necessarily produce the same results, and the smaller hand-held analysers do not show the actual expiratory flow and nitric oxide graph. Hence, different equipment cannot be used interchangeably unless formal comparisons have shown equivalence.

Methodology of measuring F_{ENO}

The recommended technique to assess F_{ENO} is an online measurement during a single breath with constant expiratory flow of 50 mL·s^{-1}, for ⩾10 s (6 s for children with vital capacity <3 L), through a mouthpiece. Contamination with air from the nose should be avoided, as the nose and paranasal sinuses produce nitric oxide in much higher amounts than the lower airways. This is accomplished by exhaling against a positive pressure that ensures closing of the soft palate, thus closing the nose off from the lower airways. As spirometry manoeuvres may decrease F_{ENO} values, F_{ENO} measurements should be performed before spirometry.

Ideally, the equipment provides one or more biofeedback signals to help the patient to standardise the expiration flow and duration, and accepts only attempts that fulfil quality criteria. The recommended procedure has increasing success rates of 40% at age 4 years to almost 100% at age 10 years; in younger children the success rate falls rapidly. For preschool children, a number of offline methods have been described, which make use of collection devices where exhaled air is stored and analysed, with or without tidal flow control. In infants, F_{ENO} measurements have been performed by collecting mixed nasal–oral exhaled air samples in a nitric oxide inert collection bag, or online using various, often complicated approaches, that require an academic setting and dedication. Such methods have not been well standardised and are not suitable for clinical practice.

Alternatively, F_{ENO} may be measured online using tidal breathing, although agreement with F_{ENO} measured with the single-breath technique is moderate. Newer technology with fast-response chemiluminescence analysers and flow control devices may make it feasible to measure F_{ENO} using a single-breath technique in children as young as 3 years. In addition, with mathematical algorithms single-breath constant flow values may be derived from tidal breathing F_{ENO} values.

Several factors can affect F_{ENO}, and should be taken into account when F_{ENO} is interpreted. Maximal forced breathing manoeuvres, including spirometry, should be avoided, as these reduce F_{ENO} for several minutes. Inhaling nitric oxide free air before the measurement is desirable, as high ambient values may increase F_{ENO}. For this purpose, a nitric oxide scrubber can be used that removes ambient nitric oxide from the inhaled airstream.

Cigarette smoke reduces F_{ENO}, whereas nitrate- or arginine-rich foods, such as vegetables, may slightly increase the levels. However, the impact of food is limited and does not need to be taken into account. Airway infections have been reported to either slightly increase or reduce F_{ENO}.

Assessing F_{ENO} at different expiratory flows makes it possible to calculate bronchial and alveolar components of F_{ENO}. It is unclear how this information could be clinically useful, and such measurements are still limited to research.

Clinical applications of F_{ENO} in children

Normative values of F_{ENO} in children have been published, and show an age-dependent increase during childhood (figure 2). The upper level of normal ranges from 15 ppb in early childhood to 25 ppb in adolescence, and is slightly higher in males than in females. Higher normal levels are seen in atopic individuals and in certain non-Caucasian ethnic groups. In asthma, F_{ENO} shows daily fluctuations and the minimal

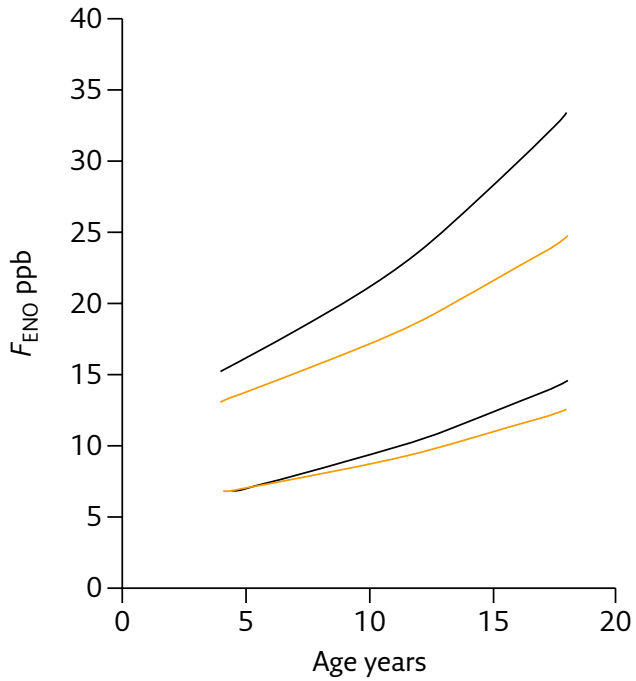

Figure 2. Normative values of F_{ENO} *in children. Black lines show mean and upper 95%* F_{ENO} *(n=405). Orange lines show mean and upper 95%* F_{ENO} *excluding outliers and atopics (n=332). Reproduced and modified from Buchvald* et al. *(2005) with permission.*

change that may be clinically relevant has been proposed as 10 ppb if F_{ENO} is <50 ppb or 20% with higher values. Others suggested that a 50% increase in F_{ENO} from baseline was associated with poorer asthma control in the following months.

High F_{ENO}, especially above 40–50 ppb, is strongly associated with eosinophilic airway inflammation. An abnormally low F_{ENO} may be seen during suppurative airway infection, *e.g.* in CF, and is of some diagnostic value in PCD. For the latter purpose, nasal nitric oxide measurements have better specificity and sensitivity.

A large number of clinical studies, both in adults and in children, support the clinical use of F_{ENO}; however, firm evidence of added benefit as compared to conventional practice is often lacking. In practice, F_{ENO} should be considered as one of the many pieces of information that clinicians may want to use when making a diagnosis or for treatment decisions.

F_{ENO} can be of help in the diagnosis of atopic asthma, especially if symptoms are indeterminate. Most published studies on the diagnostic value of F_{ENO} in asthma compared clear asthma cases with normal patients, thus providing a strong contrast that is often lacking in daily practice. Hence, the diagnostic value will be lower in less clearly defined populations of children. In contrast to spirometry, which is often normal in children with asthma, elevated F_{ENO} commonly persists in asymptomatic episodes and, as a diagnostic test, F_{ENO} performs better than FEV_1 or other tests of airway patency. A limitation of F_{ENO} is that it reflects eosinophilic inflammation, but not other types of inflammation. F_{ENO} may be low in neutrophilic inflammation, which occurs in a considerable proportion of asthmatic children, and this may alternate with eosinophilic patterns. The British Thoracic Society guidelines suggest using F_{ENO} in clinical practice (if available), as a positive test increases the probability of asthma, although a negative test does not exclude asthma.

In preschool children, F_{ENO} may be helpful in defining different wheezing phenotypes, and assessing the risk of developing asthma later in life. However, data are conflicting on the added value over clinical parameters. Two studies in schoolchildren suggested that high F_{ENO} is predictive for asthma development and for lower lung function growth. Inhaled corticosteroids (ICS) reduce F_{ENO}, an effect that occurs within a few days of daily treatment. Therefore, the diagnostic value of F_{ENO} is limited in subjects who are already on ICS treatment. The effect of ICS on F_{ENO} may be used to alert for nonadherence, in particular in atopic children with poorly controlled asthma, if a child with a documented F_{ENO} response on ICS exhibits high F_{ENO} levels. Elevated F_{ENO} is predictive of successful treatment with ICS, and an increase in F_{ENO} has been shown to precede loss of control in children who stop or taper their ICS dose while in clinical remission. F_{ENO} above 40–50 ppb is associated with an increased risk of exacerbation and loss of control. However, in an individual, the predictive value is limited and the benefits of regular F_{ENO} assessment to prevent loss of control remain to be shown.

Studies in adults with difficult-to-treat asthma and in schoolchildren with asthma indicated that F_{ENO} monitoring may be helpful to identify patients who have an accelerated decline in lung function, and to identify subjects who might benefit from higher doses of ICS.

Several studies in children and adults have tried to improve asthma management by titrating the dose of ICS in F_{ENO}. Although most of these studies report some significant benefit of F_{ENO} monitoring on secondary end-points, only a few found an effect on the primary end-point which differed between studies. In a meta-analysis, a significant

reduction in exacerbations was found for titrating ICS based on F_{ENO} as compared to conventional therapy.

The potential benefit of F_{ENO} as a monitoring tool in asthma treatment still requires more study, focusing on well-defined subgroups and exploring the effects of different algorithms. Guidelines do not recommend F_{ENO} for routine monitoring of children with asthma.

Induced sputum

Sputum induction is a relatively safe, noninvasive procedure that allows a direct assessment of airway inflammation, providing information on cellular components and on inflammatory mediators in supernatant. Furthermore, induced sputum may be valuable for the diagnosis of airway infections in children who do not expectorate and has been used as a diagnostic tool for example in CF, in PCD, in protracted bacterial bronchitis (PBB) and in pulmonary TB.

Sputum induction is obtained by inhalation of nebulised hypertonic saline solution followed by coughing and expectoration of airway secretions. Pretreatment with inhaled salbutamol and monitoring of lung function during the process are necessary to ensure the safety of sputum induction. In children aged >6 years, both induction and processing of sputum samples are standardised as reported in the European Respiratory Society (ERS) recommendations and the success rate for induced sputum collection is 80–85%. In younger children the success rate is lower, and the technique for collection is not yet standardised.

As for the role of induced sputum in the study of airway inflammation, several studies demonstrated that children with controlled or uncontrolled asthma have increased counts of eosinophils and increased levels of soluble mediators in induced sputum. Furthermore, in asthmatic children it has been shown that these biomarkers correlate with the degree of asthma control. In addition, in children with severe asthma the analysis of induced sputum showed a potential for contributing to the characterisation of inflammatory phenotypes and endotypes.

In adults the benefits of a treatment strategy that takes into account sputum eosinophilia as a marker of airway inflammation have been proved. In contrast, the studies in children on the possible role of induced sputum as a guide for anti-inflammatory treatment are not unanimous. A real-life study showed that measuring induced sputum eosinophils every 3 months in children with severe asthma does not provide significant benefits on the number of exacerbations or the degree of asthma control. Conversely, a previous study demonstrated that the absence of sputum eosinophils is a predictor for successful ICS dose reduction in children with asthma.

Of note, in children aged ⩾12 years, like adults, the Global Initiative for Asthma (GINA) guidelines published in 2019 state that sputum-guided treatment, if available, improves outcomes in moderate–severe asthma.

Considering that bacterial infections are associated with morbidity and mortality in patients with CF and PCD, a thorough understanding of the airway microbiology of both diseases is fundamental to improve patient care. In these patients, sputum monitoring is recommended, in order to prescribe antibiotic therapy directed against the predominant organisms. Sputum has also been used extensively to assess inflammation in CF airways, measuring cytokines (such as tumour necrosis factor-α,

interleukin (IL)-1β, IL-6 and IL-8), proteases, markers of oxidative stress, nitric oxide metabolites and markers of structural airway injury. Nowadays, even if sputum biomarkers of inflammation in CF are generally biologically relevant, repeatable, sensitive to treatment effects and generally feasible, we do not have sufficient data to recommend their regular use in clinical practice.

As far as PBB is concerned, according to the ERS technical standard published in 2017, in children with isolated chronic (>4 weeks' duration) wet or productive cough, lacking symptoms and signs of an underlying disease and with normal chest radiograph, a spontaneous or induced sputum specimen should be collected to guide antibiotic therapy. As most children are too young to expectorate and provide a reliable sputum specimen, in PBB the choice of antibiotic is frequently empirical. Sputum induction may help to get adequate samples for microbiological analysis.

The diagnosis of pulmonary TB in children is based on the presence of recent close contact with an infectious case, a positive tuberculin skin test (TST) or interferon-γ release assay (IGRA) and suggestive findings on chest radiography or physical examination. In children with suspected pulmonary TB, if these diagnostic criteria are not helpful, bacteriological confirmation is needed, through sputum examination (microscopy and mycobacterial culture), followed by BAL fluid analysis. Unfortunately, the microbiological diagnosis is only achievable in <50% of children and <75% of infants, because this disease typically presents with paucibacillary, noncavitary pulmonary disease. With PCR techniques higher sensitivity (up to 64%) and specificity (up to 100%) can be reached in induced sputum samples.

Despite the relative safety and tolerability of sputum induction in children, the technique has several potential limitations, *e.g.* the amount of time to perform and process (average of 3 h); the technical support and expertise required to process, stain and interpret the samples; the ability (of the child) to provide acceptable samples; and the risk of developing bronchospasm.

In conclusion, several data support the possible role of induced sputum for assessing and phenotyping airway inflammation in children with asthma and other respiratory diseases. Nonetheless, for now, there is no evidence of a clear benefit from this inflammation measurement in routine clinical management. However, sputum induction can be used to obtain material for bacterial cultures in CF, TB and other infectious diseases.

Exhaled breath analysis

Among noninvasive methods to investigate the pathogenic mechanisms underlying airway inflammation in children, one of the leading players is the analysis of exhaled breath and exhaled breath condensate.

Exhaled breath temperature measurement has been suggested as a noninvasive method to detect airway inflammation and airway remodelling, even if nowadays there are no clear recommendations on the usefulness of this biomarker in asthma diagnosis and monitoring in children, nor on the method that should be applied for the measurement.

Exhaled breath condensate (EBC) is a vehicle for components from lower airways, thus enabling the study of pulmonary biochemical and inflammatory processes. EBC collection is based on a noninvasive technique that only requires tidal breathing, the

condensate being obtained by cooling exhaled air on contact with a cold surface or a condenser. Different condensers have been proposed: from a simple tube system to be cooled in a refrigerator, to more sophisticated devices that use cooled containers through which the exhalate passes and in which EBC is retained. Recently, an ERS technical standard provided technical norms and recommendations for the collection and analysis of EBC samples. During collection, the use of a nose clip and a saliva trap is recommended, and the material of tubing and condenser should be inert for substances of interest.

In children with chronic lung disease (in particular asthma and CF), EBC has been studied through both targeted (measurement of single analytes) and untargeted (-omic techniques) approaches.

Through a targeted approach, many single mediators related to inflammation and oxidative stress have been searched in EBC. Among them are:

- pH, which tends to be lower in severe or acute asthma, but not in mild and stable disease
- Leukotrienes, *e.g.* LTB4, a potent inflammatory mediator and a chemoattractant for neutrophils, which are increased in the EBC of asthmatic children; and cysteinyl leukotrienes, *e.g.* LTC4, LTD4 and LTE4, powerful constrictors and pro-inflammatory mediators, which are increased in particular in unstable or severe asthma
- 8-Isoprostane, hydrogen peroxide and other markers of oxidative stress that are increased in asthma and in CF
- 3-Nitrotyrosine and other nitric oxide metabolites that are more concentrated in asthmatic children than in healthy controls

Since no single biomarker can fully describe the pathogenic processes underlying complex chronic diseases, a number of studies have applied an untargeted approach (-omic approach), usually based on spectroscopic techniques, to study the overall biochemical–metabolic composition of exhaled air and EBC, with the potential for identifying analyte profiles characteristic of specific conditions.

EBC in particular has been studied through proteomic and metabolomic approaches.

- Proteomics studies the peptidic composition of biological samples. A different peptide arrangement was found in children with asthma compared to healthy children.
- Metabolomics studies the metabolic composition of biological samples. It was possible to discriminate healthy from asthmatic children, and different subphenotypes among the latter.

By means of an -omic approach, the volatile organic compound (VOC) profile of exhaled air can be analysed. VOCs originate from the upper airways or lung and from blood circulation, spreading from the pulmonary capillary bed into the alveoli. VOC profiles have been studied using two different techniques: gas chromatography with mass spectrometry, a quantitative method (individual components); and the electronic nose (e-Nose), a qualitative method (biomarker profiles). The analysis of exhaled VOC profiles has shown interesting results in asthma diagnosis, monitoring and phenotyping.

Although very promising, -omic findings cannot yet be applied to clinical practice, because they still need to be replicated in multicentre studies (external validation), and biomarkers identified need to be confirmed and quantified using targeted approaches.

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Assessing respiratory risks of air travel, altitude and diving

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As altitude increases, the fall in barometric pressure causes a proportional reduction in partial pressure of oxygen. Commercial aircraft cabins are pressurised to the equivalent of 1500–2400 m altitude. During air travel, passengers breathe the equivalent of 15–17% oxygen (as opposed to 21% at sea level). The large fall in alveolar partial pressure of oxygen (98 mmHg at sea level to 55 mmHg at maximum cruising altitude) is only accompanied by a small decrease in oxygen saturation in healthy children. However, in those with underlying pathology, the fall in oxygen tension may result in a marked fall in S_{pO_2}. Longer exposure to hypobaric hypoxia during travel to altitude can result in high-altitude illness, which encompasses acute mountain sickness (a collection of symptoms including headache, gastrointestinal symptoms and sleep disturbance), high-altitude cerebral oedema and high-altitude pulmonary oedema.

Healthy individuals compensate for the relative hypoxia of the in-flight/high-altitude environment with an increase in heart rate and V'_E, mostly by increasing tidal volume. Longer-term compensation to altitude includes increasing red cell mass and renal bicarbonate excretion. Physiological factors, such as poorer respiratory system compliance, a more horizontal rib placement, higher airways resistance and fewer alveoli make infants and young children less able to adjust to hypobaric hypoxia, meaning they are at greater risk than adults of developing hypoxaemia. In addition, young infants are at risk of even greater hypoxaemia due to the presence of fetal

Key points

- Infants and children with chronic respiratory and cardiac disease are at risk of developing hypoxia and respiratory symptoms during air travel and travel to altitude.
- The hypoxia challenge test is the currently recommended tool for the assessment of at-risk individuals, but is unreliable in preterm-born infants at term-corrected age, and is of limited reliability in infants and young children.
- As well as those with lung disease, children predisposed to pulmonary hypertension are at increased risk when travelling to high altitude.
- Overall health, exercise tolerance and maturity need to be assessed when determining fitness to dive. Certain lung and cardiac pathologies are contraindications to diving.

haemoglobin, persistence of right-to-left shunt in the first week of life, labile pulmonary vascular reactivity and the immature biphasic hypoxic ventilation response.

Scuba diving exposes individuals to changes in ambient pressure. The increased hydrostatic pressure with underwater descent results in an increase in cardiac and respiratory workload. Changes in barometric pressure can cause barotrauma to the sinuses, ears and lungs, as well as decompression sickness. Breathing gas at increased pressure can result in complications such as nitrogen narcosis and oxygen toxicity. In addition, divers can be exposed to cold temperatures, hypertonic saline mist, the physical rigours of having to navigate currents and situations that require composure and sound judgement. PADI (the Professional Association of Diving Instructors) allow children aged as young as 8 years to dive using scuba equipment. Children may have less physiological reserve to cope with the physical stressors of diving, and certain underlying pathologies can place them at higher risk of complications. Potential scuba divers are generally required to have their fitness to dive certified by a physician, but the specific medical requirements vary from country to country.

The aim of this review is to highlight the key points for medical professionals considering the safety of air travel, travel to high altitudes and scuba diving in at-risk paediatric patients.

Methods of assessing fitness to fly

Resting oxygen saturations at sea level have been shown to be poorly predictive of in-flight hypoxaemia. The hypoxia challenge test (HCT) has been validated in a variety of adult populations prior to flight to identify patients who are at risk of significant in-flight respiratory symptoms. The HCT may be performed in a body plethysmograph with inspiratory oxygen fraction (F_{IO_2}) of 14–15% or with 14% oxygen *via* a face mask over the mouth and nose for 20 min. While the HCT is a valuable tool, there are a number of unanswered questions, including its reliability in infants and children. The HCT may not accurately predict in-flight hypoxaemia in neonates and infants. Physiological responses in this group may be influenced by flight duration, age, feeding and sleep stage. HCT has been shown to be more accurate in older children and adolescents. There have been no studies comparing results between the face mask technique and formal body box testing method and few comparing HCT results with actual in-flight behaviour. There are concerns that the face mask method may be less reliable, possibly due to issues with mask seal. Infants have been shown to desaturate while feeding during HCT, and this can only be assessed using the body plethysmograph method. In addition, the saturation cut-off for "normal" *versus* "abnormal" HCT result is unclear in early life. The British Thoracic Society (BTS) guidelines recommend that infants aged <1 year with an HCT result of <85% should fly with supplemental oxygen, but in children aged >1 year the cut-off is 90%. Studies have reported variable accuracy around these results, and asymptomatic desaturations below 90% are common in healthy infants and children.

Specific groups at risk during air travel

Preterm birth and BPD

Clinical studies have demonstrated that preterm-born neonates with BPD and preterm-born infants who have not yet reached term-corrected gestation are at the highest risk of desaturation during airline flights. One study showed that HCT could not accurately predict which ex-premature infants flying near term-corrected age would desaturate in-flight. The BTS guidelines recommend that preterm infants fly

with supplemental oxygen available until they are beyond term-corrected age. Infants with a history of BPD should be assessed by HCT prior to air travel.

Cystic fibrosis

CF patients with a lower baseline FEV_1 tend to desaturate more in hypoxic settings. The humidity of the air in an aircraft at altitude is very low, which could theoretically affect the viscosity of airway secretions and a CF patient's ability to expectorate. Studies of the ability of HCT to predict in-flight desaturation in children with CF have found mixed results. Current BTS guidelines recommend that children old enough to perform spirometry and with FEV_1 <50% predicted should undergo HCT prior to flying.

Asthma

There have been no studies of in-flight responses of children with asthma, despite this being the most common chronic childhood respiratory condition. Low cabin humidity may provoke bronchospasm in susceptible individuals. It may be pertinent to consider HCT in children with severe asthma (adult BTS guideline recommends FEV_1 <30% predicted), and all should fly with their regular medications.

Congenital heart disease

The few data available suggest that children with actual or potential left-to-right shunt, unrepaired lesions or who have undergone "palliative" surgery are at the highest risk of desaturating in response to hypoxia. These children should undergo an HCT prior to air travel.

Neuromuscular disease

Patients with neuromuscular disease may be unable to increase minute volume in response to the relative hypoxia of the in-flight environment, and hence may desaturate. The BTS recommends preflight HCT for all individuals who require ventilatory support at home.

The European Lung Foundation (www.europeanlung.org/) has developed a database that provides information to help patients and healthcare providers arrange air travel and supplemental oxygen.

The most relevant fitness-to-fly guidelines are from the BTS. Those not already discussed are summarised as follows.

- Infants born at term (>37 weeks) should delay air travel for 7 days after expected term date to ensure they are healthy
- Infants and children receiving supplemental oxygen at the time of air travel should have their oxygen flow doubled
- Infants and children with recent long-term oxygen therapy (in the past 6 months) should have an HCT

Travel to altitude

A number of popular tourist destinations are situated at significant altitudes, and children with underlying susceptibilities that travel to these locations may be at increased risk of high-altitude illness. Higher rates of sudden infant death syndrome, persistent pulmonary hypertension of the newborn and symptomatic pulmonary hypertension after the neonatal period have been observed in infants residing at high

altitude, suggesting that they are particularly vulnerable to adverse consequences of a hypoxic environment. Scant data exist as to the risks associated with lowland-residing infants travelling to higher altitude areas. Given the findings of HCT studies, preterm-born infants not yet at term-corrected age and infants with BPD would be anticipated to be at the highest risk of altitude-associated illness. In addition, infants and children with a predisposition to pulmonary hypertension are known to be at increased risk of high-altitude illness, in particular pulmonary oedema. This includes children with Down syndrome, BPD, OSA, certain congenital cardiac lesions and severe scoliosis. The HCT has been used to try to predict response to travel to higher altitude in at-risk populations, but is not well validated. The risk of high-altitude illness is reduced if ascent is gradual.

Scuba diving

When considering a child's fitness to scuba dive, general physical wellbeing, exercise tolerance and decision-making maturity should be taken into account. Lung disease with cysts or bullae, a history of spontaneous pneumothorax, or severely reduced lung function are considered absolute contraindications to diving. Middle ear and sinus pathologies may pose a risk of barotrauma. Cardiac arrhythmias can be exacerbated or provoked by immersion in cold water. Congenital cardiac lesions with actual or potential right-to-left shunting are contraindications to diving due to the risk of paradoxical gas emboli. Patients with asthma are at risk of bronchospasm when saline mist and/or cold air is inhaled. Asthmatic potential divers should be assessed using spirometry. Hypertonic saline provocation test can help assess risk of symptoms during diving. Asthmatics should only dive when symptom-free, having not needed to use bronchodilators in the past 48 h.

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Flexible airway endoscopy

Ernst Eber, Jacques de Blic and Fabio Midulla

Since its introduction in the 1970s, flexible airway endoscopy has become an increasingly important tool for the diagnosis and treatment of many disorders of the respiratory tract in infants and children. With an expanding number of indications and applications in children, it has been the subject of recent European Respiratory Society (ERS) and American Thoracic Society (ATS) task forces. Flexible bronchoscopes allow for anatomical and functional examination of the upper and lower airways and for taking samples, by BAL (see chapter "Bronchoalveolar lavage: techniques and indications"), bronchial brushing and bronchial and transbronchial biopsies (see chapter "Bronchial brushing and bronchial and transbronchial biopsies"). With technological evolution in available instruments and the increased use of general anaesthesia with concomitant changes in airway management, the number and types of procedures performed have expanded further (see chapter "Rigid and interventional airway endoscopy"). Flexible

Key points

- Flexible airway endoscopy is a safe procedure, provided the child is adequately prepared and the procedure is performed by skilled and trained personnel, even in children with unstable respiratory status or under mechanical ventilation. In almost all circumstances the entire airway should be examined for full and correct understanding of airway anatomy, dynamics and pathologies.
- The primary indication for diagnostic airway endoscopy is when, based on the available clinical data, the information from the lungs or airways is most safely, effectively and easily obtained by airway endoscopy. In many settings, stridor is one of the most common indications for diagnostic airway endoscopy, especially in neonates and infants.
- The results of an airway endoscopy and associated procedures (*e.g.* BAL) must be interpreted in the context of history, clinical findings, imaging, lab results, the type of sedation, the route and mechanical factors.
- Complications may be prevented by detection of high-risk children, administration of inhaled β_2-agonists in children with bronchial hyperresponsiveness, careful local anaesthesia, liberal oxygen supplementation, use of the lowest flexible bronchoscope diameter, appropriate anaesthesia, and training.

airway endoscopy is a safe procedure, provided the child is adequately prepared and the procedure is performed by skilled and trained personnel, even in children with unstable respiratory status or under mechanical ventilation in neonatal or paediatric intensive care units (ICUs).

Equipment

Bronchoscopes

Two technologies are used to transmit light and images: while light is always transmitted *via* glass fibres, images are transmitted either *via* coherent glass fibres or *via* charge-coupled devices (CCDs).

- The classic fibreoptic bronchoscope uses fine filaments of flexible glass fibres. With this old technology, the larger the bronchoscope, the better the image obtained, due to the higher number of fibres.
- In a video bronchoscope, a CCD is incorporated into the tip of the instrument; in contrast to the fibreoptic bronchoscope, the video bronchoscope does not contain an eyepiece. These instruments provide a very high image quality.
- In a hybrid video fibreoptic bronchoscope, the two technologies are combined. The images are transmitted *via* glass fibres to a CCD located in the body of the instrument, which improves the image quality and allows for video processing.

Table 1 summarises the main characteristics of the different instruments available for infants and children. The external diameter determines the presence (and size) or absence of a working channel. The 2.2-mm flexible bronchoscope does not have a working channel and is limited to visualisation of airways, *e.g.* in ventilated neonates. The 2.7–3.7-mm flexible bronchoscopes have 1.2–1.7-mm working channels, which allow suction and BAL to be performed, and are wide enough to allow the use of instruments such as a cytology brush or biopsy forceps (the specimens obtained are very small). The 4.1–5.1-mm flexible bronchoscopes have 2.0–2.2-mm working channels, which allow for more and bigger instruments to be used, *e.g.* biopsy forceps.

In addition to these instruments, single-use bronchoscopes are available in various sizes. The size of the flexible bronchoscope is chosen according to the age of the patient and the diameter of the cricoid cartilage, but also according to the procedures that are to be performed. In general, the smallest instrument available should be used, to minimise airway obstruction. As a general rule, there must be a ⩾2-mm difference between the external diameter of the flexible bronchoscope and the diameter of the cricoid cartilage. In neonatal and paediatric ICUs, it may be necessary to pass

Table 1. Flexible bronchoscopes

External diameter mm	Imaging technique	Age years	Working channel mm	BAL	Brushing	EB	TBB
2.2	FB	Neonate	No	No	No	No	No
2.7–2.8	FB/HB	0–2	1.2	Yes	Yes	Yes	Yes
3.1	VB	0–2	1.2	Yes	Yes	Yes	Yes
3.4–3.7	FB/HB	2–5	1.2–1.7	Yes	Yes	Yes	Yes
4.1–4.2	HB/VB	2–5	2.0	Yes	Yes	Yes	Yes
4.4–5.1	HB/VB	>5	2.0–2.2	Yes	Yes	Yes	Yes

EB: endobronchial biopsy; TBB: transbronchial biopsy; FB: fibreoptic bronchoscope; HB: hybrid video fibreoptic bronchoscope; VB: video bronchoscope.

the flexible bronchoscope through an endotracheal tube; here, the recommended difference in diameter is ⩾1 mm.

Endoscopy room

Flexible airway endoscopies may be performed in an operating room, in an ICU or in a dedicated bronchoscopy suite. Mobile bronchoscopy carts allow procedures to be performed in various settings. A bronchoscopy suite needs to be fully equipped with:

- An operating table
- A workstation, including a bright light source, a video system centre (with adaptors for older fibreoptic bronchoscopes), a monitor, a keyboard and a recording system (for videos and still pictures)
- A trolley containing room-temperature saline, syringes, cytology brushes, biopsy forceps, specimen traps for BAL fluid, *etc*.
- Monitoring equipment (ECG, pulse oximeter and blood pressure monitor)
- An oxygen supply system
- High-power suction sources
- Equipment and drugs for intubation and resuscitation
- Protective equipment (face masks, goggles, gloves, gowns)

Depending on the setting, dedicated and experienced personnel including trained theatre nurses and/or other support staff are needed to run a bronchoscopy service.

Cleaning, disinfection and storage

After each use, flexible bronchoscopes must be manually cleaned and disinfected to prevent cross-infection and contamination. Accessories such as biopsy forceps require manual cleaning and sterilisation between uses. Flexible bronchoscopes should be tested regularly for leaks before cleaning to prevent permeation of any fluids into the optical system. Disinfection may be performed by immersion in an appropriate disinfectant (2% alkaline glutaraldehyde) or in an automated disinfection device. Established guidelines and manufacturers' recommendations should be strictly followed. A record should be kept for each procedure, including patient identification, date of the procedure and an identifier of the bronchoscope used. Checks for micro-organism colonisation should be performed once a week with a culture of saline solution used for rinsing the bronchoscopes. Flexible bronchoscopes should always be stored in a dedicated storage cabinet, hanging in a straight vertical position.

Procedure

The procedure may be performed under moderate sedation or deep sedation (general anaesthesia) (see chapter "Sedation for airway endoscopy"). Spontaneous breathing should always be preserved. Sedation that is too deep may lead to overestimation or wrong diagnosis of pharyngomalacia, glossoptosis and laryngomalacia. Positive-pressure ventilation may mask dynamic airway pathologies (tracheomalacia and bronchomalacia, and possibly pharyngomalacia and laryngomalacia).

Airway entry techniques

Generally, the choice of the airway entry technique should be driven by the indication for airway endoscopy. In almost all circumstances the entire airway (from the nostrils to at least the subsegmental bronchi) should be examined for full and correct understanding of airway anatomy, dynamics and pathologies (figure 1). Thus, the flexible bronchoscope is usually passed through the nose; this technique allows for insufflation of oxygen and anaesthetic gas using a cannula through the other nostril.

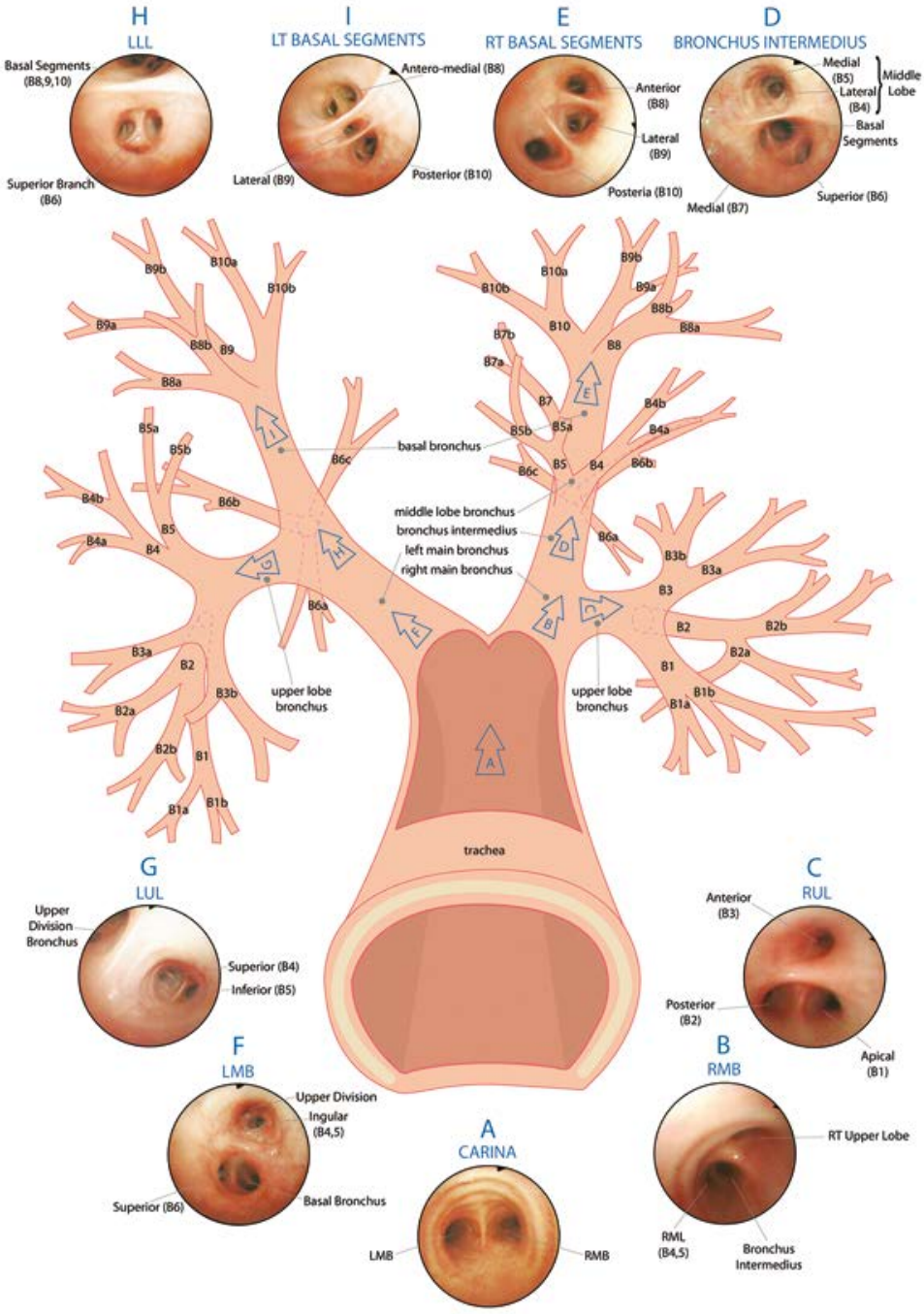

Figure 1. Bronchoscopic views of the normal bronchial tree. Reproduced from Priftis et al. *(2010) with permission.*

The flexible bronchoscope can be passed through a face mask, again allowing for inspection of the entire airway and evaluation of airway dynamics, but possibly limiting movement of the bronchoscope.

If evaluation of airway anatomy and dynamics is not indicated, other airway entry techniques may be preferable, *e.g.* to avoid the upper airway in order to minimise the potential for contamination of BAL fluid in an immunocompromised child. A laryngeal mask airway provides easy access to the trachea and allows for positive-pressure ventilation. However, bypass of the upper airway from the nostril to the glottis may result in missed or erroneous diagnoses. Pressure on the post-cricoid area and arytenoids may lead to altered vocal cord movement and impaired ability to visualise

a laryngeal cleft, and traction on the post-cricoid mucosa may lead to reduction or prevention of arytenoid prolapse (laryngomalacia).

An endotracheal or tracheostomy tube provides easy and fast access to the lower airways, may be essential to maintain ventilation or oxygenation during the (prolonged and/or difficult) procedure, and potentially avoids contamination of lower airway specimens by upper airway secretions, of particular importance in immunocompromised patients. However, it may limit the size of the bronchoscope, and bypass of the upper airway from the nostril to the upper part of the trachea may result in missed or erroneous diagnoses, including erroneous estimation of airway dynamics (tracheomalacia, bronchomalacia).

Indications

Diagnostic airway endoscopy provides two different types of information, one by direct visualisation of airway anatomy and function and the other through the samples taken during the procedure (mainly BAL fluid, brushing and biopsy specimens). Indications for diagnostic bronchoscopy in infants and children are listed in table 2.

Airway obstruction is the main indication for endoscopy in many settings. Stridor is one of the most common indications for diagnostic airway endoscopy, especially in

Table 2. Main indications for diagnostic airway endoscopy in infants and children

Airway obstruction
Noisy breathing
Stridor (inspiratory and/or expiratory)
Severe recurrent/persistent wheezing
Chest radiograph abnormalities
Persistent atelectasis
Recurrent/persistent pneumonia
Localised hyperinflation
Bronchiectasis
Mediastinal adenopathy
Infectious diseases
Immunocompetent children
TB
Severe acute pneumonia, severe acute interstitial pneumonia (not responding to standard broad-spectrum antibiotic therapy within 48 h)
CF (under certain conditions)
Immunocompromised children
Acute onset of diffuse interstitial pulmonary infiltrates
Acute focal infiltrates (not responding to standard broad-spectrum antibiotic therapy within 48 h)
Chronic interstitial pneumonitis
Chronic recurrent bronchopneumonia in HIV-infected children (if organisms are not found by less invasive techniques)
Monitoring of lung allograft (transbronchial biopsy as part of a routine surveillance programme and/or for the diagnosis of suspected lung disease)
Unexplained chronic cough
Suspected foreign body aspiration
Chronic ILD
Haemoptysis and pulmonary haemorrhage
Monitoring of artificial airways

neonates and infants. Inspiratory stridor is indicative of functional narrowing of the larynx and/or the extrathoracic trachea, while biphasic (inspiratory and expiratory stridor) suggests fixed laryngeal and/or tracheal obstruction. The term "stridor is visible" implies that when a child is stridulous during endoscopy, at least one causative pathology has to be detected. The primary indication for diagnostic airway endoscopy is when, based on the available clinical data, the information from the lungs or airways is most safely, effectively and easily obtained by airway endoscopy. Thus, many respiratory pathologies, especially persistent or recurrent clinical symptoms and/or radiological abnormalities, will lead to endoscopic airway exploration. The results of an airway endoscopy and associated procedures (*e.g.* BAL) must be interpreted in the context of history, clinical findings, imaging, lab results, the type of sedation, the route and mechanical factors.

Endoscopic findings

Upper airways

At the upper (extrathoracic) airways level, laryngomalacia is the most common congenital laryngeal anomaly and the most common cause of persistent stridor in infancy. Endoscopy identifies anatomical characteristics (*e.g.* short aryepiglottic folds) or functional problems (collapse of the epiglottis and/or aryepiglottic folds and/or arytenoids into the glottis, posterior displacement of the epiglottis against the posterior pharyngeal wall). Direct visualisation of the airways is indicated in all children with persistent stridor, unless the stridor is very mild and there are no associated respiratory signs or symptoms. In a significant number of patients with persistent stridor, lower airway lesions are associated with upper airway lesions. Thus, the entire airway should be examined whenever possible. The examination must be performed carefully, and the airways should be monitored during the various stages of sedation. Local anaesthesia may worsen laryngomalacia.

Other abnormalities causing persistent stridor include the following:

- Subglottic stenosis: congenital types (membranous forms causing symmetrical narrowing due to thickening of the soft tissues in the subglottic area, webs, and cartilagineous forms with variable appearance due to malformations of the cricoid cartilage) are distinguished from acquired types caused by endotracheal intubation or tracheostomy, with an irregular appearance (ulcerations, granulation tissue and cysts).
- Vocal cord paralysis (unilateral or bilateral, adductor or abductor paralysis): evaluation must be performed when the child is awake or under light sedation only.
- Haemangioma: this is the most common tumour in infancy and typically presents as an asymmetrical subglottic mass.
- Laryngeal cyst, laryngeal web, laryngeal cleft: congenital laryngeal cysts are typically located at the supraglottic level; incomplete or complete laryngeal webs are mainly found at the glottic or subglottic level; laryngeal clefts vary in length from supraglottic interarytenoid clefts to clefts with extension into the thoracic trachea; clefts may be associated with other anomalies of larynx, trachea or oesophagus.
- Laryngeal papillomatosis: typically the papillomas appear as multiple irregular masses, most commonly on the vocal cords and sometimes extending into the trachea and bronchi.
- Inducible laryngeal obstruction (formerly vocal cord dysfunction): this pathology is characterised by paradoxidal adduction of the vocal (sometimes also the false) cords during inspiration, or both inspiration and expiration; evaluation must be performed without sedation.

Lower airways

In the lower (intrathoracic) airways, endoscopy may provide information on airway anatomy, the presence and degree of fixed or dynamic airway obstruction, inflammation and secretions.

Large airway anatomy usually does not show variation in humans. Most of the abnormal bronchi are variants and supply normal lung parenchyma. A tracheal bronchus, which is observed in ~1% of flexible bronchoscopies, is the most common. In this case, the bronchus originates from the right lateral wall of the trachea and may supply either the entire right upper lobe or only the apical segment. Abnormal airway anatomy includes situs inversus (potentially associated with PCD), left or right isomerism (two right or two left bronchial patterns, frequently associated with congenital heart defects and abdominal visceral heterotaxy), and lung agenesis/aplasia. In the latter, a more or less rudimentary bronchus is observed at the main carina. Finally, the opening of a tracheo-oesophageal fistula can be found in the posterior tracheal wall. A fistula can be confirmed by injecting methylene blue or radiopaque material into the fistula and detecting its presence in the oesophagus (the same result can be obtained when injecting methylene blue or contrast material into the oesophagus to be detected in the trachea).

Airway patency may be affected by intrinsic or extrinsic lesions. Intrinsic airway obstruction may be caused by an inhaled foreign body, a congenital (*e.g.* complete tracheal rings, web) or acquired (post-endotracheal intubation/mechanical ventilation) tracheal and/or bronchial stenosis, a granuloma, an endobronchial tumour, a bronchial cast (also known as plastic bronchitis) or mucus plugging.

Extrinsic airway obstruction may be due to compression by a congenital malformation (*e.g.* bronchogenic cyst), an adenopathy (*e.g.* TB, malignancy), a tumour or a vascular anomaly. The most frequent form of vascular compression is by a vascular ring (double aortic arch or right-sided aortic arch with a left patent ductus arteriosus or ligamentum arteriosum). A double aortic arch causes obstruction of the distal trachea and possibly also the right mainstem bronchus. The trachea is distorted in the shape of a comma or drop, with the narrowest part directed to the right. An aberrant left pulmonary artery (pulmonary artery sling) compresses the posterior wall of the distal trachea and the origin of the right mainstem bronchus, and is strongly associated with congenital tracheal stenosis. Congenital heart disease with left-to-right shunt and enlarged pulmonary arteries may compress the right mainstem and right middle lobe bronchus. The left mainstem bronchus may be compressed by heart enlargement, and between the right pulmonary artery and the descending aorta. An absent pulmonary valve is associated with an enlarged pulmonary artery, which compresses the distal trachea, both mainstem bronchi and the bronchus intermedius. Significant anterior compression of the trachea by an anomalous innominate artery or an anomalous left carotid artery associated with tracheomalacia is rare. Similarly, posterior tracheal compression by an aberrant subclavian artery is usually not clinically relevant.

Tracheo- and/or bronchomalacia are caused by localised or generalised weakness of the airway wall (due to reduction and/or atrophy of the longitudinal elastic fibres of the pars membranacea, impaired cartilage integrity or reduced circumference of the tracheal cartilage). They result in dynamic airway obstruction, defined as an abnormal collapse (>50%) of the intrathoracic trachea and/or the main bronchi during expiration. There is no universally accepted classification of severity; the functional changes are usually arbitrarily described as mild (50–75% reduction), moderate (75–90% reduction) or severe (>90% reduction). Tracheo- and/or bronchomalacia may be

congenital (primary or secondary) or acquired; secondary congenital forms are mainly seen in children with vascular malformations and oesophageal atresia with tracheo-oesophageal fistula.

Inflammation and secretions

In children, the bronchial mucosa appears thicker than in adults and the mucosa is salmon-pink. The appearance of the mucosa can change to pale, reddish, thinned or thickened. Airway endoscopy can identify granulations (*e.g.* due to chronic aspiration or sarcoidosis). Secretions are usually characterised as moderate or abundant, localised or diffuse, being renewed or not after aspiration, mucous, muco-purulent, purulent or haemorrhagic.

Bronchoscopy in paediatric ICUs

Children in paediatric ICUs may require airway endoscopy for a primary airway problem or a secondary complication. These children are often unstable and/or ventilator-dependent. In these situations, sedation should be increased appropriately, monitoring should include capnography and the procedure should be as short as possible, performed by an experienced bronchoscopist, assisted by a senior intensivist. Flexible airway endoscopy has been shown to be useful and safe and well tolerated in very sick children. Adverse effects of bronchoscopy in paediatric ICUs include hypoxia, hypercapnia, inadvertent PEEP, hypotension, raised intracranial pressure and prolonged hypoxaemia following BAL. Main contraindications are severe hypoxaemia, bleeding diathesis, severe pulmonary hypertension, cardiac failure, cardiac instability/hypotension and procedures that will not provide useful information. Indications for bronchoscopy in paediatric ICUs are listed in table 3.

Bronchoscopy in neonatal ICUs

Persistent airway obstruction resulting in atelectasis or hyperinflation is a constant concern in the neonatal ICU and flexible airway endoscopy allows for rapid evaluation of the tracheobronchial tree. Sudden unexplained deteriorations in the respiratory status also provide reasons for endoscopic evaluation.

In spontaneously breathing infants, flexible bronchoscopy carries the risk of inducing respiratory failure, particularly in small patients (≤2500 g) or those with a borderline respiratory status. A 2.2-mm flexible bronchoscope can be passed through a 2.5-mm

Table 3. Main indications for airway endoscopy in paediatric and neonatal ICUs

Paediatric ICU
Endobronchial toilet
Assessment of lobar collapse
Ventilator-associated pneumonia
Difficult intubation
Selective intubation
Failure to extubate
Foreign body assessment/removal
Airway stent assessment
Neonatal ICU
Unexplained cyanotic spells
Failure to wean from mechanical ventilation
Persistent atelectasis/hyperinflation

endotracheal tube, but has no working channel. A 2.8-mm flexible bronchoscope can be passed through a 3.5-mm endotracheal tube and has a working channel for aspiration of secretions and BAL. Similar to paediatric ICUs, an experienced paediatric bronchoscopist must perform the procedure quickly in a neonatal ICU; heart rate, blood pressure, oxygen saturation and temperature should be constantly monitored throughout the procedure. The absence of a working channel with the ultra-thin flexible bronchoscope prevents suctioning of secretions, and the administration of topical anaesthesia or normal saline. However, careful suctioning prior to ultra-thin flexible bronchoscopy adequately prepares the airways for the procedure. Risks of complications are increased, including the risks of hypothermia, hypotension, hypoxia, apnoea, bradycardia and intracranial haemorrhage.

Flexible bronchoscopy may reveal endoluminal abnormalities (*e.g.* granuloma, inflammatory stenosis), malformations (*e.g.* tracheal bronchus), severe extrinsic compression, or severe tracheo- and/or bronchomalacia. These airway anomalies can exist simultaneously, and their correct diagnosis is paramount to the management of these patients, also providing information for possible surgical interventions.

Tolerance and complications

Flexible bronchoscopy is well tolerated in most cases and the risk of major complications remains low. However, the potentially dangerous nature of these complications necessitates careful analysis of indications and clinical status for each patient and proper monitoring during the procedure. Moreover, the skills of both the bronchoscopist and anaesthesiologist may decrease the incidence of complications, demonstrating the value of training. Complications can be divided into physiological, mechanical, infectious and anaesthetic complications, and post-BAL fever.

Physiological complications

These represent the most frequent complications and include hypoxaemia, with or without hypercapnia, laryngospasm and bronchospasm, as well as cardiac arrhythmia and bradycardia. Partial or total airway obstruction by the bronchoscope and depression of respiratory drive due to sedation are the most frequent causes of oxygen desaturation during flexible bronchoscopy in children, and may worsen pre-existing hypoxaemia. Upper airway pathology, persistent radiographic changes, oxygen dependency, weight <10 kg and age <2–3 years are significantly associated with increased risk of adverse events. Oxygen desaturation may also be a consequence of laryngospasm or bronchospasm. In children undergoing bronchoscopy, when the airways are compromised by both the underlying condition and the procedure itself, any depressant effect of sedation is likely to be poorly tolerated. Oxygen supplementation may delay detection of reduced ventilation but the latter should be sought by close observation of the child, and capnography when appropriate. If desaturation episodes are moderate and transient (no decrease in oxygen saturation to <90%, episodes lasting <1 min) they do not affect or preclude completion of the procedure. However, if desaturation decreases to <90%, intervention is required and, if needed, the procedure should be terminated.

Mechanical complications

These include epistaxis, haemoptysis (which may be favoured in patients with coagulopathy or if the platelet count is <20 000 cells·mm^{-3}), pneumothorax and post-bronchoscopy subglottic oedema.

Infectious complications

These complications are rare and, by default, are related to the cleaning of the bronchoscope and accessory equipment. The spread of infection appears to be a very rare complication.

Anaesthetic complications

Most life-threatening adverse events during flexible bronchoscopy involve drug overdose, inadequate monitoring or inappropriate sedation, with respiratory depression being the most concerning adverse effect.

The following reduce the risk of complications:

- Detection of high-risk children (aged <2 years, with known or suspected laryngotracheal abnormalities; children with pulmonary hypertension)
- Nebulisation (or administration *via* metered-dose inhaler and spacer) of β_2-agonists in children with pre-existing bronchial hyperresponsiveness, to avoid bronchospasm
- Careful local anaesthesia to prevent excessive cough and laryngospasm
- Liberal oxygen supplementation
- Use of the lowest flexible bronchoscope diameter
- Appropriate anaesthesia
- Training

Post-BAL complications

Post-BAL fever is observed in up to 52% of cases. It usually begins a few hours after the procedure, with spontaneous defervescence occurring within 24 h. It has been attributed to the release of biologically active mediators, such as cytokines, and to transient bacteraemia. Factors such as young age, a positive bacterial culture and abnormal bronchoscopic findings, including whether a topical anaesthetic and saline are administered, are related to a higher risk of developing post-BAL fever. It has been shown in immunocompetent children that the use of intramuscular dexamethasone prior to the procedure caused a significantly greater reduction in the incidence of fever than placebo, favouring the hypothesis of inflammatory cytokine-induced fever. Thus, antipyretics are recommended for treatment of post-BAL fever.

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Bronchoalveolar lavage: techniques and indications

Fabio Midulla, Raffaella Nenna and Ernst Eber

BAL is a procedure used to recover cellular and noncellular components of the epithelial lining fluid from the alveolar and bronchial airspaces.

Techniques

Bronchoscopic BAL involves the instillation and immediate withdrawal of prewarmed sterile 0.9% saline solution through the working channel of a flexible bronchoscope, which has been wedged into a bronchus with a matching diameter. Generally, paediatric bronchoscopes with external diameters of 2.7–3.7 mm and working channels of 1.2–1.7 mm are used in children aged <6 years, whereas instruments with external diameters of 4.1–5.1 mm and working channels of 2.0–2.2 mm are used in children aged >6 years. The preferred sites for bronchoscopic BAL are the middle lobe or the lingula, because, being the smallest lobe/region of the respective lungs, they offer better fluid recovery. In particular, these sites are the least likely to undergo bronchial collapse during suction; they are the most accessible because of the favourable angles of the bronchial carina; they have a small volume and a high resistance to collateral ventilation; and gravity aids return in these lobes when supine. When lung disease is localised, BAL must target the radiologically or endoscopically identified involved lobe or segment and be performed in multiple sites if more than one lobe is affected. In patients with CF and protracted bacterial bronchitis, samples from multiple sites should be obtained in order to avoid underestimation of the extent of infection. When aspiration is suspected, multiple segments that are normally dependent should be sampled.

Alternatively, a non-bronchoscopic BAL can be performed by inserting a catheter through an endotracheal tube. Unfortunately, this method does not allow visualisation of the lavage site, although turning the child's head to the left predictably directs the catheter into the right lung.

Key points

- BAL is a procedure used to recover cellular and noncellular components from the alveolar and bronchial airspaces.
- Clinical applications involve microbiological studies and/or evaluation of cellular components.
- BAL is performed for diagnostic and therapeutic indications.

To avoid contamination, BAL must precede any other planned bronchoscopic procedure. Even if the optimal total volume or the number of aliquots to be instilled have not been established yet, two methods are generally used: two to four aliquots of equal volume (10 mL for children aged <6 years and 20 mL for children aged >6 years) or three aliquots, each consisting of 1 mL·kg^{-1} body weight for children weighing up to 20 kg, and three 20-mL aliquots for heavier children. For small-volume BAL, to clear the suction channel of the instillate, 2 mL of air should follow the saline.

While maintaining the tip of the bronchoscope wedged at the selected site, gentle manual or mechanical suction (3.3–13.3 kPa, *i.e.* 25–100 mmHg) is applied in order to collect the lavage specimen in a syringe or in a dedicated collection trap. BAL is considered technically acceptable if >40% of the total saline instilled is recovered and the lavage fluid (except for the first sample) contains few epithelial cells.

Processing

BAL specimens should be processed as soon as possible. To optimise cell viability, BAL fluid must be kept at 4°C until analysed. The first unfiltered BAL aliquot is usually processed separately for microbiological studies. Bacteria, fungi, protozoa and virus inclusions are detected by direct light microscopy after centrifugation or alternatively by smears. Special stains such as Gram, Papanicolaou, Gomori–Grocott or toluidine blue are used in air-dried preparations. In addition, the samples that are to be cultured for fungi and protozoa are centrifuged, whereas those for bacterial cultures are processed without centrifugation. Viruses are detected using PCR. The rest of the aliquots are filtered through sterile gauze to remove mucus; then they are pooled and submitted for cytological studies and analysis of BAL solutes.

BAL fluid can be prepared in two ways:

- Cytospin preparations of the whole BAL fluid
- Resuspension of the cell pellet in a small amount of medium

At least three or four slides should be prepared for each patient. The number of cells per mL of the recovered BAL fluid is counted using a cytometer on whole BAL specimens stained with trypan blue or with a cytoscan. Slides can be stained with May–Grünwald, Giemsa or Diff-Quik stains for differential cell counts and the evaluation of cellular morphological features. In particular situations, slides can also be prepared with specific stains, *e.g.* oil red O stain to detect lipid-laden macrophages, iron stain to identify iron-positive macrophages in patients with alveolar haemorrhage and periodic acid–Schiff (PAS) to identify glycogen. Immunocytochemical staining of lymphocyte surface markers is used to differentiate lymphocyte subsets in specific clinical situations, such as chronic diffuse parenchymal lung disease (DPLD).

The parameters measured include the percentage of the instilled normal saline that is recovered (compared to the amount of saline instilled), as well as various BAL fluid cellular and noncellular components (table 1). The mean BAL fluid total cell count ranges from 10.3 to 59.9×10^4 cells·mL^{-1}, with a range of 81.2–90% for macrophages, 8.7–16.2% for lymphocytes, 1.2–5.5% for neutrophils and 0.2–0.4% for eosinophils. The BAL fluid neutrophil percentage appears to be higher in children aged <12 months than in children aged 13–36 months. Normal values of BAL fluid lymphocyte subsets in children resemble those found in healthy adults, except for the CD4/CD8 ratio, which is lower in children. Establishing reference values for noncellular components is a complex task owing to the absence of valid BAL fluid dilution markers. Studies designed to investigate noncellular BAL fluid components have few clinical indications and are more important in the research setting.

Table 1. Differential cell counts in BAL fluid from control children

	Clement, 1987	Ratjen, 1994	Riedler, 1995	Midulla, 1995	Tessier, 1996
Alveolar macrophages %					
Mean±SD	89.7±5.2	81.2±12.7	NR	86±7.8	89.9±5.5
Median (range)	89 (82–99)	84 (34.6–94)	91 (84–94)‡	87 (71–98)	92.5 (77–98)
Lymphocytes %					
Mean±SD	8.7±4.6	16.2±12.4	NR	8.7±5.8	8.9±5.6
Median (range)	10 (1–17)	12.5 (2–61)	7.5 (4.7–12.8)‡	7 (2–22)	8 (2–22)
Neutrophils %					
Mean±SD	1.3±0.9	1.9±2.9	NR	5.5±4.8	1.2±1.2
Median (range)	1 (0–3)	0.9 (0–17)	1.7 (0.6–3.5)‡	3.5 (0–17)	1 (0–3)
Eosinophils %					
Mean±SD	NR	0.4±0.6	NR	0.2±0.3	NR
Median (range)	NR	0.2 (0–3.6)	0.2 (0–0.3)‡	0 (0–1)	NR

NR: not reported. ‡: interquartile range.

Indications

BAL is performed for diagnostic and therapeutic indications. Clinical indications for BAL include nonspecific chronic respiratory symptoms, nonspecific radiological findings and clinical signs and symptoms suggestive of chronic DPLD. Clinical applications involve microbiological studies and/or evaluation of cellular components.

Microbiology

BAL is an important tool in the diagnosis of lung infection in both immunocompromised and immunocompetent patients, including children with chronic pneumonia, CF and suspected TB. BAL is diagnostic when pathogens not usually found in the lung are recovered, such as *Pneumocystis jirovecii*, *Toxoplasma gondii*, *Legionella pneumophila*, *Histoplasma capsulatum*, *Mycobacterium tuberculosis*, *Mycoplasma pneumoniae* and respiratory viruses. Other infectious diseases, in which isolation of the infectious agent from BAL fluid is not diagnostic, but may contribute to their diagnosis and management, include infections with herpes simplex virus, cytomegalovirus, *Aspergillus*, *Candida albicans*, *Cryptococcus* and atypical mycobacteria. The presence of $>10^4$ CFU·mL^{-1} BAL fluid will identify patients with bacterial pneumonia with reasonable accuracy. Hence, the physician must consider this cut-off together with the underlying disease and the overall clinical picture. In the absence of an inflammatory reaction, the presence of bacteria increases the likelihood that it represents contamination, while the finding of >5% of BAL-obtained cells containing intracellular bacteria on direct microscopic examination increases the likelihood of infection. Furthermore, in children who present with chronic wet cough, a positive culture with $>10^4$ CFU·mL^{-1} is indicative of PBB.

Cellular components

The evaluation of BAL fluid cellular components may have important clinical indications in children with chronic DPLD, a group of disorders characterised by alveolitis, tissue

Table 2. Forms of alveolitis in children with respiratory disorders

Lymphocytic alveolitis	Neutrophilic alveolitis	Eosinophilic alveolitis
Prevalence of CD4 cells	Idiopathic pulmonary fibrosis	Eosinophilic pneumonia
Sarcoidosis	COP	Diffuse parenchymal lung diseases
Crohn's disease	Wheezy bronchitis	Asthma
Prevalence of CD8 cells		
Exogenous allergic alveolitis (hypersensitivity pneumonitis)		
Langerhans cell histiocytosis		
Diffuse parenchymal lung diseases associated with collagen diseases		
COP		

COP: cryptogenic organising pneumonia.

remodelling, fibrosis or a combination thereof. In these patients BAL may be a useful tool for characterising the alveolitis and for monitoring the patient during treatment, follow-up and in reaching or confirming a specific diagnosis (table 2). Three different forms of alveolitis can be identified (figure 1):

- Lymphocytic
- Neutrophilic
- Eosinophilic

Findings from BAL may help in providing a specific diagnosis in children with alveolar proteinosis, pulmonary haemorrhage, pulmonary Langerhans cell histiocytosis, chronic lipoid pneumonia and pulmonary alveolar microlithiasis.

Because BAL fluid recovered from infants with alveolar proteinosis contains PAS-positive, diastase-resistant, basophilic and mucin-negative amorphous material it typically appears milky. Electron microscopy of the BAL fluid sediment discloses abundant extracellular, multilamellar bodies and tubular myelin structures consistent with abnormal surfactant forms. Differential cell counts predominantly show lymphocytes with alveolar macrophages, which, on electron microscopy, have an

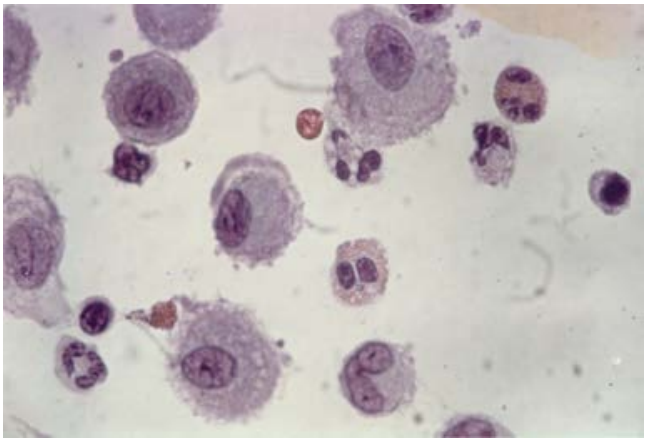

Figure 1. BAL fluid cytology features in eosinophilic alveolitis (May–Grünwald–Giemsa stain, ×100 magnification).

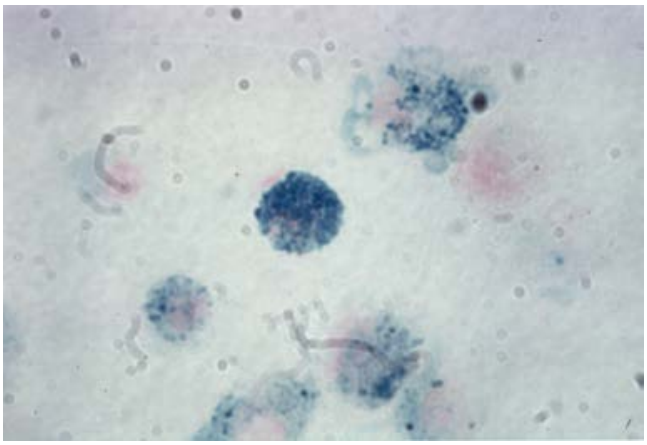

Figure 2. Haemosiderin-laden alveolar macrophages in the BAL fluid of a patient with alveolar haemorrhage (Prussian blue stain, ×100 magnification).

enlarged foamy cytoplasm containing numerous extracellular, concentrically lamellar surfactant bodies (lamellar bodies).

When the BAL fluid appears bloody or orange-pink in children with anaemia and infiltrates on chest radiographs, the suspected diagnosis is alveolar haemorrhage. The BAL fluid characteristically becomes progressively bloodier with each sequential sample. Specific haemosiderin staining detects haemosiderin in alveolar macrophages (figure 2). When haemosiderin-laden alveolar macrophage percentages exceed 20%, the diagnosis of diffuse alveolar haemorrhage is usually confirmed. The diagnosis can sometimes be delayed because haemosiderin-laden macrophages may take >48 h to appear after bleeding.

In patients with pulmonary Langerhans cell histiocytosis, Langerhans cells can be identified in BAL fluid through immunostaining for S-100, CD1a and langerin. The threshold of 5% CD1a-positive cells in BAL fluid used for diagnosing pulmonary Langerhans cell histiocytosis has excellent specificity, but low sensitivity.

BAL has also been used to document the diagnosis of pulmonary alveolar microlithiasis by demonstrating microliths in the BAL fluid, which stain pink with PAS stain. Well-formed microliths stain black with von Kossa stain, because they have a high calcium content.

A cytological examination showing vacuolated alveolar macrophages may indicate chronic lipoid pneumonia (figure 3). The diagnosis can be confirmed by specific staining with oil red O. Lipid-laden macrophages can be quantified using the lipid-laden macrophages index, assigning to each lipid-laden macrophage a score ranging from 0 to 4 according to the amount of cytoplasmic lipid. A lipid-laden macrophage index >100 has 100% sensitivity, 57% specificity, a negative predictive value of 100% and a false-negative rate of zero.

BAL, together with video fluoroscopy, remains the procedure of choice to diagnose chronic pulmonary aspiration by determining the lipid-laden macrophage index and/or by measuring gastric pepsin concentrations. A lipid-laden macrophage index of >100 is considered positive for aspiration. With respect to other potential biomarkers, tracheal pepsin has been used as a marker of reflux aspiration. Pepsin detection in the BAL fluid has been shown to have high sensitivity and specificity for reflux-related pulmonary aspiration. Milk proteins detection by histological staining has been proposed, but only in the research setting.

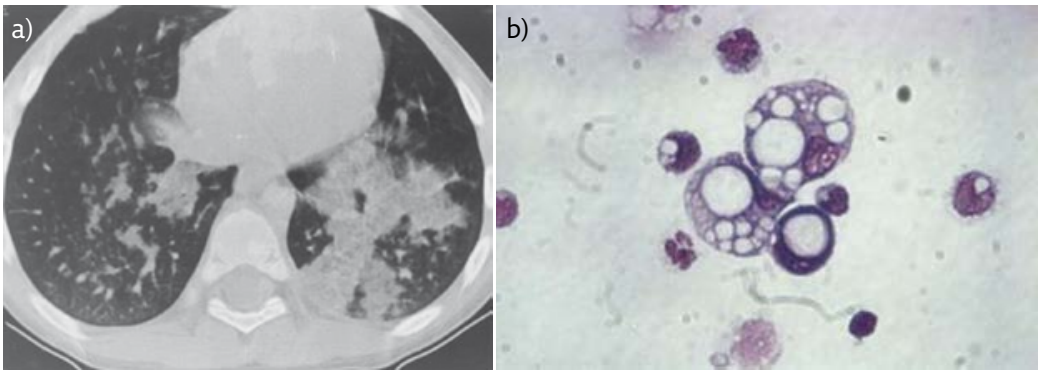

Figure 3. Lipoid pneumonia. a) Contrast-enhanced CT scan of the chest showing lipoid material in the lungs; b) BAL fluid cytology showing vacuolated alveolar macrophages (May–Grünwald Giemsa stain, ×100 magnification).

Therapeutic BAL

BAL has a major role in the therapy of certain lung diseases, in the form of whole-lung lavage (WLL) or mucus plug removal. In particular, children with persistent and massive atelectasis, especially CF patients, seem to successfully undergo selective lavage with DNase or surfactant.

WLL is performed under general anaesthesia in alveolar filling disorders (*e.g.* alveolar proteinosis or lipoid pneumonia) and only one lung is washed during each session. Prewarmed normal saline (total volume 200–300 mL·kg^{-1}) is instilled using passive gravity or using a syringe with aliquots of 20–120 mL. The lavage is continued until the effluent is satisfactorily clear. WLL frequently causes hypoxaemia and hypercapnia.

Complications and contraindications

BAL is a well-tolerated and safe procedure; however, on occasion fever, cough, transient wheezing and pulmonary infiltrates have been observed, which usually resolve within 24 h.

The most frequent complication, usually lasting <24 h, is fever; the only treatment needed is antipyretics. In immunocompromised patients, antibiotic therapy must be performed for ⩾48 h.

BAL may cause hypoxaemia, hypercapnia, or both. Severe bleeding, bronchial perforation, mediastinal emphysema and pneumothorax are extremely rare. Contraindications to the procedure include bleeding disorders, severe haemoptysis and severe hypoxaemia that persists despite oxygen treatment.

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Bronchial brushing and bronchial and transbronchial biopsies

Petr Pohunek, Václav Koucký and Pierre Goussard

Visual assessment of the bronchial mucosa using flexible bronchoscopes gives some basic information about inflammation, swelling, atrophy or other pathologies. For detailed information about the inflammatory or structural changes in the mucosa, additional methods are needed. For sampling of bronchial mucosa, tools are available that can be passed through the working channel of the flexible bronchoscope.

Bronchial brushing

Bronchial brushing is a method used for sampling superficial samples of bronchial mucosa. A protected brush is a brush enclosed in a plastic tube that covers the brush and prevents unwanted contamination during the passage of the brush through the working channel (figure 1). After the brush is passed fully through the channel it is pushed out of the cover and used for sampling in the desired area. Then it is withdrawn back into the covering tube and pulled back out of the channel. Sampled cellular material is washed in appropriate medium or smeared on a slide for further examination. The protected brushes are available in sizes appropriate for paediatric bronchoscopes with channel diameters of 1.2–2.2 mm. If only an unprotected brush is available (without the plastic cover), the sampling is usually performed as a final method before the end of the bronchoscopy. An unprotected brush is passed through the channel and then, under visual control, the mucosal surface is sampled. The unprotected brush is then withdrawn only into the tip of the bronchoscope just to be hidden in the channel. Then, with the brush left in place, the whole bronchoscope is withdrawn from the patient, the brush is then pushed out of the channel and either cut and dropped into a vial containing the appropriate medium, or washed in

Key points

- Bronchial brushing is a useful complementary method for assessing cytological changes in the superficial mucosal layer.
- Endobronchial biopsy allows more detailed evaluation of inflammation and structural damage of the bronchial wall. In addition, it allows direct histological analysis of endobronchial lesions, *e.g.* tumours.
- Transbronchial lung biopsy effectively samples lung parenchyma without the need for thoracoscopy or thoracotomy.

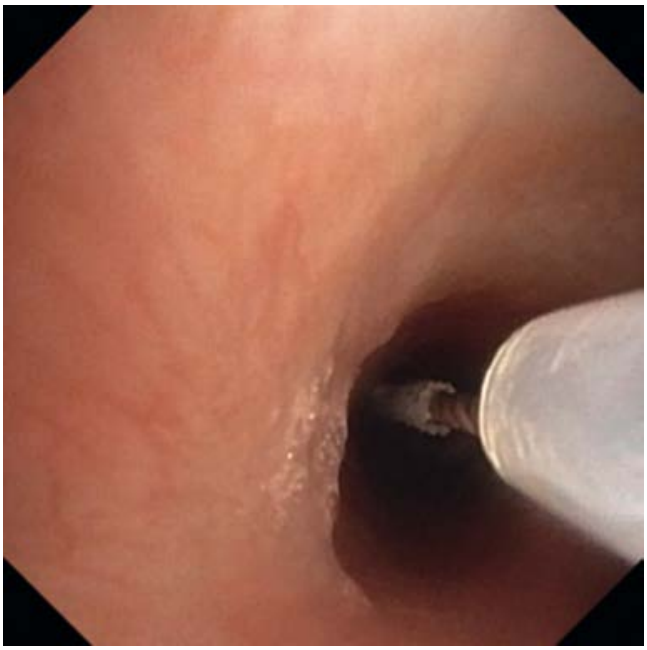

Figure 1. Protected brush sampling of the mucosal surface.

the medium or smeared on a slide. This method prevents contamination or loss of collected material during the passage of the brush through the working channel.

Bronchial brushing is mostly used for cytology and has been used successfully both for clinical and research purposes. It can also be used to collect material for microbiological testing.

Usually, bronchial brushing is performed from mucosa or lesions within the visual reach of the bronchoscope. Cytology may provide a specific diagnosis; in general conditions mucosal dysplasia or metaplasia and intensity and type of inflammation can be assessed. In selected situations, blind sampling can be performed for cytology or culture from a peripheral lesion. Sampling into culture media allows collection of material for microbiological analysis.

Bronchial brushing is generally safe, as it is limited to the mucosal surface. Minor superficial self-limiting bleeding can be seen. With blind sampling there is a possible risk of pneumothorax and the patient should be properly monitored post-procedure with this possibility in mind. Routine follow-up chest radiography is not necessary after a bronchoscopy with bronchial brushing.

Bronchial biopsy

Bronchial (or endobronchial) biopsy is a method allowing sampling of a small piece of bronchial mucosa for histological examination.

Targeted biopsy is essential for histological diagnosis in focal intraluminal processes, such as tumours, mucosal nodules, granulation tissue, *etc*. Biopsy may be indicated as a supplementary method for the evaluation of diffuse pathological processes in the bronchial wall (*e.g.* asthma, CF, chronic bronchitis and PCD). Bronchial biopsy only provides information about processes occurring in the superficial layer of the bronchial wall; however, a properly obtained biopsy usually comprises all the relevant structures involved in most pathological processes. In a bronchial biopsy, bronchial epithelium, basement membrane, the subepithelial layer with mucus glands and vessels, and usually the smooth muscle bundles are visible. Various staining methods besides the standard haematoxylin and eosin can be used to increase the yield of

the method, including specific staining for collagen and other matrix proteins (*e.g.* trichrome) and immunohistochemistry. This allows for detailed evaluation of airway wall inflammation (eosinophilic, neutrophilic or lymphocytic) and remodelling changes (basement membrane thickening, smooth muscle hyperplasia, mucus gland hypertrophy, *etc.*). In addition, the endobronchial biopsy samples may be processed for electron microscopy. This procedure requires different fixation media (*e.g.* glutaraldehyde) and is currently used nearly exclusively to diagnose structural defects of the axoneme in PCD.

The size of a bronchial biopsy depends on the size of the biopsy forceps. Larger paediatric bronchoscopes, with diameters of 4.4–5.1 mm, have 2.0–2.2 mm working channels. This allows the use of standard biopsy instruments. The most commonly used type for a standard bronchial biopsy are oval fenestrated cup forceps. These forceps allow appropriate embedding in bronchial mucosa and sampling without undesired damage to the sample. Various other types are available, including alligator forceps. These may also be used for bronchial biopsy to increase yield, but may cause more damage to the sample. For smaller paediatric bronchoscopes with diameters of 2.7–3.7 mm and 1.2–1.7 mm working channels, only limited types of biopsy forceps are available. These are usually provided as oval non-fenestrated cup with or without a rat tooth at the tip. These small instruments are generally much less efficient in obtaining proper samples of bronchial mucosa, and their use, especially handling of the tiny samples, requires greater experience.

Bronchial biopsies in diffuse processes are usually taken from secondary or tertiary carinae. It is not recommended to sample from the main carina as the mucosa at this level may present nonspecific changes. Sampling from a carina is technically rather easy, as the forceps can be easily positioned. The forceps are then closed and withdrawn carrying the sample between the closed branches (figure 2). The forceps are then pulled out of the channel and handed to an assistant who places the sample into a vial containing appropriate fixation medium. Depending on a visual assessment of the sample size and quality, biopsy is repeated to guarantee a sufficient sample for further diagnostic evaluation.

In focal pathology located in the bronchial wall a different technique must be used. Using the flexion of the tip of the bronchoscope, the forceps must be pressed against the wall with the branches open parallel to the wall and the pathological structure

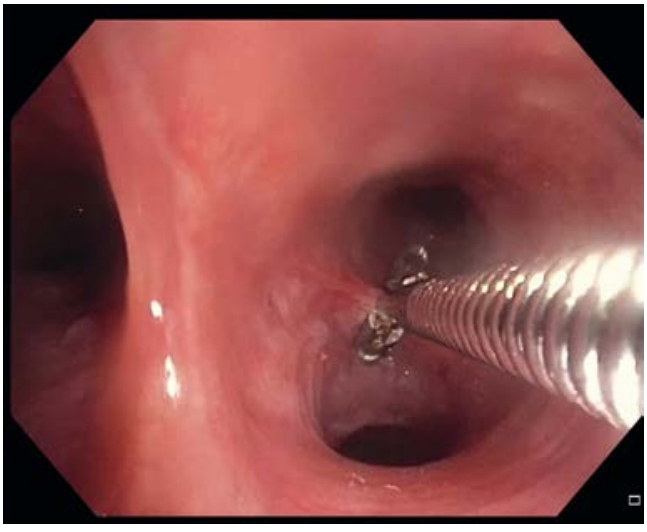

Figure 2. Position of the biopsy forceps for sampling from a secondary carina.

kept between the branches. The forceps are then closed and the mucosa grabbed between the branches.

Bronchial biopsy is generally a very safe method. As it samples only a superficial layer of bronchial mucosa, bleeding is negligible in most cases and the risk of pneumothorax is almost zero. It has been shown to be safe even in children with CF whose bronchial mucosa is generally inflamed and hyperaemic. Bronchial biopsy has been shown to be safe and effective even in very young children evaluated for recurrent wheezing. It is recommended that bronchial biopsies be taken from one lung only to avoid the theoretical risk of a bilateral pneumothorax. In a child with no clinically relevant bleeding disorder the pre-procedure coagulation screening is not necessary; however, it may be part of a pre-procedure protocol in some institutions. Chest radiography is not performed routinely after the procedure.

Logically, any supplemental procedure prolongs the time required to perform bronchoscopy. Sampling of three adequate biopsy specimens requires ~5 min and this should be taken into account when planning a procedure.

Few studies have looked at the value of endobronchial tissue as a source for culture in the diagnosis of TB in children. The lymph nodes ulcerate into the airway, making it possible to biopsy the tissue. Tissue can be used for GeneXpert testing as well as culture. This intervention has a low complication rate and the aim is to sample the caseating material to improve the quality of the biopsy.

Transbronchial lung biopsy

Transbronchial lung biopsy (TBLB) is a special procedure that allows sampling of pulmonary tissue *via* endobronchial approach.

A main and well-established indication for TBLB is evaluation of rejection in patients with transplanted lungs. Less often, TBLB has been used for diagnostic evaluation of diffuse parenchymal lung diseases or for evaluation of infection. Successful diagnostic TBLB has been documented mainly in homogeneous pathologies, such as pulmonary sarcoidosis and hypersensitivity pneumonitis. The main advantage of TBLB is its repeatability, which is not the case with video-assisted thoracoscopy or open thoracic surgery. It has been recommended that TBLB be targeted using preceding high-resolution CT.

The technique of TBLB is relatively simple; however, it needs experience and practice. TBLB is performed using standard biopsy forceps, preferably with an oval fenestrated cup. Use of alligator forceps may provide larger samples, but may cause more complications. Use of larger instruments through 2.0–2.2 mm channels has better yield; however, successful TBLB can be obtained even with small forceps used through a thin paediatric bronchoscope. For TBLB, the bronchoscope is positioned into a relevant segmental or subsegmental bronchus. Biopsy forceps are then inserted through the working channel and gently pushed into the periphery beyond direct vision. Fluoroscopy is mandatory, as it helps to position the forceps, avoid pleura and allows monitoring of the whole procedure, including possible immediate complications, such as pneumothorax (figure 3). Once the closed forceps are wedged with an elastic resistance, the forceps are withdrawn ~10 mm, opened and pushed down with the aim of breaking the bronchial wall and accumulating adjacent lung tissue between the branches. The forceps are then closed and withdrawn back through the channel. If there is strong resistance and the forceps cannot be withdrawn, opening and repositioning of the forceps is recommended. Three to six samples from one side are usually taken to ensure sufficient amount of tissue. Sampling from both sides may

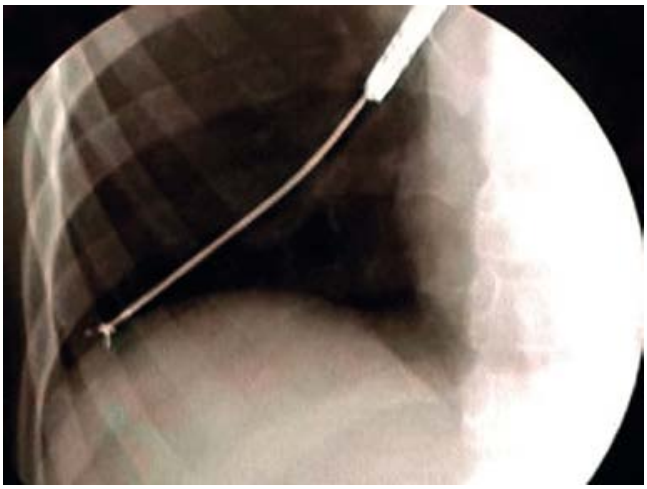

Figure 3. Biopsy forceps during TBLB as shown on fluoroscopy.

potentially lead to bilateral pneumothorax and severe respiratory compromise and should be avoided. Any bleeding from the area should be carefully monitored using the bronchoscope, which should be left in place for ~3 min after the last sampling to ensure that no major haemorrhage has occurred. If significant bleeding occurs the bronchoscope or Fogarty catheter with inflated balloon can be wedged into the relevant subsegmental bronchus to help to stop the bleeding. Coagulation screen should be part of the routine pre-procedure investigation before bronchoscopy with planned TBLB.

TBLB may be useful in diagnosing miliary TB or in HIV-positive children to distinguish miliary TB from lymphocytic interstitial pneumonia. This remains a theoretical possibility, as there are no studies published on the use of TBLB in the diagnosis of childhood TB.

Recently, the cryoprobe has been suggested for transbronchial lung biopsy in adult patients. It can provide larger samples of tissue and allow therefore for more accurate pathological evaluation. In children there is still not enough experience with this method and certainly any experience from adults cannot be simply translated into paediatric practice.

Compared to endobronchial biopsy, TBLB carries a higher risk of complications. The most frequent are bleeding and pneumothorax. Overall, the frequency of any complications has been shown to be <10%.

Transbronchial needle aspiration

Transbronchial needle aspiration (TBNA) has been used as a diagnostic technique in adult patients, in whom it has been shown to be safe and effective in making the definitive diagnosis in both malignancies and TB. In young children, the use of TBNA has been limited due to the size of the working channel which does not allow the introduction of the aspiration needle. Paediatric bronchoscopes with larger working channels make it possible to do TBNA in children *via* a laryngeal mask with 4.1–5.1 mm bronchoscopes. A preceding chest CT scan is performed to determine the location and size of the subcarinal lymph nodes and to reduce the risk of aspirating and taking biopsy from other conditions such as a subcarinal bronchogenic cyst. Only enlarged subcarinal lymph nodes can be aspirated blindly in children, as the safety of aspirating paratracheal and hilar lymph nodes in children has not been established. The technique used in adults and described by Wang (1985) has been adapted for children. Best results are achieved by having a cytologist in the bronchoscopy room

who immediately assesses the adequacy of the sample. This allows not only for a rapid diagnosis, but can also determine the site for obtaining tissue for culture and molecular genetic methods (*e.g.* GeneXpert). Specimens are collected for cytology as well as fungal and *Mycobacterium tuberculosis* culture. The reported complications include self-limiting bleeding visible at the site of the TBNA. Post-operative chest radiography is performed to exclude a pneumothorax. The advantage of TBNA is that it provides a rapid diagnosis based on the histology and culture without performing an open thoracotomy. TBNA has been shown to be of value in HIV-positive children as well as those infected with drug-resistant TB or other conditions with enlarged mediastinal lymph nodes. In a series of 30 children, a definitive diagnosis was made using TBNA in 54% of patients with a median age of 41 months (range 9–168 months); the diagnoses made were *M. tuberculosis* lymph node enlargement (n=13), metastatic nephroblastoma (n=1) and fibrosing mediastinitis (n=1). In 25% of the cases, the TBNA was the sole source of the specimens from which the diagnosis was made. No serious complications were encountered during or after the procedure. The use of endobronchial ultrasound (EBUS)-guided TBNA is limited in small children, due to the size of the EBUS bronchoscope and the cost of the apparatus. However, EBUS bronchoscope sizes are decreasing and mini probes are available, which will make EBUS possible even in smaller children in the near future.

Summary

Cytology and (mainly) histology may significantly contribute to diagnosis and therapeutic decision making in specific cases (such as tumours, TB, PCD or chronic inflammatory airway diseases). Biopsy is generally safe when performed by experienced personnel, but every procedure should be properly planned in advance with possible risks kept in mind and with an understanding of how it will influence or change clinical management. As endobronchial biopsies contribute significantly not only to immediate diagnosis, but also to general understanding of pathological processes, it has been considered ethically acceptable to use part of the biopsy material for research. This must be based on an appropriate protocol, informed consent of legal representatives of the patient and approval by the institutional review board.

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Rigid and interventional airway endoscopy

Ernst Eber, Thomas Nicolai and Fabio Midulla

Rigid bronchoscopy was introduced in 1896 as the first method to visualise the lower airway; in 1897, Gustav Killian accomplished the first foreign body removal using rigid bronchoscopy with an attached Kasper electrical handle to illuminate the airways. The technique was simple and has basically remained unchanged. A rigid hollow tube is used to intubate the trachea or a large bronchus, and ventilation can be maintained through this tube. Initially, direct vision was used to inspect the airway, with the tube being illuminated internally by means of a prism. Later improvements included a rigid telescope introduced into the hollow bronchoscope (table 1). These telescopes consist of fibreglass rods protected by a metallic covering, with a lens at the distal end and an eye piece at the proximal end. Light is transmitted through this instrument with a coupling device from an external light source. Today, the eye piece at the proximal end can be connected to a charge-coupled device camera; thus, the image can be converted to a digital signal and displayed on a video screen.

Technical considerations

The use of a rigid bronchoscope in the tracheobronchial tree is only possible when the larynx can be exposed and the bronchoscopy tube can then be advanced into the intrathoracic airway. In children with difficult airways, due to severe forms of Pierre Robin sequence or other craniofacial anomalies, or large head and neck tumours, this may be impossible.

As the introduction of a rigid tube into the airways is very irritating, full anaesthesia is always necessary. Because ventilation of the patient has to be performed through the rigid bronchoscope, appropriate connectors are necessary and different sizes of rigid

Key points

- Flexible and rigid airway endoscopy are complementary techniques, both of which may be warranted in diagnostic and therapeutic indications.
- For a number of indications, such as foreign body removal, balloon dilation, laser treatment and placement of endobronchial devices, rigid bronchoscopy is generally preferred over flexible airway endoscopy.
- The number of children requiring interventional bronchoscopic procedures is small; thus, training paediatric bronchoscopists for these indications is a challenge.

Table 1. Rigid bronchoscopes for children

Tubes: internal diameter mm	Telescopes: outer diameter mm
3.0	1.8
3.5	2.0
4.0	2.7
4.5	3.4
5.0	4.0
5.5	
6.0	

These are typical examples; exact actual sizes may vary for different manufacturers. Typical lengths are 28, 30 and 35 cm.

tubes are used to intubate differently sized airways to achieve a reasonable seal and allow adequate ventilation of the patient.

Although the rigid endoscope has smooth edges at the distal end, airway damage could still occur. The rigid tube can only be advanced safely if its distal edge is visible during its movement. If this principle is adhered to, rigid bronchoscopy is a safe procedure.

When the rigid tube is advanced into the lower airways, care must be taken to smoothly align the long axis of the rigid tube with the airway. This is achieved by turning the head to the right when intubating the left bronchial system, and the converse for the right bronchial system.

Rigid bronchoscopes have small lateral slits allowing the passage of air into the more proximal airways, even when the tip of the bronchoscope has been advanced into distal bronchi or when it is occluded by a foreign body during an extraction procedure. So-called tracheoscopes are rigid tubes with the same diameters as bronchoscopes, but without lateral openings, to avoid loss of ventilation pressure when the tip of the tracheoscope is placed in the trachea. In this position, lateral openings would still be proximal to the glottis.

Rigid bronchoscopes allow for the use of various instruments through the lumen (figure 1), including:

- Forceps
- Suction catheters
- Special magnets
- Biopsy needles

Special bronchoscopes even allow the transmission of a carbon dioxide laser through a set of mirrors, thus making laser surgical procedures in the lower airways possible with no deeper or transmural tissue damage.

Indications

As flexible bronchoscopes allow for both anatomical and functional examination of the upper and lower airways (including peripheral airways), examination *via* artificial airways and taking samples (*e.g.* BAL fluid, biopsy specimens), today most diagnostic airway endoscopies are performed using a flexible instrument (see chapter "Flexible airway endoscopy"). With technological evolution in available instruments and the increased use of general anaesthesia with concomitant changes in airway management, the number of indications and the types of procedures performed with flexible bronchoscopes have expanded further. Flexible and rigid airway endoscopy are complementary techniques, both of which may be warranted in diagnostic

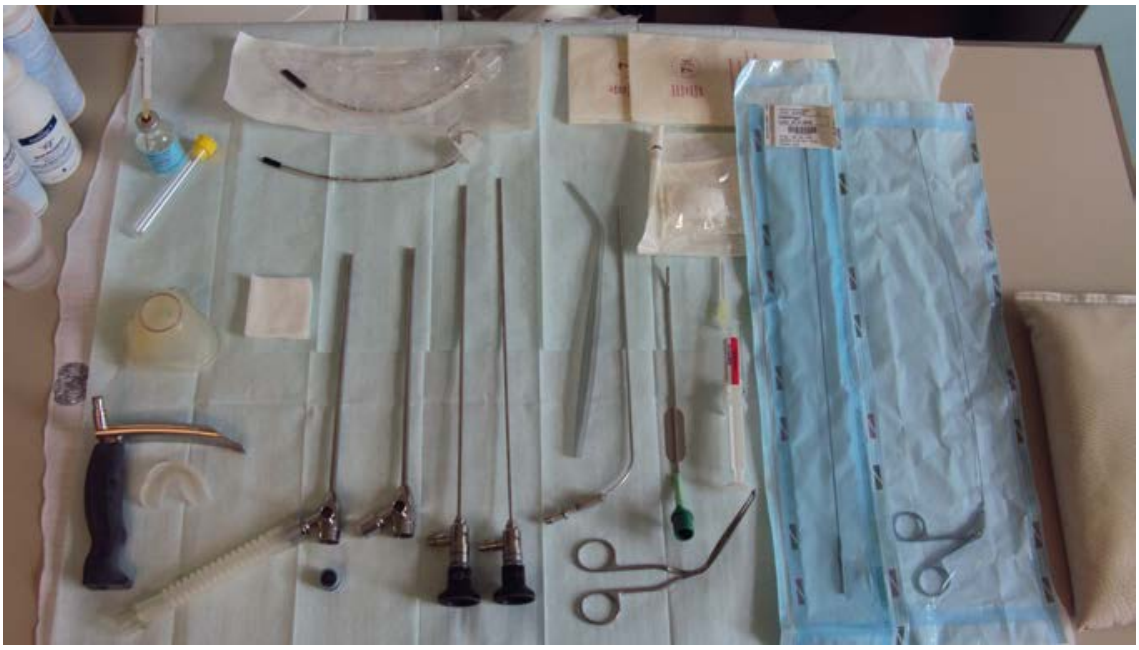

Figure 1. Instrument tray for rigid bronchoscopy in children, including bronchoscopy tubes, telescopes and suction tubes.

and therapeutic indications (*e.g.* laryngeal cleft, H-type tracheo-oesophageal fistula, peripheral foreign body). For a number of indications, rigid bronchoscopy is generally preferred over flexible airway endoscopy (*e.g.* foreign body removal, balloon dilation, excision of mass lesions in central airways, laser treatment, placement of endobronchial devices), as has been emphasised in a recent European Respiratory Society task force report on interventional bronchoscopy in children.

Foreign body removal

Airway endoscopy is indicated in each child with a history of choking, even in the absence of respiratory symptoms, and in each child with suggestive respiratory symptoms and/or suggestive physical and/or radiological findings, even in the absence of a history of choking. Rigid bronchoscopy has traditionally been used for foreign body removal and is still considered the procedure of choice, not only in the case of an asphyxiating foreign body (figure 2). It guarantees a secure airway, and allows to introduce various instruments and to control bleeding or secretions, thus ensuring safety particularly in potentially life-threatening situations due to large foreign bodies.

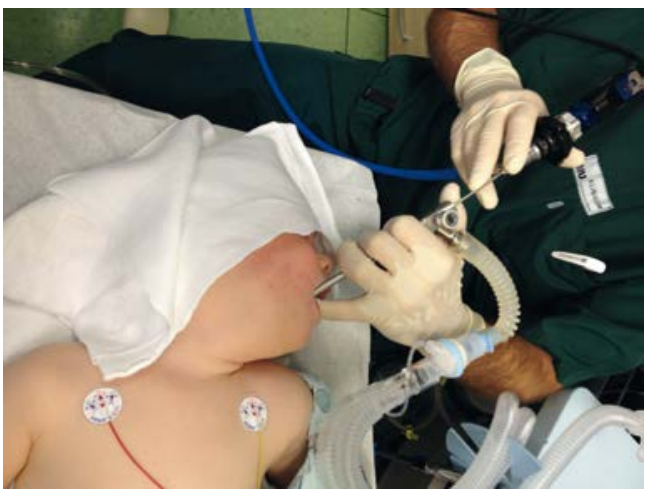

Figure 2. Rigid bronchoscopy for the removal of a foreign body.

In children with a history of choking only, flexible airway endoscopy is considered the primary tool for confirmation or exclusion of foreign body aspiration, reducing the rate of negative rigid bronchoscopies. There is accumulating evidence that flexible bronchoscopes can also be used for foreign body removal, using biopsy or grasping forceps, or wire baskets. In particular, small and peripherally located foreign bodies may be more easily extracted using a combination of both methods (flexible through rigid endoscope). If nature and location of a foreign body allow, removal may be attempted with a flexible endoscope, securing the airway with a laryngeal mask airway or endotracheal tube and ventilating the child, and provided a rigid instrument is immediately available in case removal attempts fail or complications occur. In children with delayed diagnosis of foreign body aspiration and intervention, complications occur more frequently.

Complex interventional procedures

Today, a number of complex interventional procedures are performed at specialised institutions with highly experienced bronchoscopy and anaesthesiology teams. Here we discuss balloon dilation, laser treatment, airway stents and whole-lung lavage, as well as other interventions requiring bronchoscopes.

Balloon dilation

Balloon dilation is applied alone or together with other techniques (*e.g.* laser treatment, stent placement). The procedure is usually performed with a rigid bronchoscope, under general anaesthesia and topical anaesthesia with lidocaine to reduce airway irritability, and preferably muscle relaxation to avoid coughing. Serial balloon dilation can be used to manage severe complications following slide tracheoplasty in children with congenital tracheal stenosis, and to treat acquired tracheal or bronchial stenosis (*e.g.* due to tracheal or bronchial stents). Airway ballooning can be performed to achieve endobronchial occlusion (*e.g.* in patients with massive haemoptysis).

Laser treatment

With technological development, laser treatment has become feasible even in the airways of infants. While the carbon dioxide laser is the most frequently used type in the larynx, KTP (kalium-titanium-phosphate) and diode lasers are the most frequently used types for tracheobronchial lesions in infants and children. Laser treatment is performed under general anaesthesia with muscle relaxation to avoid inaccurate targeting, and specific safety measures are to be addressed during the procedure (*e.g.* reduction of the inspiratory oxygen fraction to <0.25 before firing to diminish the risk of airway ignition). Currently, laser treatment in children is mainly applied for resection of granulomas or obstructive granulation tissue, and for incision of acquired web-type tracheal stenosis (the latter usually in association with subsequent balloon dilation).

Airway stents

Airway stents are routinely applied in adults with malignant diseases. In contrast to adults, airway obstruction in children is usually histologically benign; airway structures are soft; and airway growth is substantial. Silicone stents tend to dislocate; they should not be used in central airways apart from after surgery. Metal mesh stents tend to cause granulation or wall damage and need to be considered as permanent; with airway growth, they may cause secondary stenosis. In theory, biodegradable stents would be preferable, as long-term consequences such as an ingrown mesh stent as well as secretion retention, granulation and displacement issues of removable covered or silicone stents could be avoided. However, they tend to dissolve too early and severe complications including death have been reported. With material improvements and

more experience this may change in the future. Stents may be used for stabilisation of the airway lumen following airway surgery, and as a last resort when all other conservative and surgical treatment options have failed to wean off a ventilator over a long period of time or have failed to relieve life-threatening obstructive episodes or are contraindicated. Complications occur frequently and their management requires extensive expertise. Typical complications include the formation of granulation tissue requiring laser treatment and/or stent replacement, stent dislocation, ovalisation requiring dilation, airway perforation and infection.

Whole-lung lavage

Whole-lung lavage is performed under general anaesthesia and usually muscle relaxation, with extensive monitoring. In children aged ⩾8 years, the technique is the same as in adults, using a double-lumen endotracheal tube. For infants and small children, different techniques have been described. Whole-lung lavage is performed in children with various alveolar filling disorders.

Other interventions using bronchoscopes

While the application of drugs and other liquids for atelectasis treatment, tracheo-oesophageal fistula repair and bronchopleural fistula treatment is usually performed with flexible endoscopes, haemoptysis control and the removal of bronchial casts in plastic bronchitis or solidified airway secretions in severe bacterial tracheobronchitis are best performed with rigid bronchoscopes. Due to the scarce experience reported, the most appropriate techniques to treat these airway problems are unclear.

Other endoscopic interventions include transbronchial and endobronchial biopsy (see chapter “Bronchial brushing and bronchial and transbronchial biopsies”), transbronchial needle aspiration with endobronchial ultrasound, usage of microdebriders and cryotherapy. Studies to assess the utility, efficacy and safety of these techniques in children are lacking.

Flexible airway endoscopy plays a well-established role in the intubation of children with difficult airways; thus, every paediatric bronchoscopist should be trained in endoscopic intubation of children of all ages.

Airway endoscopy with a rigid telescope

A variant of rigid airway endoscopy consists of the use of a rigid telescope alone (without a rigid bronchoscopy tube).

The larynx is exposed by means of a laryngoscope. For a more complex examination or intervention the laryngoscope can be fixed to the operating table with a special device (suspension laryngoscopy) (figure 3). During a period of apnoea, the rigid telescope is advanced through the vocal folds, taking great care to not touch the airway surface. This technique provides detailed images of the glottis, subglottic region and trachea and thus can be used for preoperative documentation and instrumentation. It also allows for the use of instruments, apart from the telescope, without the limitations of space within a rigid bronchoscopy tube. Distance measurements can be made with great accuracy. The method is particularly suited to inspect the subglottic region without touching the airway surface, which may be very useful to exclude a foreign body in the diagnostic workup of atypical croup. The procedure can be completed very quickly under short anaesthesia such as for an intubation procedure, even in an unstable patient.

The method may also be used to inspect the subglottic region in children with an endotracheal tube by retracting the tube, inspecting the subglottic region and

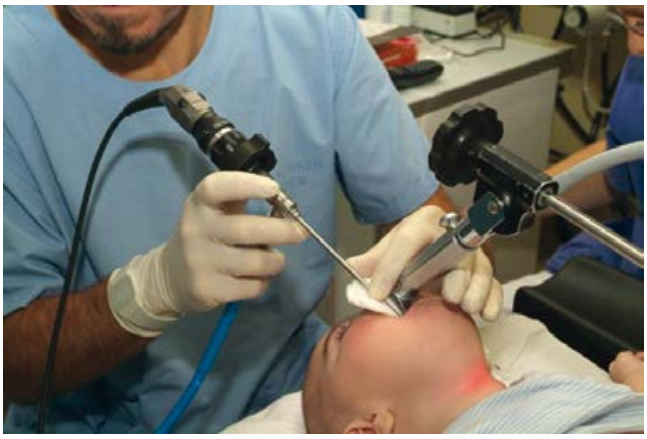

Figure 3. Rigid laryngoscopy with a telescope and laryngoscope blade fixed to the operating table (suspension laryngoscopy).

immediately reintroducing the tube. In addition, it allows local treatment, such as laser resection or infiltration of laryngeal papillomas with substances such as cidofovir.

Contraindications and difficulties

Contraindications to rigid airway endoscopy include an airway that cannot be intubated with a rigid bronchoscopy tube without excessive force or when the use of a laryngoscope exposing the larynx is contraindicated, such as in vertebral instability.

Bleeding diathesis or severe thrombocytopenia increase the risk of complications, but do not represent absolute contraindications. As bacteraemia may ensue from rigid bronchoscopy, the recommendations for antibiotic coverage in children with congenital heart disease must be followed.

Rigid airway endoscopy is an inadequate technique for the diagnosis of any dynamic airway pathology (*e.g.* airway malacia).

Future developments

Almost all diagnostic airway endoscopies are performed with flexible endoscopes and both number of indications and types of procedures performed with flexible instruments have further expanded. As the number of children requiring interventional bronchoscopic procedures is small, training experience for paediatric bronchoscopists in rigid as well as flexible bronchoscopy for these indications is constrained. This calls for novel approaches such as training of paediatric bronchoscopists in collaboration with adult bronchoscopists, simulation-based training, the establishment of paediatric centres of excellence in interventional bronchoscopy and multicentre collaboration for the benefit of children with airway disorders.

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Sedation for airway endoscopy

Jacques de Blic

The value of airway endoscopy is now widely accepted as a diagnostic as well as an interventional procedure. Bronchoscopy, like any invasive technique, may induce anxiety, fear, pain and unpleasant memory of the experience, and paediatric patients should almost always be moderately or deeply sedated. Sedation should provide patient comfort, haemodynamic stability and adequate gas exchange. Details of the main drugs used for sedation in paediatric flexible bronchoscopy are given in table 1.

Prebronchoscopic procedures

A detailed history and a complete physical examination should be performed. Pre-operative assessment of the child is essential, including general history, allergies and previous adverse drug reactions, current medications, sedation/anaesthesia history with focus on complications and airway problems, history of upper airway problems and sleep disordered breathing or snoring, major medical illnesses, physical abnormalities and neurological problems, recent acute illnesses (*e.g.* upper respiratory infection, fever, *etc.*). Written, fully informed consent should be obtained.

Key points

- Appropriate sedation is important for a well-tolerated bronchoscopic procedure. The available techniques include moderate and deep sedation. Cooperation between the anaesthesiologist and the bronchoscopist is essential.
- Various protocols may be used that entail the administration of a single drug or drug combination (midazolam, meperidine, propofol, ketamine, remifentanil, *etc.*) or inhalational agents (premixed 50% nitrous oxide and oxygen, sevoflurane).
- Supplemental oxygen is often recommended to prevent hypoxaemia. Whichever the choice of sedation and the technique of oxygen delivery (nasal prongs, face mask, laryngeal mask, endotracheal intubation), it is essential to maintain and preserve ventilatory function.
- Rigid bronchoscopy should always be performed under deep sedation.

Table 1. Main drugs used for sedation in paediatric flexible bronchoscopy

	Actions	Dose	Onset of action min	Duration of action min	Antagonist
Midazolam	Anxiolysis Amnesia	*i.v.* (bolus) 75–300 $\mu g \cdot kg^{-1}$	1–5	90	Flumazenil 0.01 $mg \cdot kg^{-1}$
Meperidine	Analgesia	*i.v.* (bolus) 0.5–2 $mg \cdot kg^{-1}$	5	180–240	Naloxone 0.01 $mg \cdot kg^{-1}$
Ketamine	Analgesia Anaesthesia Amnesia	*i.v.* (intermittent bolus) 0.25–0.5 $mg \cdot kg^{-1}$	2–4	10–20	
Propofol	Anaesthesia	*i.v.* (intermittent bolus) 0.5–1 $mg \cdot kg^{-1}$ *i.v.* (continuous infusion) 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	<1	30	
Remifentanil	Anaesthesia Analgesia	*i.v.* (intermittent bolus) 0.25–0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (continuous infusion) 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$	2–5	2–3	

Minimum fasting periods prior to the procedure are usually 2 h for clear liquids, 4 h for breastmilk, 6 h for infant formula or a light meal and 8 h for a full meal.

Premedication may be necessary in a child who is distressed or unable to cooperate.

Oral atropine (0.01–0.02 $mg \cdot kg^{-1}$) minimises bradycardia induced by vasovagal stimulation and decreases airway secretions. Oral or intramuscular atropine premedication has yielded conflicting results regarding utility and safety.

Appropriate equipment in a dedicated bronchoscopy suite is necessary, including pulse oximeter, blood pressure measuring device, electrocardiography, capnography and suction apparatus, and, if possible, a temperature monitor.

Deep sedation

Deep sedation may be achieved either by an intravenous drug or a volatile agent. They can be used alone or in combination. The presence of a trained anaesthesiologist is necessary. Drugs used for deep sedation in children include the following.

- Propofol is an *i.v.* sedative hypnotic agent with a rapid onset and a short duration of action. The level of sedation and that of respiratory depression are dose dependent.
- The use of ketamine as an anaesthetic agent is less common in children. It has been associated with laryngospasm and bronchospasm. Ketamine can be used successfully, but requires attention to topical anaesthesia of the airway in order to reduce the risk of laryngospasm; the addition of a benzodiazepine is recommended to prevent the emergence of hallucinations.
- Remifentanil is a synthetic opioid agent, and is a strong analgesic. It has a short duration of action and a short half-life. Its adverse effects include respiratory depression, hypotension, vomiting and rigid chest syndrome. It is rarely used in anaesthesia for flexible bronchoscopy, but it is used in rigid endoscopy.

- Inhalational agents are commonly used. Sevoflurane has a rapid onset of action, its effects quickly resolve after the discontinuation of drug administration and it has minimal cardiovascular and no bronchoconstrictive effects. It allows deep sedation with preservation of spontaneous ventilation. When using inhalational agents, the preferred technique for administration is usually by face mask with the bronchoscope passed through a port on the mask while the anaesthetic gas is delivered. An alternative technique is the use of a laryngeal mask airway.

Moderate sedation

There is no unique protocol for inducing moderate sedation. It may be achieved either by an *i.v.* drug (*e.g.* midazolam, meperidine) or a volatile agent (inhalation of premixed 50% nitrous oxide and oxygen). Combinations of agents are more effective than single agents. Sedation should be given in small incremental doses until the desired effect is obtained. The following drugs are used for moderate sedation in children.

- Midazolam is a water-soluble benzodiazepine. It reduces anxiety and causes amnesia of the procedure. Flumazenil is used as an antagonist. Midazolam is not intended as a sole agent for paediatric sedation, but should be administered in association with an opioid or nitrous oxide *via* face mask.
- Meperidine is a synthetic opiate that produces both sedation and analgesia; it has the advantage of rapid onset of action and easy reversibility (naloxone). Meperidine is preferably administered intravenously by fractional doses to achieve the desired effect with the minimum drug dose. The use of a benzodiazepine reduces the dosage of meperidine needed. Known adverse effects are respiratory depression that may last longer than the drug's other clinical effects, transient urticaria due to release of histamine, transient hypotension, nausea and vomiting.
- Dexmedetomidine is a highly selective α_2-adrenergic receptor agonist. It is administered intravenously associated with an opioid agent. Dexmedetomidine plus sufentanil has been used safely and efficaciously in children undergoing flexible bronchoscopy.
- Anxiolysis and analgesia may also be achieved with inhalation of premixed 50% nitrous oxide and oxygen administered *via* a face mask. Onset of action is 3 min and duration of action 5 min. Side-effects, especially nausea, may occur when it is administered for >15 min.

Local anaesthesia

Local anaesthesia is of particular importance when conscious sedation is used. Lidocaine 2–5% is applied on the nose and the larynx and 0.5–1% applied below the larynx. Lidocaine may be instilled directly, sprayed or nebulised (1–5 mL of 2–4% lidocaine according to the child's weight). The total dose should not exceed 5–7 $mg \cdot kg^{-1}$, but the exact amount applied is difficult to assess as most of the lidocaine is removed by suction, spitting or swallowing. Insufficient topical anaesthesia will result in pain, cough, and increased risk of laryngospasm and/or bronchospasm. Topical lidocaine may worsen laryngomalacia.

Techniques to ensure adequate ventilation during flexible bronchoscopy

Oxygen desaturation is the main adverse event during bronchoscopy. During the procedure it is essential to maintain ventilatory function independently. Different techniques are available to ensure such adequate ventilation and to prevent hypoxaemia.

Figure 1. Face mask.

- Nasopharyngeal prongs are easy to pass down one nostril, while the bronchoscope is passed through the other. This allows inspection of most of the upper airway and assessment of the airway dynamics.
- A face mask allows the inspection of the entire airway and the assessment of its dynamics. This method permits application of PEEP. The bronchoscope is passed through an adaptor on the face mask (figure 1). Problems may arise if a complication occurs, as the airway is shared during the entire process between the bronchoscopist and the anaesthesiologist.
- A laryngeal mask airway (figure 2) is easy to place and can assist ventilation with positive airway pressure. It is generally well tolerated. Its disadvantages are that the upper airways and vocal cord movement cannot be assessed.
- Endotracheal intubation enables the bronchoscope to be re-passed easily and quickly when necessary. Its disadvantages are that upper airways, vocal cord movement and airway dynamics cannot be assessed and that the endotracheal tube may limit the size of the bronchoscope.

Moderate or deep sedation for flexible bronchoscopy?

Some drugs or gases clearly induce a deep sedation (propofol, remifentanil, halothane) while others are used only for moderate sedation (midazolam, nitrous oxide+oxygen). Between the two are drugs which, according to their association and their dosage, may be considered to induce deep or moderate sedation (ketamine, meperidine).

The level of sedation depends on respiratory, psychological and emotional status of the patient, underlying disease, drugs available, availability of an anaesthetist, and

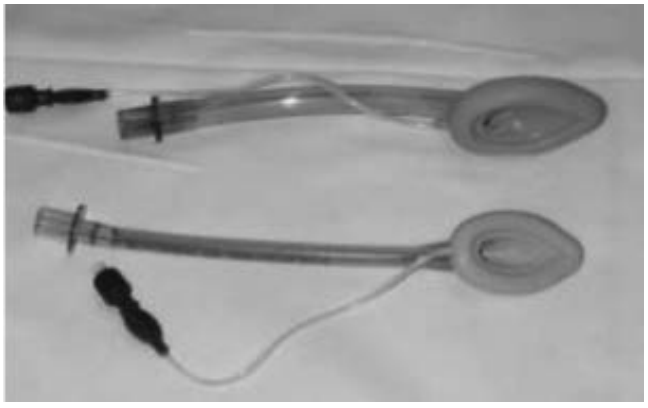

Figure 2. Laryngeal mask airway.

procedures to be performed. The main objective of moderate sedation is to maintain a spontaneous ventilation, but bronchoscope insertion may induce cough reflex, laryngospasm or ventilatory depression. For these reasons, whereas in the past most flexible bronchoscopies were performed under moderate sedation, most centres now use deep sedation.

Sedation for rigid bronchoscopy

Rigid bronchoscopy should always be performed under deep sedation. Induction of anaesthesia is similar to that for flexible bronchoscopy. Inhalational anaesthesia and oxygen delivery are maintained through a T-piece connected to the side arm of the rigid bronchoscope. Two modes of ventilation are routinely used: spontaneous ventilation or (preferably) positive-pressure controlled ventilation; the use of jet ventilation has also been reported. The use of a muscle relaxant (*e.g.* suxamethonium 1.5 $mg \cdot kg^{-1}$) has been proposed for cases when interventional endoscopy is performed; however, it appears to be less useful in children than in adults.

Recovery and post-procedural care

Upon completion of the procedure, the child must remain in the recovery area until awake and orientated, and cardiovascular and respiratory stability are assured. An *i.v.* line should be left *in situ* until the child is completely awake and tolerating oral fluids.

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Conventional chest radiography

Matthias C. Schaal and Meinrad Beer

Conventional radiography is the backbone of chest imaging. It allows a rapid, flexible (even bedside) and comprehensive overview of all essential pulmonary and cardiac pathologies in a second. The digitalisation of chest radiography in recent years has substantially reduced the radiation dose accompanied by significantly improved imaging parameters (especially with the possibility of post-processing of images). The application of artificial intelligence for image interpretation is one of the most recent advances in chest radiography.

The role of chest radiography includes the following:

- Primary diagnosis
- Monitoring of the patient's progress
- Assessment for interventional procedures

Thorough consideration of radiation protection based on optimised equipment includes the protection of relatives and medical staff. Fluoroscopy allows the generation of functional information and should be available as an advanced diagnostic modality in special circumstances. Typical indications for chest radiography and fluoroscopy for different age groups are listed in table 1. Digital imaging has revolutionised chest radiography in recent decades. The increasing number of severely ill children (stem-cell transplantation, very low-birthweight preterm babies and polytrauma children) demands a well-equipped radiological unit with specialised paediatric radiologists and trained assistance.

Key points

- Chest radiography is the backbone of radiological diagnosis of chest diseases, while the use of fluoroscopy is restricted to special clinical indications.
- The advent of digital imaging and pulsed fluoroscopy significantly improved the imaging quality of chest radiography and allowed a tremendous reduction of radiation dose.
- Careful attention is necessary for consideration of radiation protection and necessity of imaging (role of routine follow-up examinations).

Table 1. Typical indications for chest radiography and fluoroscopy for different age groups

Age years	Radiography	Fluoroscopy
0–2	IRDS/SDD BPD Tubes and lines Pneumonia	Oesophageal atresia Hernia Diverticula Feeding/swallowing problems
2–5	Pneumonia Aspiration Tubes and lines	Foreign body aspiration
5–10	Pneumonia Asthma CF Tubes and lines Tumours	
10–18	Pneumonia Asthma CF Tubes and lines Tumours	

IRDS: infant respiratory distress syndrome, increasingly called surfactant deficiency disorder (SDD).

Chest radiography

Technique

For newborns and infants, the anterior–posterior (AP) view in supine and later in the upright/sitting position is the accepted standard for conventional chest radiography, as the time point for deep inspiration is more readily detectable. For newborns, specially designed holder systems are available, which allow the optimal positioning of the field of view (properly centred) and radiation protection; the movements of the child also are minimised. The AP projection is also used in critically ill children in the paediatric intensive care unit (PICU) for bedside imaging. However, the technical capabilities of bedside radiography machines are limited, leading to impaired quality of images. Moreover, as in adults, heart size seems to be increased due to the expiratory momentum of most images and pleural effusions are more difficult to quantify.

The posterior–anterior (PA) projection is the accepted standard for conventional chest radiography in older children. Historically, this was the position that allowed the most exact judgement of the size of the heart. Moreover, the radiation dose is about one-third higher at the site of entry. Most radiosensitive structures and organs, such as eyes, thyroid glands, thymus and mammae, are on the distant/opposite side from the radiography machine (*i.e.* anterior). In some conditions (TB, oncological follow-up and special scoring systems for CF), the PA projection may be combined with the lateral projection. However, the radiation dose of these lateral views is about two to three times as high as a standard PA view.

A direct readout matrix (conversion of X-ray intensity into electrical signals) is the hallmark of digital radiography. Direct (selenium-based) systems are distinguished from indirect (scintillator/photodiode) systems. Both systems provide high-quality images with a resolution of ~10 pixels·mm^{-1} and allow a considerable reduction

Table 2. Criteria for image quality and technical parameters

Size of focus	≥0.6 to ≤1.3 mm
Additional filtering	1 mm aluminium plus 0.1–0.2 mm copper
Anti-scatter grid	Use only in children and adolescents with chest thickness >12–14 cm or weight >25 kg
Distance focus detector	90/100–120 cm (AP) in children without the chance to cooperate 140–160 cm (AP) in children with the possibility of cooperation
Tube voltage	50–80 kV
Automatic exposure control	Should not be used in infants; if used, then use with both lateral detectors
Time of exposition	≤5[#] to 8 ms
Radiation protection	Wrapped around, including the gonads (lead)

Chest radiography in the AP/PA projection from the newborn stage up to 10 years is shown in the table as an example. [#]: for newborns, ideally 1 ms.

of radiation dose (depending on the desired resolution). With the advent of dual-reading systems, the spatial resolution is now comparable to the older conventional radiographic systems. Individual optimisation of the software for image calculation is essential. However, artefacts from extrafocal radiation may be exaggerated by the digital systems.

The criteria for image quality and technical parameters are listed in table 2. The optimal balance between image quality and necessary radiation dosage is summarised by the ALARA ("as low as reasonably achievable") principle. The field of view (*i.e.* the area that contributes to the image and is irradiated) should be as small as possible. This is especially important for preterm/term infants. Moreover, the correct adaption of tube voltage and current to age and weight is an essential prerequisite for dose reduction, as well as the age-adapted use of filters. The distance between the child and the tube should be not too narrow. Dose reference values allow an estimation of the correctness of the radiologist's own dose values. In recent years, the ranges of the dose reference values have been lowered substantially. Most European national guidelines recommend a range for the radiation dose of chest radiographs from 0.3 (preterm child) to 4 $cGy \cdot cm^{-2}$ (10-year-old child). This is far below the natural annual irradiation burden (extraterrestrial and terrestrial). Whenever possible, shielding (of at least the mammae/abdomen) should be adopted with appropriate materials. In addition, radiation protection of parents and/or medical staff and/or other children (*e.g.* in the PICU) is important.

Besides the exact positioning of the radiograph on the child, deep inspiration and minimal rotation are important quality factors. A straight run of the trachea is an indicator of a properly inspired radiographic image in newborns and infants. For older children, the scapulae should be rotated so that they are projected outside the lung parenchyma. Exposure to the X-ray machine should be as short as possible to reduce radiation exposure and minimise potential distortion caused by movements of the child.

Special training programmes for chest imaging in infants and small children are available. Thus, even nonspecialist medical staff can learn a high standard of data acquisition prior to primary patient contact. This is especially important for low-birthweight infants.

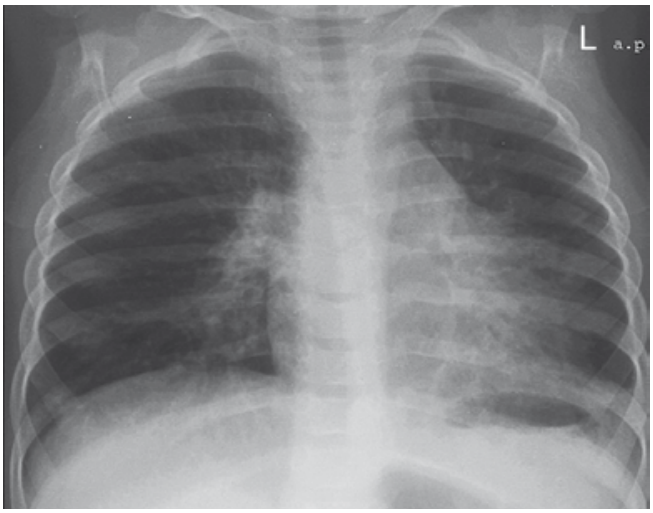

Figure 1. A 15-month-old girl with fever, cough and wheezing. Bilateral pneumonia is seen, with pleural effusion on the left side.

Clinical examples

Most chest radiographs are taken for assessment of children with suspected infectious diseases of the lung, focusing on exclusion/verification of pulmonary opacities and pleural effusions, and sometimes also of pulmonary hyperinflation (obstruction). There is lively discussion of whether chest radiography allows the differentiation between viral and bacterial infections. Moreover, some authors doubt the necessity of routine chest radiography in the assessment of ambulatory acute lower respiratory tract infection. Figure 1 shows the value of chest radiography in detecting complicated pneumonia with relevant pleural effusion in a young child. Ultrasound may be used as a follow-up modality to reduce the radiation dose.

For PICUs/neonatal intensive care units, the value of chest imaging is less debated. In critically ill newborns, especially in (very) low-birthweight infants, it is used to assess the correct position of different tubes and lines, such as tracheal and gastric tubes, temperature sensors and, first and foremost, for the position control of central arterial and venous catheters (figure 2).

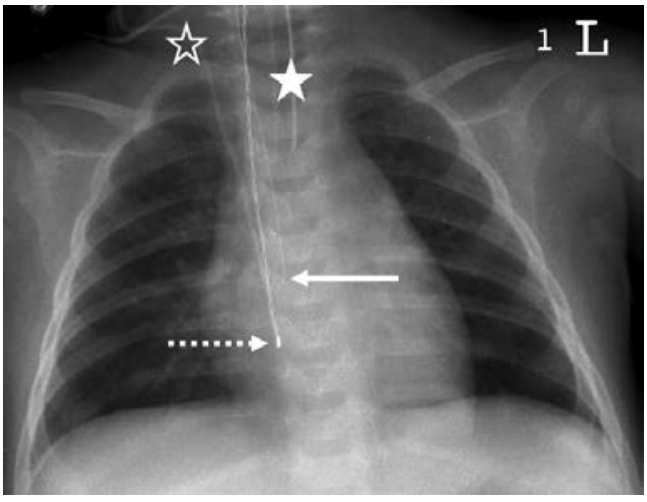

Figure 2. A newborn child with fever. Central opacifications (bilateral pneumonia) are seen, as well as the endotracheal tube (closed asterisk), gastric tube (too high; arrow), temperature sensor (correct; dotted arrow) and central venous catheter from the right jugular vein (open asterisk).

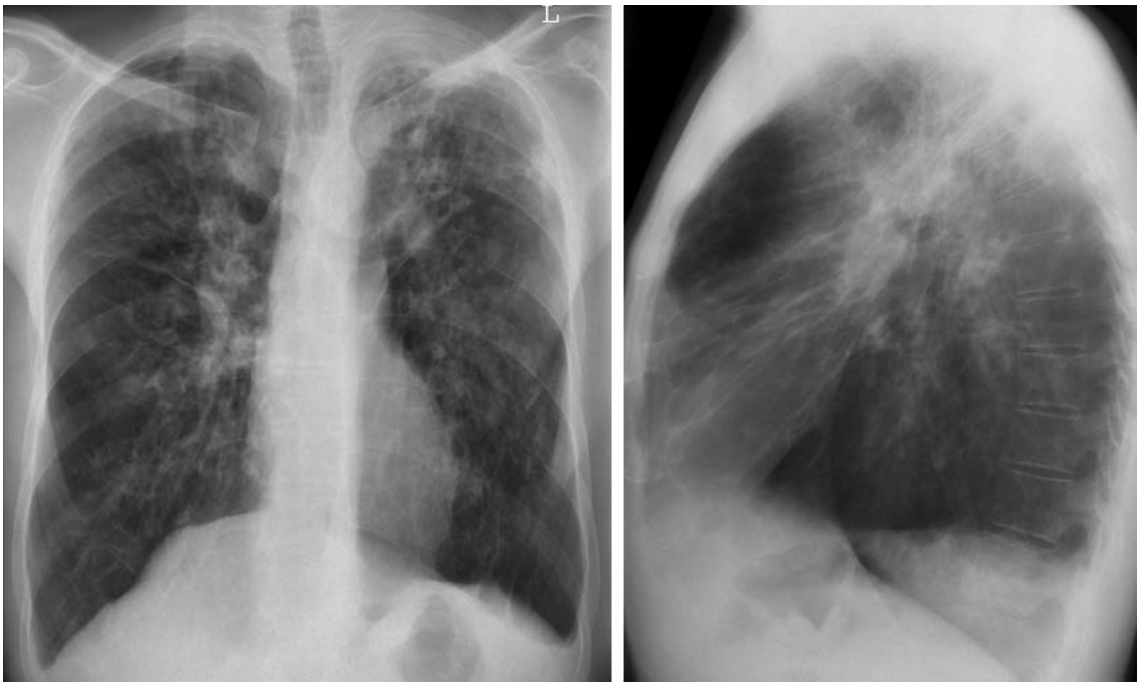

Figure 3. A 22-year-old male patient with CF. Increased lung volumes (obstruction) with a low diaphragm, increased retrosternal space and a kyphotic thoracic spine are seen. Marked pulmonary round, linear and confluent opacities are also evident (CN score 27).

Conventional chest imaging plays an important role in the detection of the salient radiographic features of CF. Different scoring systems, such as the Brasfield or Chrispin–Norman (CN) scores, have been developed to provide objective parameters for longitudinal assessment of potential disease progression. These scoring systems allow an objective assessment of disease severity with low interobserver variability. Included criteria encompass structural changes of the lung parenchyma/tracheobronchial system itself, as well as secondary changes in thorax shape and displacement of adjacent organ systems (figure 3). Complications of advanced CF such as atelectasis, mucous impaction, pneumothorax, pulmonary haemorrhage and cor pulmonale can be detected. However, CT is superior in detection of the extent of bronchiectasis or special kinds of infections (*e.g.* allergic bronchopulmonary aspergillosis). MRI is unique in the assessment of functional pulmonary parameters such as perfusion and ventilation.

Chest radiography also constitutes the first step in the radiological diagnosis of noninfectious chest diseases such as tumours, trauma, malformation and foreign bodies.

Fluoroscopy

Technique

The last decade has also brought significant technical improvements in fluoroscopy. The most important was the advent of pulsed imaging. State-of-the-art fluoroscopy allows the option of different extents of pulse rates. Thus, functional imaging affording high (*e.g.* motility disorders of the oesophagus) and low (*e.g.* slow breathing) temporal resolution is possible with a reduction in radiation exposure of up to 70% (low temporal resolution and low pulse rate).

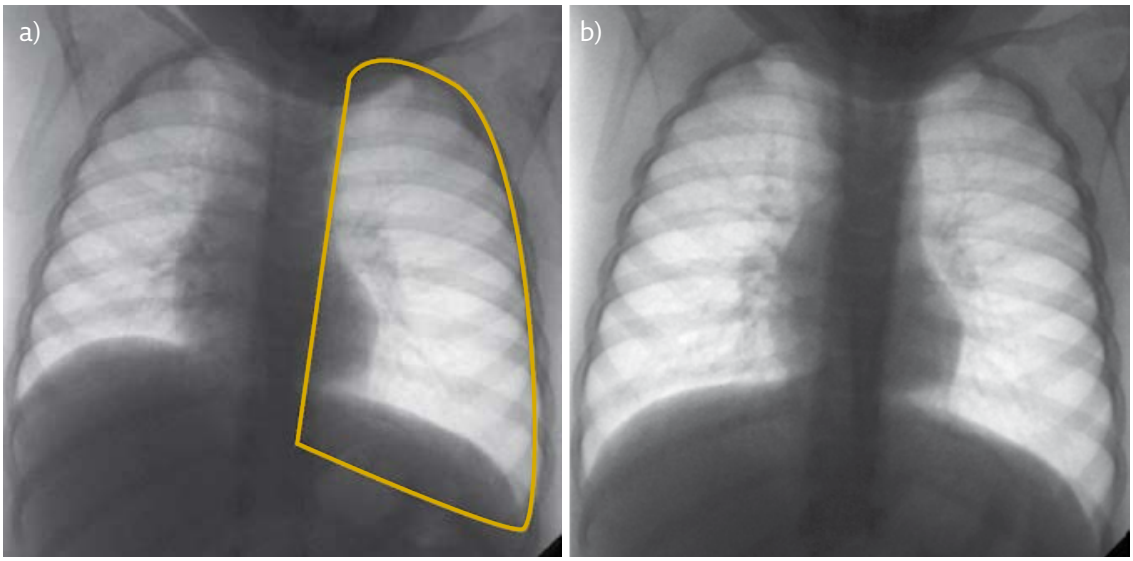

Figure 4. A male infant with suspected aspiration of a foreign body. Fluoroscopy detected regional hypertransparency/hyperinflation in the left lower lobe, most likely due to a valve mechanism: a) increased volume on the left side in end-expiration, compared with b) end-inspiration.

Clinical example

Determination of regional hyperinflation is one possible indication for chest fluoroscopy. Fluoroscopy allows the storage of a series of digitally acquired images ("cine loop" and extended "last image hold"). Retrospectively, images in maximum end-inspiratory and end-expiratory phases can be selected to judge or rule out aspiration of foreign bodies (figure 4).

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Lung/chest ultrasonography

Michael Riccabona

Newborns, infants and children present a similar lung ultrasound to that of adults, although some entities and diseases are different and quite unique, particularly in neonates. High-resolution, high-frequency linear probes (5–18 MHz) are recommended for the near field and the chest wall, and in young patients; for deeper pathology or transabdominal access to the supradiaphragmatic aspects of the lung, lower-frequency curvilinear or sector transducers (10–2 MHz) are necessary, particularly in older children. The examination usually includes longitudinal and transverse sections of the anterior, lateral and posterior chest wall, supplemented by transabdominal or mediastinal access. Unless performed in a point-of-care (POC) fashion, the study is usually completed by an upper abdominal survey (if accessible); the diaphragm and mediastinum and chest wall irregularities (*e.g.* rib variations, lumps and bumps) can also be assessed.

Infants and children have a 3–10-fold higher radiation sensitivity than adults (as a result of a higher rate of dividing cells, longer expected life span for tumour manifestation and different distribution of radiation-sensitive organs), resulting in a higher risk of developing malignancies later in life. Ultrasound as a non-ionising imaging technique offers huge diagnostic potential in many of the conditions detailed in this chapter, and thus lung ultrasound may help to reduce or avoid the use of ionising radiation for imaging. Chest ultrasound has been established for a number of decades. More recently, interest in lung ultrasound has grown in the neonatal and paediatric community, reflected in a growing number of articles and even a dedicated book. However, ultrasound, particularly in neonatal respiratory disease, is mainly

Key points

- Lung ultrasound is a non-ionising imaging technique that offers huge diagnostic potential in many chest conditions.
- A high-resolution linear probe is employed for lung ultrasound in children and infants.
- Proper education and training for lung ultrasound as well as knowledge of restrictions and artefacts are important to avoid misreading.
- Despite its huge potential, lung ultrasound cannot always replace a chest film, chest CT or chest MRI.

embraced and pushed by clinicians, neonatologists and intensive care specialists, or as a POC imaging method. In these POC settings in particular, the risk of bias induced by clinical presentation or misreading from restricted experience and training needs to be considered to avoid overestimation of the potential of ultrasound. Therefore, proper education and training, as well as knowledge of restrictions and artefacts (*e.g.* by mirror effects, mistaking hyperinflation for a pneumothorax) is important to avoid misreadings.

Technique and ultrasound anatomy

The examination is performed with the child in a supine position or even sitting (only necessary for standardised effusion quantification). The probe is placed perpendicular, oblique and parallel to the ribs in the anterior, lateral and posterior (lower and upper) thorax. Posterior areas may be better viewed in a lateral recumbent position or prone. To assess the lower supradiaphragmatic lung, transabdominal access is necessary. Online teaching tools on lung ultrasound are available, as well as international evidence-based recommendations for POC lung ultrasound.

The lung ultrasound appearance of the normal newborn does not differ substantially from that of adults. The pleural line is visualised beneath the ribs, while the sliding movement of the pleural layers is best documented by a short video clip or m-mode (sliding sign). Horizontal echogenic reverberation artefacts (A lines) that appear at constant intervals below the pleural line are normal and are caused by the ventilated air surface (figure 1a).

Even in healthy children, particularly newborns, some vertical echogenic lines (B lines) can commonly be observed. In adults, these are pathognomonic of so-called alveolar-interstitial syndrome (figure 1b). These B lines derive from increased fluid either in the peripheral airspace or in the then-thickened interstitium and are seen in a variety of pulmonary but also cardiac and systemic conditions. Note that these A and B lines should not be confused with the radiographic Kerley lines.

Transient tachypnoea of the newborn

Transient tachypnoea of the newborn (TTN) is a common cause of neonatal respiratory distress with low morbidity. It should be differentiated from other pulmonary or cardiac diseases (*e.g.* pneumonia, pneumothorax, respiratory distress syndrome (RDS),

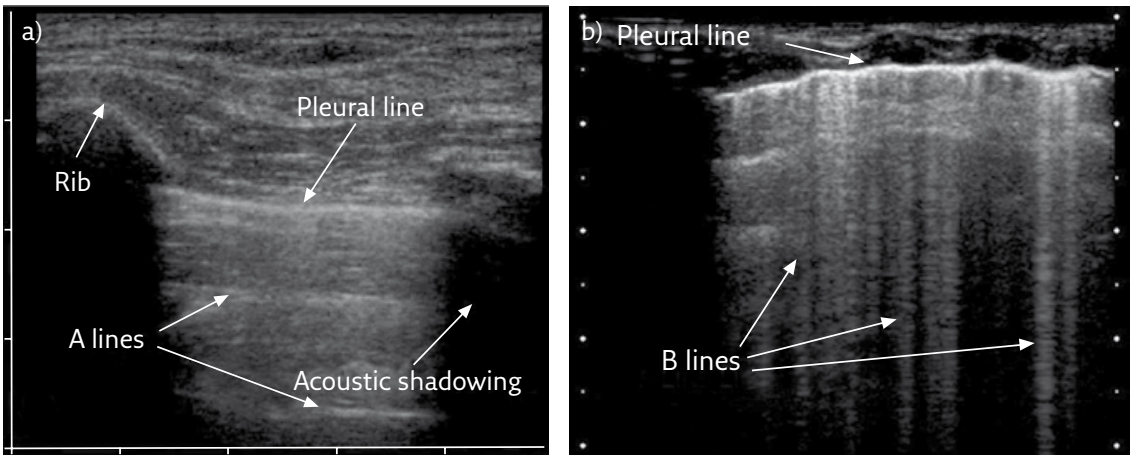

Figure 1. Normal lung. a) Longitudinal scan showing the ribs and their acoustic shadowing, the pleural line and A lines. b) Transverse scan in a healthy newborn at birth. There is evidence of numerous B lines.

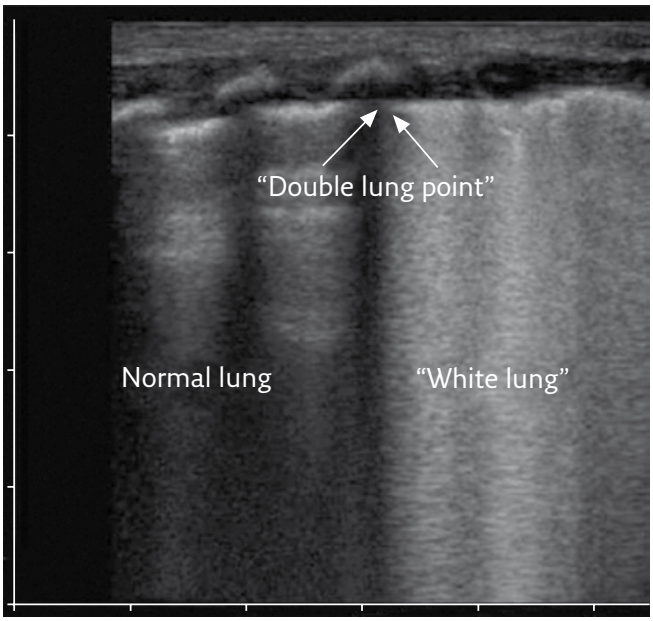

Figure 2. Longitudinal scan showing a clear and sharply delineated difference between the upper and lower lung fields ("double lung point").

congenital heart disease). On the first ultrasound examination, all infants with TTN show bilateral coalescent B lines on the lung base with a normal pleural line (sonographic "white lung") and a normal or near-normal appearance of the upper lung lobes in both lungs, although not always symmetrically. The boundary between the inferior and superior fields is often quite sharp, creating an almost specific lung ultrasound picture that has been named the "double lung point" as it looks like two different contiguous lungs in the same patient (figure 2).

Respiratory distress syndrome

RDS, also known as hyaline membrane disease, is due at least in part to insufficiency of pulmonary surfactant and is confined mainly to preterm infants. The common diagnostic imaging is plain film, allowing grading as well as assessment of complications or other intrathoracic devices such as lines and tubes. Lung ultrasound has been shown to be sensitive in the diagnosis and follow-up of neonatal (idiopathic) RDS. It always shows coalescent diffuse and symmetrically distributed B lines in both lungs and may allow some grading. If severe, this pattern again resembles a sonographically "white lung" (not to be confused with the radiographic term "white lung"), but in contrast to TTN, the pleural line is thickened, irregular, poorly defined and coarse. Multiple, generally small, subpleural hypoechoic areas are observed mainly in the posterior and lateral scans, indicating lung consolidations (possible atelectasis). Larger consolidations with a tissue-like pattern and with evidence of sonographic air or fluid bronchograms may be observed more frequently in the posterior fields. Scans of the anterior thoracic wall are sufficient for diagnosis, provided no treatment attempt such as administration of artificial surfactant has been performed, which may then (particularly with partial success or inhomogeneous distribution of the agent) cause an inhomogeneous pattern. The three most important signs for lung ultrasound diagnosis are:

- Bilateral coalescent B lines involving the entire lung ("white lung") (figure 3)
- Absence of "spared areas" (areas of lung with a normal appearance)
- Pleural line abnormalities

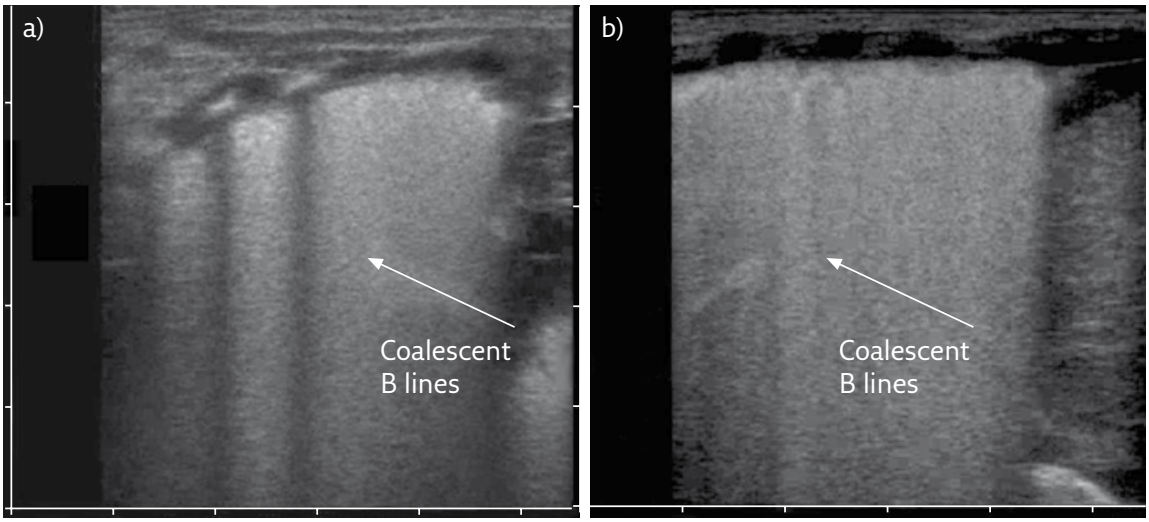

Figure 3. Lung in a newborn with a high degree of (idiopathic) RDS. a) Upper and b) lower fields showing evidence of coalescent B lines ("white lung"). The pleural line is poorly defined and coarse.

Bronchopulmonary dysplasia

BPD is a chronic lung disease that develops in preterm neonates treated with oxygen and positive-pressure ventilation, diagnosed on the basis of oxygen requirement at 36 weeks' gestation. In infants with BPD, lung ultrasound shows multiple B lines with a nonhomogeneous distribution, diffuse changes of the pleural line, which is irregularly thickened, and multiple small subpleural consolidations. Often, some areas are spared, and pleural line changes are said to correlate with disease severity (figure 4). Similar findings may also be present in older children with various chronic lung diseases.

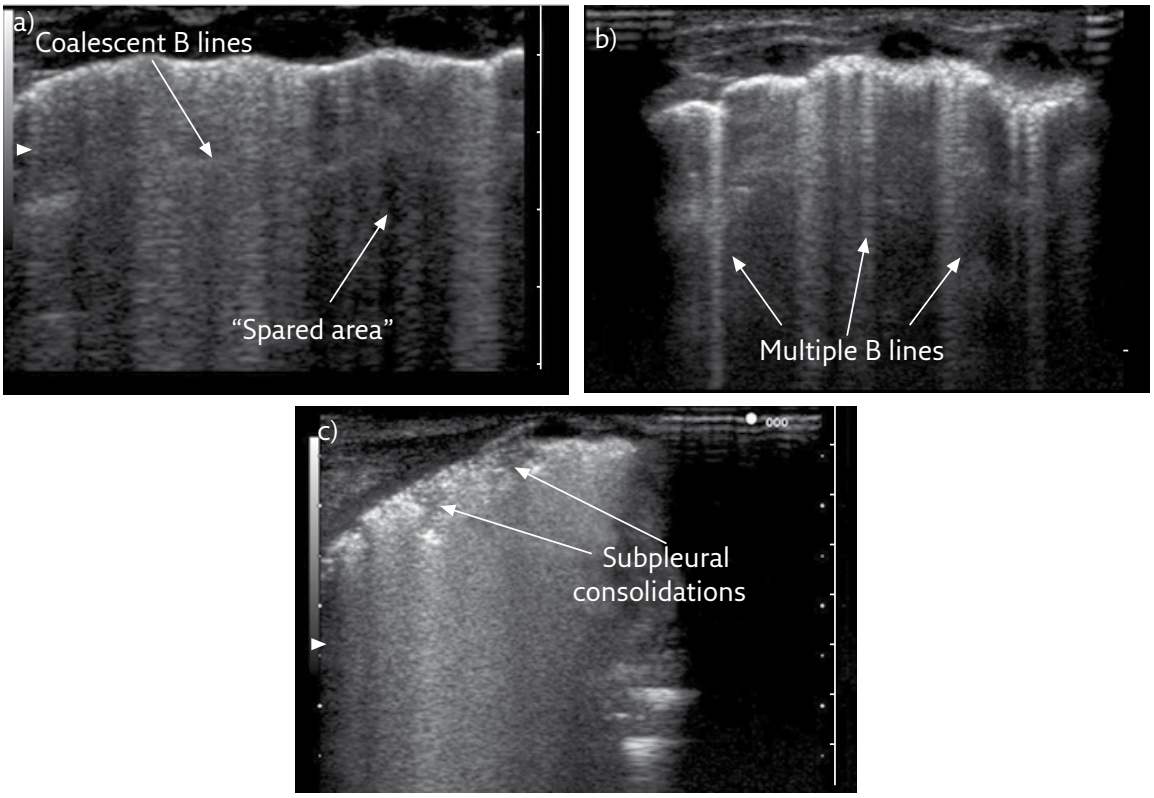

Figure 4. a) Evidence of a "spared area" in an infant affected by BPD. b) Area exhibiting the signs of alveolar-interstitial syndrome in BPD, with numerous, partially grouped B lines. c) Subpleural consolidations in BPD.

Pneumothorax

Transillumination is the bedside procedure used to diagnose pneumothorax by neonatologists. Chest radiography has the same diagnostic limitation as in adults. Lung ultrasound depicts pneumothoraces by observing the absence of lung sliding and may perform better than plain films. However, lung ultrasound is not able to completely and reliably rule out particularly small pneumothoraces. Furthermore, a massive overinflation, as in air trapping or a large bronchogenic cyst, may also mimic such an image, and therefore experience as well as clinical information is helpful in these settings. Ultrasound signs are the same as those described in adults:

- Absence of lung sliding
- Absence of B lines
- Presence of a "lung point", if there is no massive tension pneumothorax

Pulmonary atelectasis

Pulmonary atelectasis is frequent, particularly in ventilated newborns and infants, due to their more collapsible lung or alveolar collapse, or as a result of hypoventilation with low ventilatory pressure. Often, chest radiographs are difficult to read with respect to these findings, so dynamic lung ultrasound signs are very useful and may allow bedside monitoring.

The lung ultrasound appearance of atelectasis is characterised by a liver-like appearance of the lung with a "lung pulse", absence of lung sliding and a tree-like branching with a more parallel course of sonographic air (or fluid) bronchogram (figure 5a). The evidence of dynamic changes of air content in the bronchi with respiration rules out atelectasis due to complete obstruction. However, it should be noted that similar findings may be observed in pneumonia (figure 5b), and thus differentiation of these entities may be tricky and sometimes impossible; other signs that are known from radiography, such as shape and mass effect or not, will also need to be observed.

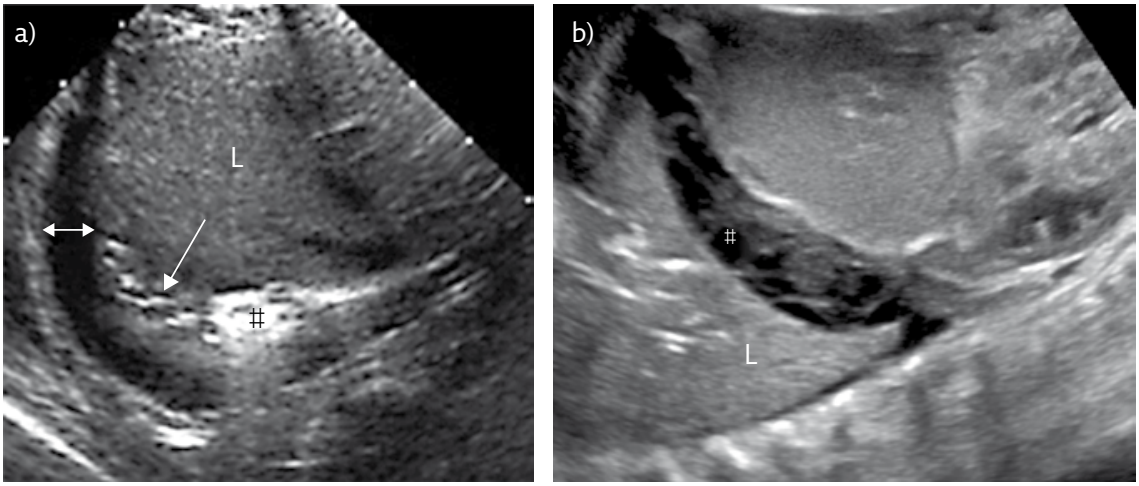

Figure 5. a) Cranially tilted image of the lung base through the liver (L), showing atelectatic lung with some bronchogram (arrow), adjacent uncomplicated pleural effusion (double-headed arrow) and adjacent dystelectatic more-central lung that is still ventilated (#). b) Complicated pneumonia seen as a partially atelectatic, nearly liver-like lung consolidation (L) with some central sonographic air bronchogram and a complicated pleural effusion exhibiting septa (#), consistent with an empyema (the longitudinal section accessed transabdominally).

Bronchiolitis

Bronchiolitis is an acute infectious inflammatory disease of the respiratory tract that may result in obstruction of the small airways.

Depending on disease severity, lung ultrasound findings may be helpful for diagnosis: bilateral involvement is consistently observed with typical areas of normal lung adjacent to areas with subpleural consolidations/atelectasis of 1–3 cm in size surrounded by B lines that may also coalesce. Larger consolidations are less frequent and are generally observed in, for example, more severe disease or secondary pneumonia and in aspiration; sometimes, small pleural effusions can be depicted. As also commonly observed with dystelectasis in other conditions of poorly ventilated, sedated and supine infants, B lines and consolidations may be found, particularly in the paravertebral-dependent lung areas.

Pleural effusion and empyema

Effusion can have numerous causes; ultrasound is said to be the most sensitive technique for depicting even small amounts of pleural fluid, particularly with proper positioning (upright for a couple of minutes to allow the fluid to gather in the lowest compartments, essential for standardised measurements) with a high-resolution transducer. An uncomplicated "simple" pleural effusion has no echoes (figure 5a), whereas complicated effusions contain echoes and/or even septa and pseudo-solid components (figure 5b). Nevertheless, the clear definition of the underlying entity (*e.g.* chylothorax, haemothorax, inflammatory process) cannot be achieved sonographically. If an adjacent atelectatic lung is observed, the differentiation whether the effusion is reactive to the atelectasis or the atelectasis is secondary to the effusion is not achievable; however, lung respiratory motion and dynamic sonographic air bronchogram as well as diaphragmatic motion can be observed.

In a clinically inflammatory condition, an echogenic pleural effusion with more or less thickened septa is consistent with an empyema, and lung ultrasound has been shown to depict these septa much better than CT and therefore is the method of choice, not only for diagnosis but also for observation of treatment success (*e.g.* after instillation of urokinase to break down the septa for clearance by percutaneous drainage). Ultrasound can also be used to guide drainage placement into the respective targeted compartments.

Pneumonia and complications

Children and infants with pneumonia may present with a number of clinical symptoms and signs such as fever, cough and tachypnoea. Chest radiography is still considered the first imaging step for diagnosing pneumonia in children, although lung ultrasound is promoted, particularly for POC settings.

On lung ultrasound, segmental pneumonia appears as a hypoechogenic area with poorly defined borders (figures 5b and 6a). Depending on ventilation, there may be adjacent B lines or just liver-like consolidations with a space-occupying aspect; there may or may not be dynamic sonographic air or air/fluid bronchograms and/or multiple lenticular echoes representing air trapping in the smaller airways (figure 6a). The pleural line is less echogenic in the affected area, and lung sliding may be reduced. Fluid bronchograms (more common in post-obstructive pneumonia) appear as anechoic tubular structures with hyperechoic walls without colour Doppler signals (but restrictions and pitfalls, such as angle dependency, should be considered). Pleural effusion is often present.

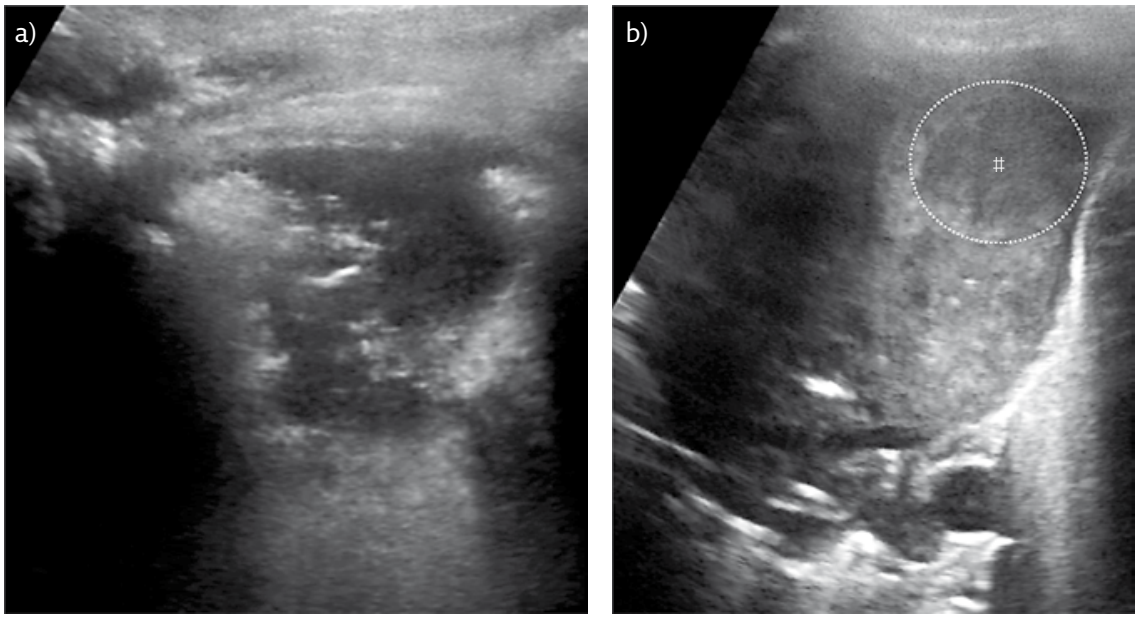

Figure 6. a) Typical ultrasound appearance of pneumonia. b) Necrotising pneumonia with the start of abscess formation, seen as a more or less demarcated darker area (#).

Pneumonia can be seen by lung ultrasound only if the area is accessible (*i.e.* not covered by aerated lung), in which case lung ultrasound is equal to or even better than a chest film. Central pneumonia or pneumonia behind the scapula or other nonaccessible areas cannot be depicted and therefore lung ultrasound cannot "rule out" pneumonia. Furthermore, lung ultrasound often depicts small peripheral consolidations that may be some sort of dystelectasis or even a small pulmonary artery embolism; thus, lung ultrasound is not specific in diagnosing pneumonia and results may be misread if biased by the clinical context and the respective expectation. Finally, lung ultrasound specificity is not yet clear due to a lack of comparative prospective studies with CT as the gold standard.

Lung ultrasound can find complications of pneumonia such as necrosis or abscesses seen as (confluent) areas of reduced structure and echogenicity that are more or less demarcated with a membrane-like border (figure 6b). (Power) Doppler sonography and potentially contrast-enhanced ultrasound will help to define nonperfused areas in equivocal situations; ultrasound can also be used for follow-up or to guide puncture/drainage.

Lung malformations

Currently, most lung malformations are depicted prenatally by fetal ultrasound and potentially confirmed by fetal MRI. Lung ultrasound is used for postnatal confirmation and work-up; in particular, sequestrations, which are usually large and echogenic, can be assessed, including depiction of large systemic feeding vessels, especially if derived from the abdominal aorta (figure 7). Cystic and solid components can be differentiated, and thus hybrid lesions/mixed foregut malformations can be diagnosed.

It is more difficult to post-natally diagnose a congenital pulmonary airway malformation or bronchogenic cysts sonographically, particularly when the adjacent lung is aerated or the cysts are filled with air. An early attempt to visualise them may be tried before these cystic structures have completely filled with air.

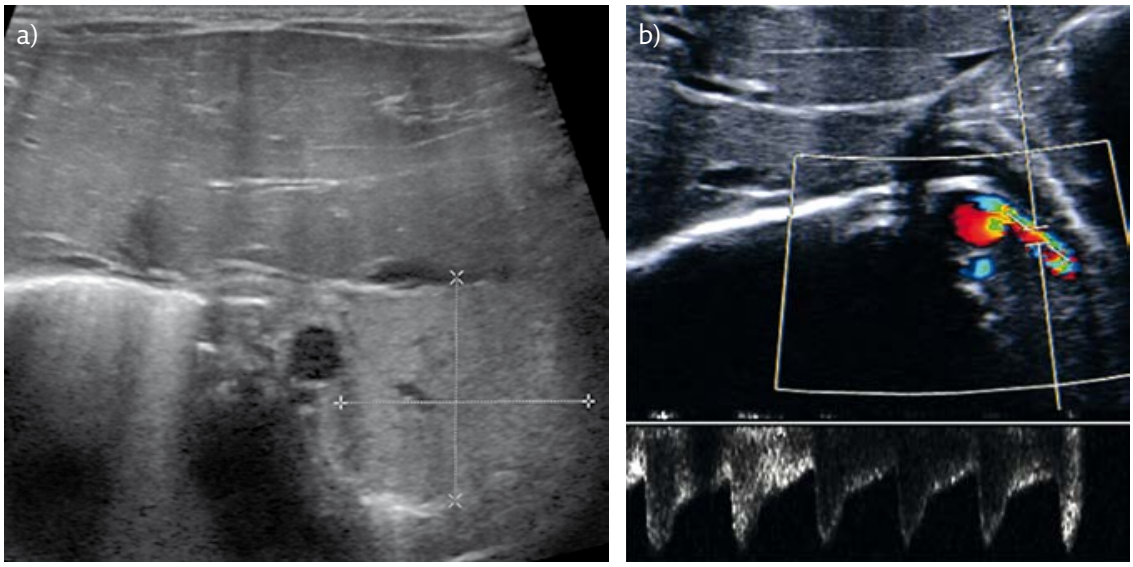

Figure 7. Sequestration on ultrasound. a) An echogenic, tumour-like sequestration (outline indicated by lines and crosses) in the left lower chest accessed abdominally through the left liver lobe. b) Colour Doppler image of a large feeding artery derived from the aorta, with the spectral trace (below) demonstrating high-velocity and low-resistance arterial flow.

Miscellaneous lung ultrasound applications and restrictions

Various findings are often unspecific, such as irregular pleural thickening, commonly observed in a severe or chronic disease (*e.g.* TB).

Other structures that may be encountered in lung ultrasound are conditions of the chest wall (*e.g.* rib anomalies, lumps and bumps), or others such as diaphragmatic palsy (excellently visualised by dynamic ultrasound and documented by video clip or m-mode), mediastinal masses or simply a large thymus (in cases of equivocal mediastinal enlargement on chest films), and the respective differential, diaphragmatic hernia, or even the rare paediatric lung and chest tumours (provided these sit at the pleura and thus can be visualised). Assessment of hilar and mediastinal nodes is much more cumbersome, and sometimes impossible, but on occasions when it is possible, it is a strong marker in, for example, necrotising pneumonia or TB.

Finally, it should be noted that many of these phenomena can be associated with cardiac or systemic conditions and do not always reflect a primary pulmonary disease. Thus, when examining lung ultrasound findings, the patient's history and all other findings (clinical, laboratory and imaging) must be considered.

Further reading

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Chest computed tomography

Harm A.W.M. Tiddens, Pierluigi Ciet and Marcel van Straten

Over the last two decades, chest CT has gained importance as a sensitive modality for the diagnosis and monitoring of structural lung abnormalities in children. Radiation exposure for a volumetric chest CT has been reduced substantially, which has lowered the threshold for its use in children. In addition, CT scanners have become much faster, making it feasible to do a chest examination within a single breath-hold or even in free breathing in preschool children. This chapter aims to give the paediatric pulmonologist background information on important topics related to chest CT imaging in children, focusing especially on image quality optimisation and safety. This information will help the paediatric pulmonologist to fill in relevant information on the chest CT order form and to discuss the best protocol for chest CT in children more efficiently with the paediatric radiologist.

CT technology

CT scanners have improved greatly since their introduction in 1972. The scan time for a chest CT has been reduced to the order of 1 s with submillimetre spatial resolution. Modern CT scanners consist of an X-ray tube that rotates around the patient while attenuation measurements are obtained from an array of detectors, which also rotates. Early scanners acquired data during a full rotation of the X-ray tube before the scanner table moved to scan the next longitudinal position (figure 1a). This technique, called sequential scanning, was used for nearly two decades.

In the late 1980s, a new technique called spiral or volumetric CT was introduced whereby the patient moves through the CT scanner while projection data of the continuously rotating X-ray source and detector array are acquired simultaneously

Key points

- When ordering a chest CT, it is important to supply a detailed patient history and a well-defined clinical question.
- Complicated cases should be discussed with the radiologist prior to the investigation to maximise diagnostic yield and minimise radiation exposure.
- A cooperative child is best trained prior to the CT investigation and coached by the same person during the investigation to reduce anxiety, optimise and standardise volume control during the procedure, and reduce movement artefacts.

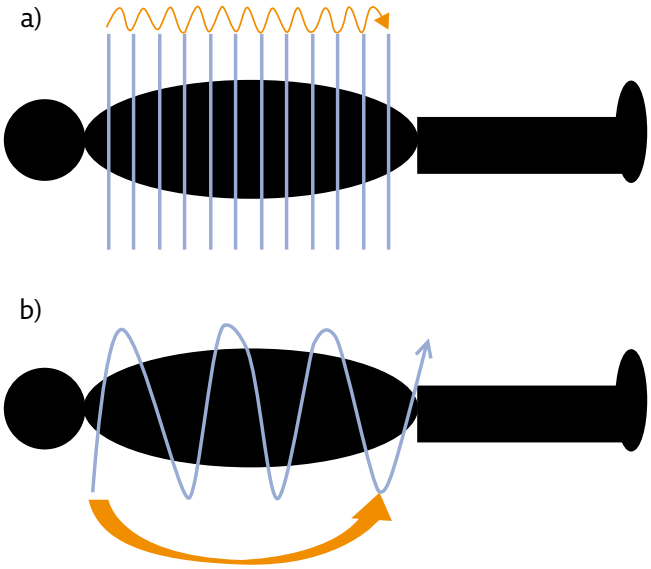

Figure 1. a) Noncontiguous sequential CT. Data are acquired during full rotation of the X-ray tube and the scanner table then moves to scan the next longitudinal position. Typically, thin slices (0.5–1.5 mm) of the lung are acquired at intervals of 0.5–2 cm using this technique. b) Volumetric or spiral CT. The patient moves through the CT scanner while projection data are simultaneously acquired from the continuously rotating X-ray source and detector array.

(figure 1b). The performance of the spiral CT scanner was further improved by detectors that measured multiple attenuation profiles simultaneously. With multi-slice spiral CT, an arbitrary number of slices can be reconstructed (note that a number of alternative terms can be found in the literature, such as multi-section, multi-channel and volumetric CT). The coverage in the longitudinal direction per full detector readout is given by the total beam collimation, calculated as the width of a single detector row multiplied by the total number of rows. Currently available CT scanners allow the acquisition of up to 256–320 profiles simultaneously, with a longitudinal coverage of up to 320×0.5 mm=16 cm. One CT manufacturer offers scanners with an additional tube-detector pair. These dual-source scanners acquire data faster, resulting in scan speeds of ~70 cm·s^{-1} and a shutter speed or exposure time <100 ms for each axial image.

Sequential or volumetric scan mode

CT scanners image the chest using either a noncontiguous sequential scan mode or a continuous volumetric scan mode. Sequential modes sample the lung by acquiring thin slices (0.5–1.5 mm) at intervals of 0.5–2 cm (figure 1a). These are usually obtained in inspiration from the apex of the lung to the diaphragm. In the early days of chest CT, this noncontiguous sequential scanning was practically the only way to obtain high-resolution images of the chest. Nowadays, the only advantage over volumetric scanning is a lower radiation exposure, which might be considered pre-eminent in specific cases.

By using a volumetric acquisition mode, the entire lung is imaged with high resolution in a short time (figure 1b). The major advantages of volumetric CT include comprehensive assessment of the lung structure, allowing reconstruction into multiple planes and of three-dimensional images. In addition, it allows matching and sensitive comparison of slices at identical anatomical positions for longitudinal follow-up.

Image resolution

The spatial resolution of the scan depends on multiple acquisition and reconstruction parameters and is technically limited by the X-ray focal spot size and the dimensions of the detector elements.

Important acquisition parameters include the pitch value and the speed of rotation of the X-ray tube. The pitch is defined as table feed per full rotation of the X-ray tube divided by the total width of the collimated X-ray beam. The lower the pitch value, the more information is collected per unit length. Young children have small airway diameters, and hence for detailed information of the lung, a relatively low pitch value is preferred. When scanning with a low pitch, thin slices can be reconstructed without interpolation artefacts at the cost of a reduced table speed. When scanning with a high pitch, artefacts due to patient breathing and the beating heart will be reduced, but reconstruction artefacts will appear. In practice, a good trade-off between resolution and motion artefacts is a pitch value of ~1. For dual-source CT, pitch values of 3 are feasible. Spatial resolution will generally also improve when the rotation speed of the X-ray tube is lowered because this allows more detailed sampling of structures. When reconstructing images, one can choose the effective slice thickness and the in-plane resolution *via* the so-called reconstruction kernel (also referred to as a "filter" or "algorithm" by some CT vendors), which is one of the most important parameters affecting image quality. Generally speaking, there is a trade-off between spatial resolution and noise for each kernel. A soft kernel generates images with lower noise but reduced spatial resolution (figure 2a). A hard kernel generates images with higher spatial resolution but increases the image noise (figure 2b).

The level of detail needed will depend primarily on the clinical question. For evaluation of trapped air and/or a mosaic pattern on an expiratory scan, a low level of resolution is often sufficient. High resolution is required for (semi-)automated image analysis of airways or for nodule detection, or when CT angiography is undertaken to allow the reconstruction of small vessels in great detail.

High-resolution images have more image noise, and this can affect the visibility of the structures of interest, despite the resolution improvement. More detailed information can only be acquired at the cost of increased exposure to ionising radiation, which compensates for the image noise increase, or by applying noise-reduction techniques when reconstructing the images.

Radiation

A disadvantage of chest CT scanning is the relatively high doses of ionising radiation needed compared with conventional chest radiography. However, thanks to technical innovations in detector technology and advanced reconstruction techniques, the radiation dose of chest CTs needed to obtain diagnostic images has been reduced considerably and the information obtained is superior relative to chest radiography. Hence, the risk/benefit balance for the use of chest CT has lowered the threshold for its use. It is assumed that exposure to ionising radiation in CT scans increases the natural lifetime risk of cancer. This risk is higher in young paediatric patients, who have a higher number of actively dividing cells than adults. Thus, for each scan, the radiation dose should be justified and minimised to a level "as low as reasonably achievable" (ALARA principle). The CT protocol should be tailored to the size of the patient, and the minimum radiation dose that will produce images of diagnostic quality allowing sensitive image analysis should be used. The risks related to exposure levels of state-of-the-art, low-dose chest CT protocols are considered to be low.

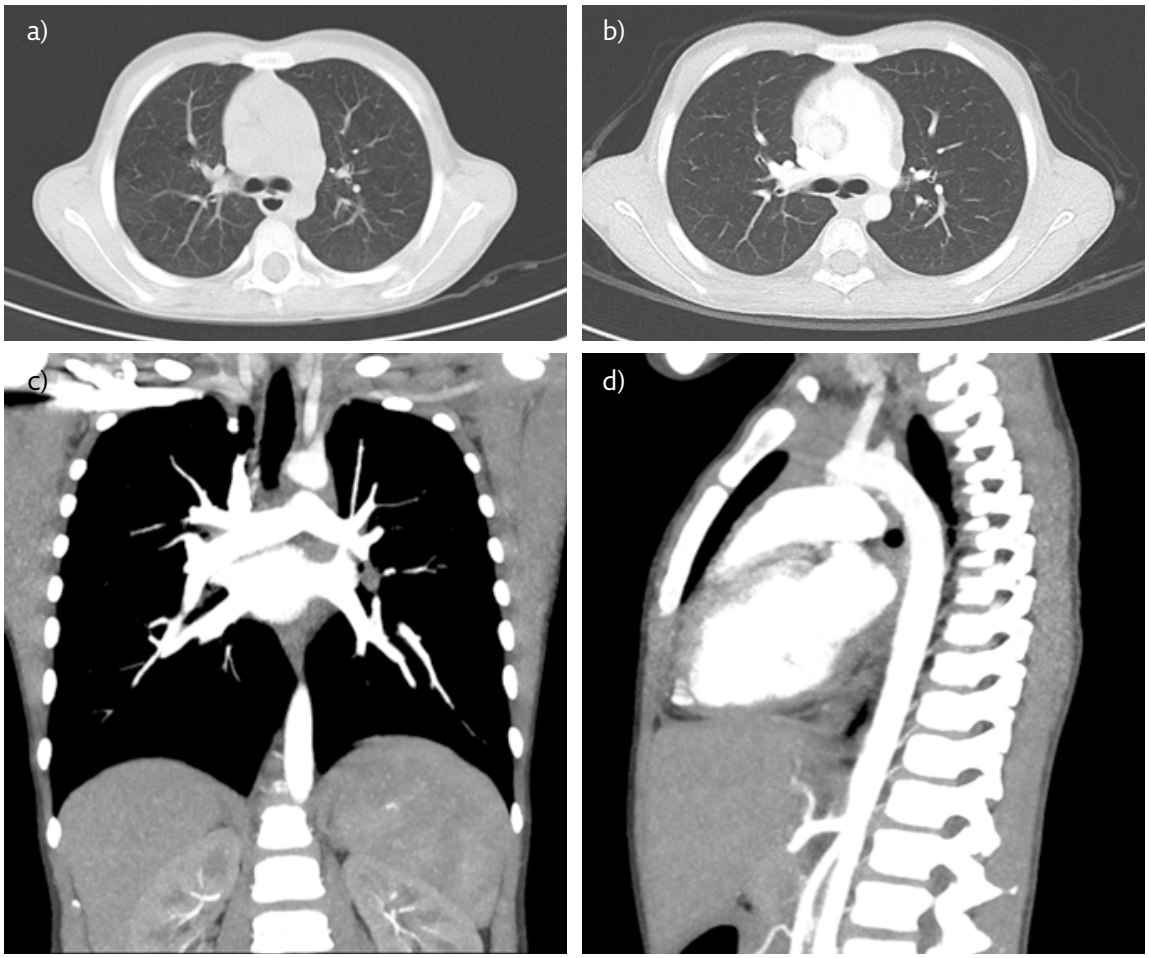

Figure 2. The effect of different reconstruction algorithms on image quality after administration of an i.v. *contrast medium. a) A slice (3 mm) in the axial plane reconstructed using a soft kernel (B60). b) The same slice now reconstructed using a hard kernel (B70). Note that the vessels are more visible. c and d) The lung reconstructed in the c) coronal and d) sagittal planes using maximum intensity projection. Note that the contrast-enhanced blood vessels contrast clearly with the surrounding lung tissue.*

Radiation exposures for a combined inspiratory and expiratory chest CT protocol are in the order of 0.5–1 year of the annual background radiation in the USA. However, radiation restricts the number of CTs that can be justified for a subject over a certain time interval for a clinical study. The required radiation dose for an expiratory scan can be half that for the inspiratory scan.

Contrast media

Administration of contrast is needed whenever the cardiovascular system and mediastinum need to be depicted. Several issues complicate the administration of intravenous contrast medium to neonates and children, including the use of small volumes of contrast medium, the use of small-gauge angiocatheters (*e.g.* 24-gauge) and unusual vascular access sites (hand or foot). Ideally, angiocatheters should be inserted 0.5–1 h prior to the chest CT so the child is not too upset to lie down quietly in the CT scanner. The contrast dose and rate depend on the patient's age, catheter size and type of study. It is now the standard of care to use non-ionic contrast material (iodine 300 mg ·mL^{-1}) in children. On average, the volume of contrast medium is ~2 mL·kg^{-1} of body weight. Smaller volumes (0.6–1 mL·kg^{-1}) are typically administered to neonates and infants, especially when combined with a low kilovoltage setting (70 kV) of the CT scanner. As the contrast medium is cleared through the kidneys,

normal kidney function is required. In cases of suboptimal renal function, the dose of contrast needs to be adjusted.

Adverse reactions to iodinated contrast media are divided into acute and late. The former occur within 1 h of contrast medium injection and are further classified as mild, moderate or severe. For this reason, resuscitation equipment, a paediatric resuscitation protocol and qualified personnel should be close at hand in case a severe allergic reaction occurs. Late adverse reactions occur 1 h to 1 week after contrast medium injection and are represented by a variety of late symptoms (nausea, vomiting, headache, musculoskeletal pain, fever) or by skin reactions, which are usually mild and self-limited. While most minor physiological side-effects of *i.v.* contrast medium administration in adults are of minimal significance, such events can be of increased importance in children. For example, local warmth at the injection site and nausea, generally regarded to be physiological side-effects to contrast medium administration, may cause a child to move or cry. Such a response to contrast medium injection may result in the acquisition of a nondiagnostic imaging study, necessitating repeat imaging and additional exposure to contrast medium and radiation.

The reported incidence of paediatric allergic-like reactions to contrast media ranges from 0.18% to 0.46%. It is generally agreed, however, that the incidence of allergic-like reactions in children is lower than that in adults.

Volume control

Lung volume and airways configuration and orientation are highly dependent on the level of inflation of the lung (figure 3). When the lung is well inflated, the lung parenchyma is positioned between the heart and the sternum. In addition, the trachea has a round appearance and the contour of the diaphragm is flattened. For an optimal diagnostic result, volume control is important and should be obtained whenever possible. It is also important that movement of both the subject and the lungs is minimised. Generally, scanning starts at the lung apices and moves towards the diaphragm. In cases of long breath-hold times, movement artefacts near the level of the diaphragm can be observed. When breath-hold times are critical, starting the scan at the level of the diaphragm and moving up towards the apices of the lung can be considered to reduce movement artefacts.

Most young children <4 years are not able to do a voluntary breath-hold at the correct volume level and at the correct moment. There are two methods available to scan the lungs in these young children. The most commonly used is a fast CT scanner, which allows virtually motion-free images of the lung to be obtained in free-breathing conditions without sedation or general anaesthesia. A disadvantage of this free-breathing method is that there is no strict control of lung volume. Spontaneous breathing will be near FRC plus or minus tidal volume. It has been shown that the sensitivity of scans to detect bronchiectasis acquired during tidal volume breathing is less compared with inspiratory scans using the pressure-controlled ventilation (PCV) technique. However, the specificity of bronchiectasis detection is good. For children <2 years, a vacuum mattress can be of help by restricting the movements of the child during acquisition of the scan. However, particularly in children <1 year of age, care should be taken that the thorax is not deformed when using the vacuum mattress.

The second technique to acquire a CT scan in children <4 years is the noninvasive PCV technique under general anaesthesia or sedation. The PCV technique starts off by hyperventilating the child by giving a short series of augmented breaths using high positive pressure applied *via* a face mask, laryngeal mask or tube to recruit all lung

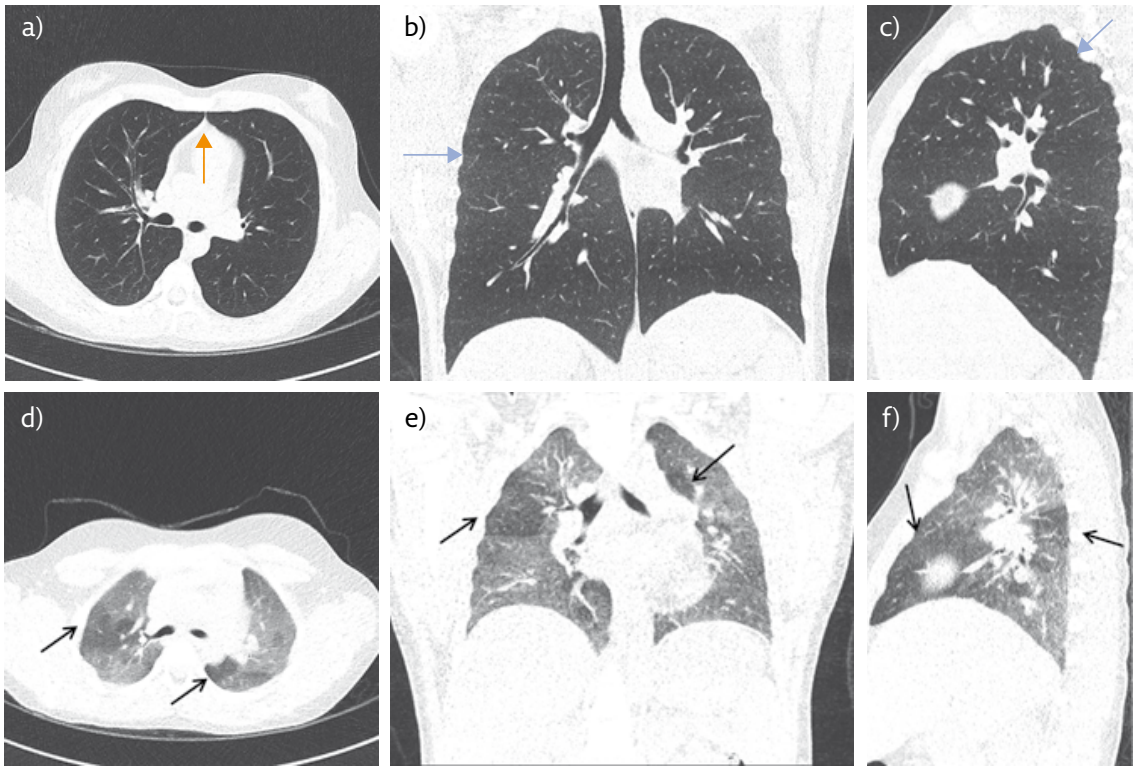

Figure 3. a–c) A spirometer-controlled inspiratory chest CT reconstructed in the a) axial, b) coronal and c) sagittal planes. Note that the lung is positioned between the heart and the sternum (orange arrow) and that the lung is protruding between the ribs (blue arrows). d–f) A spirometer-controlled expiratory chest CT reconstructed in the d) axial, e) coronal and f) sagittal planes. Arrows indicate hyperlucent regions of the lung caused by hypoperfusion and/or trapped air. The hyperlucent regions are adjacent to normal dense regions representing a mosaic pattern. Note that the images in d–f could only be matched to those in a–c based on a few anatomical landmarks such as orientation and that the volume of anatomical structures such as the bronchial tree changed considerably between maximal inspiration and maximal expiration.

areas and to allow for a respiratory pause. Next, for inspiratory images, the lung is inflated to a positive transpulmonary pressure of 25 cmH_2O and the lungs are imaged while maintaining pressure. For expiratory images, no pressure is applied, and hence the lung will deflate to a volume level near FRC. PCV techniques have been shown to be highly reproducible. A disadvantage, however, is that atelectasis can develop within minutes in children under general anaesthesia. Atelectatic regions of the lung cannot be evaluated for the presence of bronchiectasis or other structural abnormalities. When high-resolution images are required, for example when interstitial lung abnormalities are suspected, inspiratory PCV can be considered. Expiratory images can also be obtained by putting the child in the lateral decubitus position, where the lung against the table will be in expiration due to body weight compression and the contralateral lung will be in inspiration.

For children ≥4 years, chest CT can generally be done without sedation or anaesthesia. Breath-hold instructions during the inspiratory and expiratory CT scan are routinely given by a CT technician, often resulting in suboptimal volume levels. The inspiratory volume level of these radiographer-guided scans results in a lung volume in the range of 80% of TLC. The expiratory volume level of such scans in most subjects is near FRC, which is well above RV. For many years, it has been recognised that spirometer-controlled breathing manoeuvres during the CT scan result in improved standardisation of inspiratory and expiratory volume levels and fewer movement

artefacts, and thus improve the diagnostic yield of the scans substantially. In this case, the patient can be trained by a lung function technician 30–60 min prior to the CT scan. The patient practises the required breathing manoeuvres in the supine position, ideally using a spirometer. Next, the same technician instructs the patient during the CT scan. The sensitivity for the detection of low-attenuation regions of spirometer-controlled expiratory scans is superior to that of uncontrolled expiratory scans. For cooperative young children aged 4–6 years, it can be challenging to do the training with a spirometer. For these children, the lung function technician can decide to train the breath-hold manoeuvres without the use of a spirometer and just verbally instruct the child during the CT scan without the feedback from the spirometer. The success rate of high-quality chest CTs using technician-guided CT in clinical routine is >90%. As this training and coaching routine fits the ALARA principle, we feel strongly that it should be implemented in every clinic where chest CTs in children are carried out. Importantly, this routine does not increase the time needed in the CT suite, as children are well instructed and less anxious, and therefore there is no reduction of CT productivity.

Inspiratory and/or expiratory scans

For many chest CT scan indications in tertiary centres, acquisition of both inspiratory and expiratory chest CTs is relevant. An inspiratory CT scan near TLC is needed for the standardised evaluation of lung parenchyma and airway dimensions (figure 3a–c).

To diagnose bronchiectasis, the diameter of the airway is compared with the diameter of the adjacent or nearby pulmonary artery. For this comparison, the outer-wall diameter of the airway is best used as it is less sensitive to volume changes and is not influenced by mucus in the lumen. An airway/artery ratio >1 is considered to be bronchiectasis. Current consensus is that the diagnosis of bronchiectasis is best made on an inspiratory CT near TLC as it has been shown that the airway/artery ratio and airway wall thickness are dependent on the inspiration level. At lower lung volumes, the diameter of the airway is reduced more relative to that of the adjacent artery, and the airway wall appears thicker. In addition, at low lung volumes, the orientation of airways is different relative to inspiration, and airway length is reduced, making identification of abnormally widened airways cut in cross-section more difficult.

Expiratory scans are important to detect small airways pathology, central airways collapse (tracheomalacia) and perfusion defects (figure 3d–f). Airways <1 mm in diameter are in general not visible on CT scans; however, small airways disease causing obstruction can be detected indirectly as a mosaic pattern on expiratory scans. This mosaic pattern is often referred to as air trapping or trapped air, but these terms are incorrect as the mosaic pattern can be the result of trapped air at the end of an expiration and/or hypoperfusion (figure 3d–f). Areas of trapped air contrast with the adjacent healthier deflated and normal perfused or hyperperfused dense parenchyma. These areas of trapped air can be differentiated from hypoperfused areas by comparing their density in inspiratory and expiratory scans and by looking at the number of parenchymal vessels. Optimal expiration to a volume level near RV increases the contrast between trapped air and normal lung regions (figure 3).

Dynamic *versus* static imaging

Dynamic or cine-multidetector CT has been used to study the dynamic behaviour of central airways in adult patients. This method can be used as an alternative to bronchoscopy to diagnose tracheomalacia. Additionally, images can be acquired while the patient is executing a forced expiration. The forced expiration will increase airways

collapse in cases of tracheomalacia. Unfortunately, dynamic information requires longer exposure to ionising radiation. A frequently used CT protocol for the diagnosis of tracheomalacia involves a volumetric end-inspiratory and forced end-expiratory breath-hold scan.

Image reconstruction and visualisation

Generated images need to be reconstructed and stored in the correct way. Acquired data are saved primarily in a raw format requiring substantial memory space. Image reconstruction is needed to generate relevant series and specific reconstructions. The generated images are stored in the Picture Archiving and Communication System (PACS). Raw data are in general automatically deleted from the scanner 1–2 weeks after the scan. Hence, it is important that all relevant series are reconstructed and stored before the raw data are deleted. Reconstruction protocols define reconstruction planes (axial, coronal and sagittal), slice thickness (*e.g.* 0.65, 1, 1.25, 3 or 5 mm), windowing (parenchyma or mediastinum) and reconstruction kernels (soft or hard). Useful visualisation techniques are maximum intensity projection (MIP) (figure 2c and d) and minimum intensity projection (MinIP). MIP consists of projecting the voxel with the highest attenuation value on every view throughout the volume onto a two-dimensional image. This technique is normally used to detect lung nodules or, in scans with contrast, to improve depiction of the vessel. MinIP is a data visualisation method that facilitates the detection of low-density structures in a given volume. It is particularly useful for analysing the airways, which are hypodense compared with the surrounding tissue. For inspiratory CT scans at TLC, MinIP can be used to improve the detection of low-attenuation regions related to hypoperfusion and/or emphysema. For expiratory scans, MinIP facilitates the detection of low-attenuation regions caused by hypoperfusion and/or trapped air. At least one series of thin-slice images (≤1 mm) in the axial plane should be stored using an appropriate predefined reconstruction kernel. These thin slices are needed to evaluate the airways, and this series allows future post-processing, such as reconstruction of thicker slices or three-dimensional reconstruction. Thin slices are also often required for commercially available image-analysis platforms.

When assessing a chest CT image, it is very important to use consistent lung window settings, as apparent bronchial wall thickening can vary significantly using different settings. A window width of 1500 HU and a window level (or centre) of –450 HU has been shown to be the best level for accurate assessment of bronchial diameters and wall thickness.

Image analysis

In clinical practice, progression of structural lung changes can be monitored with chest CT. This can best be examined by comparing slice by slice the follow-up to the baseline examination in the axial or other planes. Most PACS viewers allow coupling of two examinations in a single window, with scrolling down through the lung from the apices to the base. These comparisons should be performed for both the inspiratory and expiratory CT scan. Slice-by-slice comparison allows determination of whether observed structural changes on the baseline CT have progressed, are stable or have improved on the follow-up CT, or whether new abnormalities have developed. Ideally, structural changes on chest CT should be quantified when possible; examples are airway wall thickening, bronchiectasis and a mosaic pattern. To date, for phenotyping CF lung disease on chest CT, the method of choice has been scoring. The reader identifies various abnormalities on the CT scans and scores their presence and

extent. Important abnormalities that are included in most of the scoring systems are bronchiectasis, mucous plugging, airway wall thickening and parenchymal opacities. Other abnormalities such as ground-glass opacities, small nodules, mosaic attenuation and sacculations on expiratory images are included in only some scoring systems. An advantage of scoring systems is that they are relatively insensitive to the CT scanner technique and protocol being used. A disadvantage is that they require training and are relatively time consuming. Therefore, automated image-analysis systems, including measurement of airway dimensions, are currently in development using artificial intelligence strategies. These systems will be used in the near future to monitor CF lung disease and other paediatric lung diseases such as non-CF bronchiectasis and asthma. Automated systems are commercially available for lung diseases in adults such as COPD and ILDs. It is likely that similar automated systems will also become available for asthma and ILDs in children. As discussed earlier, the use of automated systems requires standardisation of volume and CT protocol.

Ordering a chest CT

When ordering a chest CT, it is important to supply the relevant clinical information and well-defined questions so that the radiologist can select the appropriate scanning protocol. Standardisation of the ordering form can be of help in supplying the relevant information. For more complicated cases, it is always useful to discuss beforehand with the radiologist the best protocol to select. Training and coaching of the child for the scanning procedure should be scheduled in advance in conjunction with the planning of the CT. The workflow should be organised in such a way that the appropriate protocol is executed to obtain a diagnostic chest CT.

Summary

Chest CT is a mature technology and is now an important tool for the diagnosis and monitoring of chest diseases in children. To optimally and safely use chest CT in children, a paediatric radiologist should be involved in defining the optimal protocol based on the clinical question. The referring clinician should carefully describe relevant clinical details and the clinical questions. Standardisation of lung volume is of key importance for the inspiratory and expiratory scan to maximise the diagnostic yield of the chest CT. Lung function technicians can play an important role in preparing children for a chest CT and in coaching and monitoring breath-hold manoeuvres during acquisition.

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Chest magnetic resonance imaging

Pierluigi Ciet, Harm A.W.M. Tiddens and Piotr Wielopolski

MRI in paediatric chest disease characterisation has so far been considered a complementary diagnostic tool to CT. Although CT remains superior for spatial resolution, substantial improvements have been achieved with new MRI pulse sequences and very short scanning times, making paediatric chest MRI a viable alternative. Moreover, chest MRI has the unparalleled advantage as a combinatory tool for both structural and functional imaging without radiation exposure. In this chapter, new MRI techniques for lung, airways and diaphragm evaluation are discussed.

Patient preparation

In patients <5 years of age or those who cannot follow breath-hold instructions, free-breathing MRI techniques with sedation or anaesthesia are mandatory. A possible alternative to sedation is the "feed and swaddle" technique, where the child is fed immediately before the examination and then placed in the scanner after being swaddled. Patients who can follow breathing instructions may undergo MRI without sedation with adequate preparation and training. This preparation stage makes the patient familiar with the MRI environment; specific breathing manoeuvres can also be practised prior to MRI. Lung volume standardisation is also enhanced using an MRI-compatible spirometer. To further reduce anxiety, parents should be allowed to stay inside the MRI room with the child.

MRI system and pulse sequence selection

System and coil selection

1.5 Tesla (T) systems are usually more suitable than higher-field strengths due to the lower susceptibility to signal loss when using gradient echo sequences. Appropriate

Key points

- Chest MRI provides structural and functional information in a single examination.
- Chest MRI anatomical detail from new pulse sequences is almost comparable to that of CT.
- Chest MRI can be used to study ventilation, inflammation, perfusion and structure.

coil receiver selection also influences image quality after a radiofrequency excitation. Close-fitting coils provide a higher signal/noise ratio due to a closer proximity to the lungs. Young children and infants can benefit from smaller flexible and lightweight coil arrays in direct contact, while older patients can be imaged with a torso or head–neck–spine coil array.

Pulse sequence selection

Similar to CT, chest MRI can be performed with suspended respiration or during free breathing. End-inspiratory and end-expiratory acquisitions can only be achieved in children who can follow breathing manoeuvres. Breath-hold time should be tailored to the patient's abilities. Patients aged 6–12 years require a shorter acquisition time (6–10 s). Children <6 years who are unable to hold their breath will benefit from gated free-breathing acquisitions using respiratory triggering or navigator-based techniques at the expense of longer measurement times.

Several two-dimensional (2D) and three-dimensional (3D) techniques can be used for chest MRI. The most frequently used will be briefly discussed and summarised, and are detailed in table 1. Basic and advanced protocols for chest MRI are shown in table 2.

2D techniques

2D techniques typically have anisotropic voxel formats (voxel dimensions unequal and not suitable for scan orientation reformats in other viewing planes). Techniques include spin echo- and gradient echo-based sequences. Spin echo sequences are less susceptible to signal loss from field inhomogeneities and are typically scanned with T2 weighting to enhance (or obtain) higher contrast for fluid detection. Different acronyms are used depending on the MRI scanner manufacturer. These sequences are suitable to assess bronchial wall thickening and mucus plugging (figure 1). Bronchial walls can be further enhanced with blood suppression preparations or using very thin slices.

Gradient echo steady-state free precession (SSFP) MRI can generate T1/T2 weighting, enhancing the visibility of lung tissues with water-like characteristics, such as mucus plugs in the airways. 2D SSFP scans can cover the entire thorax in a single breath-hold with good image quality. Vascular structures appear consistently bright on these acquisitions, allowing assessment of mediastinal vessels for possible compression of central airways (figure 2).

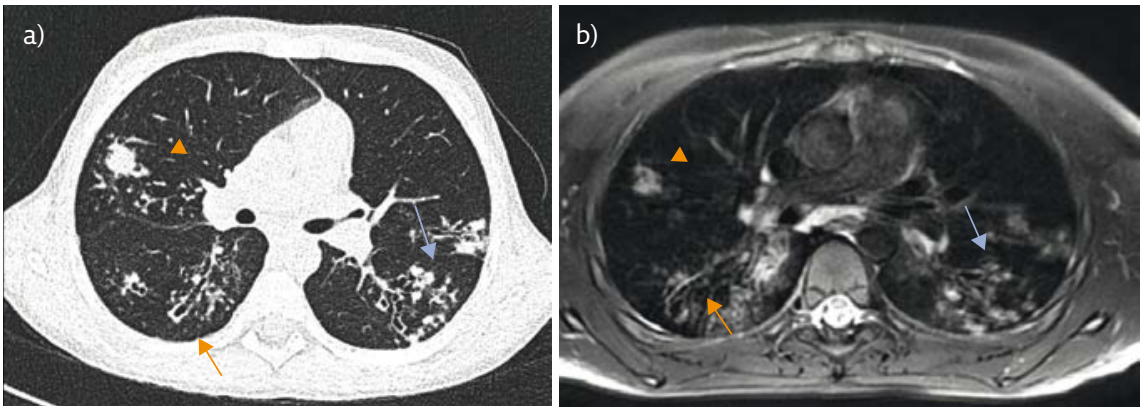

Figure 1. A 12-year-old CF patient with Pseudomonas aeruginosa *colonisation. a) End-inspiratory, 1×1×1 mm³ axial reformat CT. b) Expiratory free-breathing, 1×1×5 mm³, 2D T2-weighted MRI scan (PROPELLER; GE). Note the area of mucus plugging in the left lower lobe (blue arrows), consolidation in the right upper lobe (arrowhead) and bronchiectasis in the right lower lobe (orange arrows).*

Table 1. Imaging sequences for paediatric chest MRI

Sequence	Brand name (manufacturer)	MRI system	Average acquisition time (for entire chest coverage)	Spatial resolution	Temporal resolution	Scan parameters
Ventilation/perfusion						
2D gradient echo T1/T2w, low resolution	FIESTA (GE) TrueFISP (Siemens) bFFE (Philips)	1.5 T	3–9 min (shallow breathing)	FOV=500 mm^2 SL=12 mm, coronal Matrix=128×128	3–5 images·s^{-1}	TR=1.4–2.1 ms TE=0.7–1.1 ms FA=30–75°[#] BW=highest possible for shortest TR (*e.g.* ~2600 Hz per pixel) PIF=2–3
2D gradient echo Mildly T1w, low resolution	SPGR (GE) FLASH (Siemens) FFE (Philips)	1.5 and 3 T	3–9 min (shallow breathing)	FOV= 500 mm^2 SL=15 mm, coronal Matrix=128×128	3–5 images·s^{-1}	TR=1.2–2.3 ms TE=0.6–0.9 ms FA=5–8° BW=high (*e.g.* 1100–1500 Hz per pixel) PIF=1.5–2
Perfusion/angiography						
3D gradient echo T1w, high resolution	FLASH (Siemens) fSPGR (GE) FFE (Philips)	1.5 and 3 T	10–16 s breath-hold end-expiratory or shallow breathing	FOV=460 mm^2 Matrix=40×192×256 (isotropic voxels as low as 1 mm^3)	Medium, 1.5–4 s per volume per phase or single-phase acquisition	TR=2.5–3.5 ms TE=1.0–1.5 ms FA=15–35° PIF=2–8
3D gradient echo T1w, low–medium resolution	TWIST (Siemens) TRICKS and DISCO (GE) TRACK (Philips)	1.5 and 3 T	8–15 s breath-hold end-expiratory or shallow breathing	FOV=460 mm^2 Matrix=32×96×128	High, 0.5–1 s per volume per phase	TR=1.4–2.3 ms TE=0.6–1.1 ms FA=10–20° PIF=2–6

(*Continued*)

Table 1. Continued

Sequence	Brand name (manufacturer)	MRI system	Average acquisition time (for entire chest coverage)	Spatial resolution	Temporal resolution	Scan parameters
Structure						
2D fast spin echo PDw-T2w, high resolution ±fat saturation	BLADE (Siemens) PROPELLER (GE) MultiVane (Philips)	1.5 and 3 T	End-expiratory navigator gated, 3–7 min (depending on respiratory pace and pattern)	FOV=380–400 mm^2 SL=5–6 mm, axial and coronal Matrix=200×200	Low	TR=2500–8000 ms TE=25–80 ms BW=minimize fat/water pixel shift ETL=16–28 PIF=1.5–3
2D gradient echo T1/T2w, medium–high resolution	TrueFISP (Siemens) FIESTA (GE) Balanced FFE (Philips)	1.5 T	12–20 s	FOV=200-360 mm^2 SL=2.5–7 mm Matrix=160×160	High	TR=2.5-4 ms TE=0.8-1.2 ms FA=20-35° BW=highest possible for minimum TR PIF=2-3
3D fast spin echo T2w, medium–high resolution ±fat saturation	SPACE (Siemens) CUBE (GE) VISTA (Philips)	1.5–3 T	End-expiratory navigator gated, 5 min (depending on respiratory pace and pattern)	FOV=250–320 mm^2 SL=1.6–2 mm Matrix=160×160	Low	TR=2000–4000 ms TE=60 ms BW=shortest ETS ETL=80–140 PIF=2–6
3D gradient echo PDw, medium–high resolution	VIBE (Siemens) fSPGR (GE) THRIVE (Philips)	1.5–3 T	Breath-hold 10–12 s (inspiratory and end-expiratory)	FOV=400 mm^2 SL=2 mm Matrix=200×200	High	TR=1.5–1.8 ms TE=0.7–1.1 ms FA=2–3° BW=shortest TR

(*Continued*)

Table 1. Continued

Sequence	Brand name (manufacturer)	MRI system	Average acquisition time (for entire chest coverage)	Spatial resolution	Temporal resolution	Scan parameters
3D gradient echo PDw-T1w, medium–high resolution	StarVIBE (Siemens) Not available from GE/Philips	1.5–3 T	Free breathing, 3–5 min/ respiratory corrected/self-gated	FOV=400 mm^2 SL=4 mm Matrix=320×320	Low	TR=7.5 ms TE=2.5 ms FA=9° BW=820 Hz per pixel
3D gradient echo PDw, medium resolution	DIXON (Siemens) LAVA-Flex (GE)	1.5–3 T	Breath-hold (10 s) inspiration or end-expiration	FOV=260 mm^2 SL=3 mm Matrix=128×128	High	TR=3.7 ms TE=minimum TE FA=1°
3D gradient echo PDw, high resolution	PETRA/SpiralVIBE (Siemens) ZTE/CONES (GE) MultiVane-XD (Philips)	1.5–3 T	Free breathing, 7–10 min, respiratory pneumobelt gated/ self-navigated	FOV=360 mm^2 Matrix size=240×240	Low	TR=1.1–5.5 ms TE=0.02–0.07 ms FA=1–5° BW=highest possible

T1/T2w: T1/T2-weighted; PDw: proton-density-weighted; FFE: fast field echo; FOV: field of view; SL: slice thickness; TE: echo time; TR: repetition time; FA: flip angle; BW: bandwidth; PIF: parallel imaging factor; ETL: echo train length; ETS: echo train spacing. ♯: specific absorption rate must be considered with high FA/short TR settings.

Table 2. Basic and advanced protocols for chest MRI

	Sequence[#]	Weighting	Expected scan time
Basic morphological chest MRI			
Noncooperative patient (0–5 years)	2D PROPELLER with/without respiratory pneumobelt triggering	PD or T2 (± fat saturation)	5–7 min
	3D CUBE with respiratory pneumobelt triggering	T2 (± fat saturation)	5–7 min
	2D SPGR with respiratory pneumobelt triggering	PD	3–5 min
	2D FIESTA with respiratory pneumobelt triggering	T1/T2	3–5 min
	3D fSPGR end-inspiratory	PD	6–12 s
Cooperative patient (≥6 years)	3D fSPGR inspiratory and end-expiratory	PD	6–12 s
	2D PROPELLER with respiratory pneumobelt/navigator triggering	PD or T2 (± fat saturation)	5–7 min
	3D CUBE with respiratory pneumobelt/navigator triggering	T2 (± fat saturation)	5–7 min
Advanced option (for both noncooperative and cooperative patients)	3D ultrashort TE (UTE/ZTE) with respiratory pneumobelt/ navigator triggering	PD	5–10 min

UTE: ultrashort echo time; ZTE: zero echo time. [#]: all sequences are from GE.

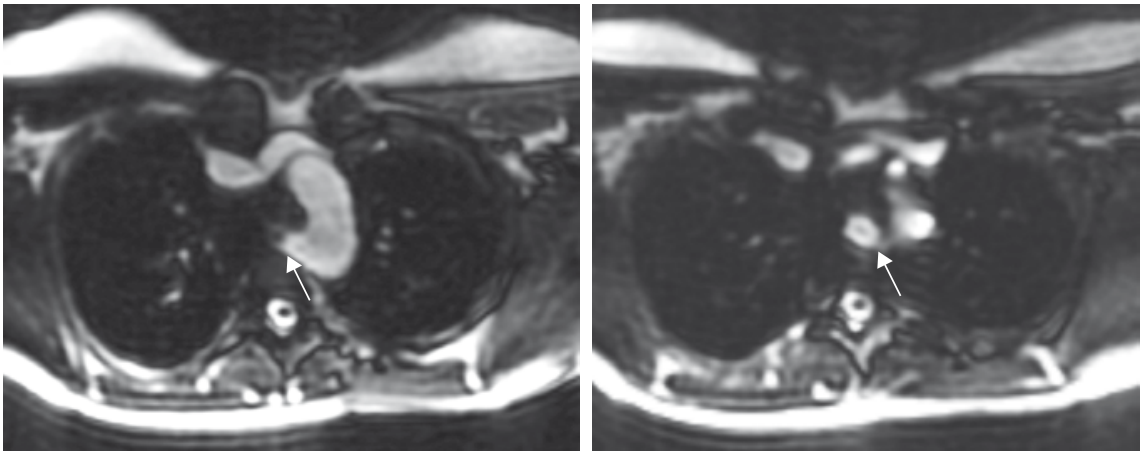

Figure 2. A 12-year-old girl with tetralogy of Fallot. Axial free-breathing 2D FIESTA MRI showing "bright blood". The two slices show the lusory right subclavian artery passing posterior to the central airways (arrows).

3D techniques

3D techniques are more suitable for isotropic voxel data collection, allowing reformatting in other views. These are particularly important to review central airway pathology. 3D techniques are usually gradient echo based, sponsoring short and

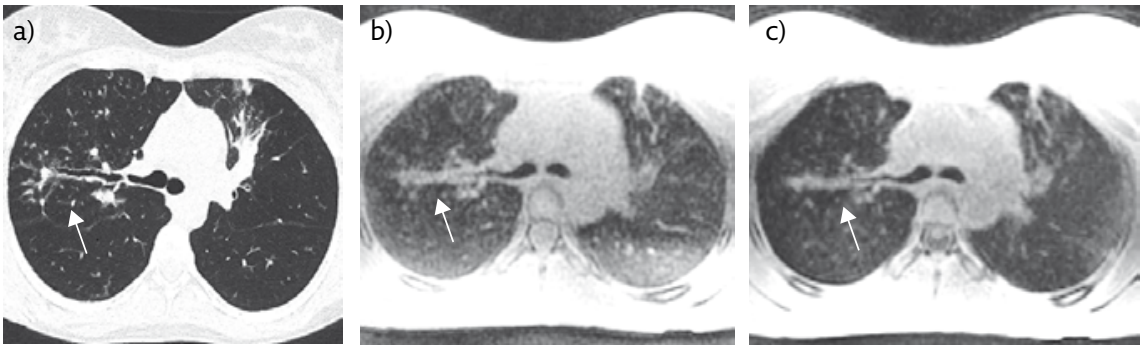

Figure 3. A 15-year-old CF patient. a) End-inspiratory, isotropic 1 mm axial CT. b) End-expiratory navigated, isotropic 1.5 mm axial PD-weighted ZTE MRI (ZTE VNAV; GE). c) End-expiratory respiratory-triggered, isotropic 1.5 mm axial PD-weighted UTE MRI (UTE CONES; GE). Note bronchiectasis in the right upper lobe (arrows).

ultrashort echo times, and can be considered the most robust acquisition format for chest MRI. Images with isotropic voxel sizes (2–3.5 mm^3) can be acquired in <10 s for full chest coverage. Gradient echo sequences provide contrasts ranging from proton-density (PD)-weighted (using a low radiofrequency flip angle) to T1-weighted (at higher radiofrequency flip angles) using short repetition times. The PD-weighted setting is the most appropriate to assess airways without the use of contrast agents, while the T1-weighted setting is used to assess vascular structures and lung parenchymal perfusion after contrast administration.

Ultrashort echo time (UTE) and zero echo time (ZTE) variants have become available with echo times in the order of microseconds leading to less signal loss. The shorter echo time coupled with higher spatial resolution settings provides acquisitions comparable to those of CT (figure 3). UTE and ZTE are usually acquired during free breathing with voxel sizes of 0.7–1.5 mm with a scan time ranging from 5 to 10 min (depending on respiratory rate).

Functional imaging

MRI can be used to study various functional aspects of the lung and airways. Coupled with gadolinium contrast injections, the pulmonary vasculature and lung perfusion can be studied effectively. Dynamic MRI (cine-MRI) has also proven useful to assess central airways and diaphragm mechanics. Inhalation of hyperpolarised gases such as helium (^3He) and xenon (^{129}Xe) has been developed to produce high-contrast images of lung ventilation. Lung ventilation and perfusion maps without contrast agents use an experimental technique known as Fourier decomposition (FD).

Magnetic resonance angiography and perfusion studies

Chest magnetic resonance angiography (MRA) can be obtained with and without intravenous administration of contrast. Noncontrast MRA acquisitions can be repeated at will without concerns, especially in children, where the possibility of tissue deposition of gadolinium in the brain has raised concern over possible long-term effects. Noncontrast MRA can be done with "bright blood" (figure 2) or "black blood" techniques according to the suspected pathology, where the former is used to assess congenital vascular abnormalities (figure 4) and the latter to assess possible vascular wall involvement, such as in cases of vasculitis. Contrast-enhanced MRA acquisitions are still considered the most robust to assess chest vasculature, because of the higher signal/noise and contrast/noise ratios allowing shorter measurements with high temporal and spatial resolution. In paediatric patients, contrast-enhanced MRA

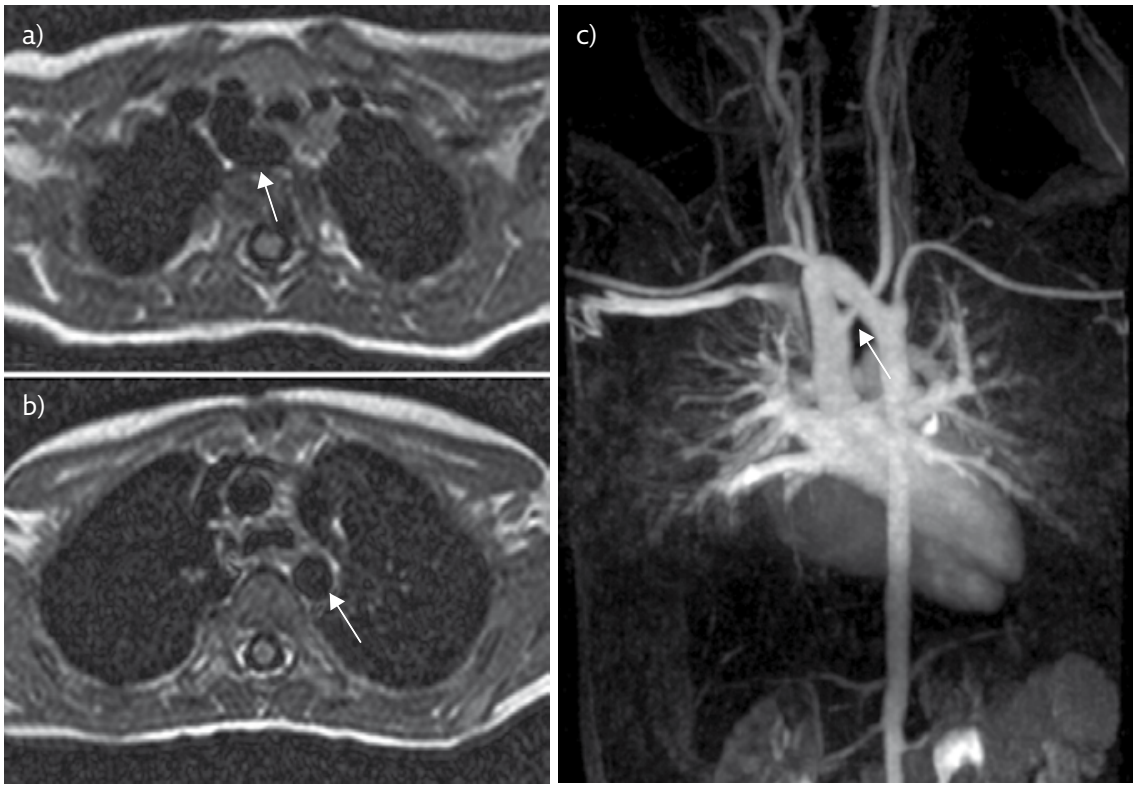

Figure 4. A 3-year-old boy with a right-sided aorta. a and b) "Black blood", fast spin echo cardiac-triggered acquisition, with 2.5 mm slice thickness. c) Coronal maximum intensity projection of dynamic contrast-enhanced MRA. Note the right-sided aorta passing posterior to the trachea (arrows).

is frequently used to study congenital vascular anomalies, such as transposition of great vessels, tetralogy of Fallot, anomalous pulmonary venous return and pulmonary sequestration (figure 5).

Pulmonary perfusion can be performed using noncontrast- or contrast-enhanced techniques. Noncontrast-enhanced techniques include arterial spin labelling and FD.

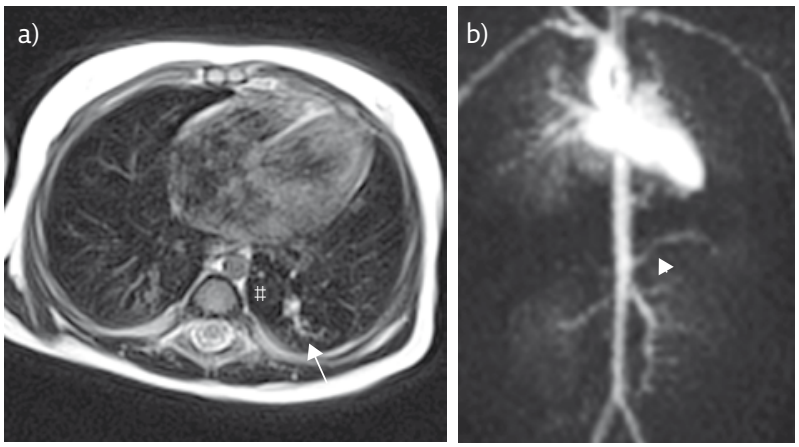

Figure 5. A 4-year-old-boy with hybrid congenital pulmonary adenomatoid malformation and sequestration. a) T2-weighted, 1×1×5 mm³ axial MRI (BLADE; Siemens). b) Maximum intensity projection of one phase of dynamic contrast-enhanced TWIST MRI (Siemens). Note the area of low signal intensity in the left lower lobe (#) and the enlarged vessel (arrow). In the post-contrast phase, an aberrant arterial vessel originates from the celiac trunk and supplies blood to the sequestration in the left lower lobe (arrowhead). Courtesy of S. Bertolo, Radiology Department, Ca'Foncello Regional Hospital, Treviso, Italy.

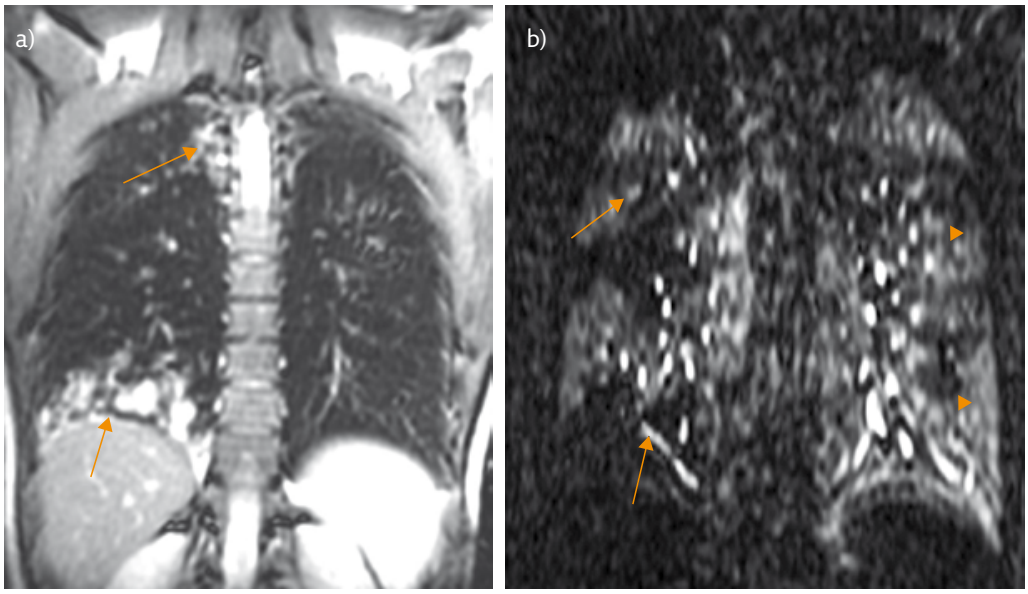

Figure 6. Perfusion study in a 13-year-old boy with CF. a) 2D end-inspiratory, coronal, 2.3×1.4 mm² in-plane resolution, 6 mm slice FIESTA MRI. b) One phase of dynamic contrast-enhanced, subtraction signal enhancement, coronal, 1.4×2.3 mm² in-plane resolution, 5 mm slice MRI (TRICKS; GE). Note the correspondence between areas of consolidation and hypoperfusion (arrows) and areas of hypoperfusion without an anatomical substrate (arrowheads).

All of these techniques aim to detect perfusion defects related to the physiological mechanism of hypoxic pulmonary vasoconstriction, with poorly ventilated lung areas receiving less blood flow in favour of normally ventilated alveoli. They have been used to assess pulmonary exacerbation in CF and asthma patients (figure 6).

Dynamic imaging

The lack of radiation has made MRI suitable for studying airways in true dynamic conditions (cine-MRI). Both 2D and 3D cine-MRI can be performed. A limitation of 2D imaging is that the trachea moves in all directions during the respiratory cycle and therefore a single slice could miss relevant airway pathology during trachea movement. Cine-MRI was used to assess tracheobronchomalacia in a group of paediatric patients (Ciet *et al.*, 2014), showing that cine-MRI is a possible alternative to bronchoscopy and cine-CT for tracheobronchomalacia (figure 7).

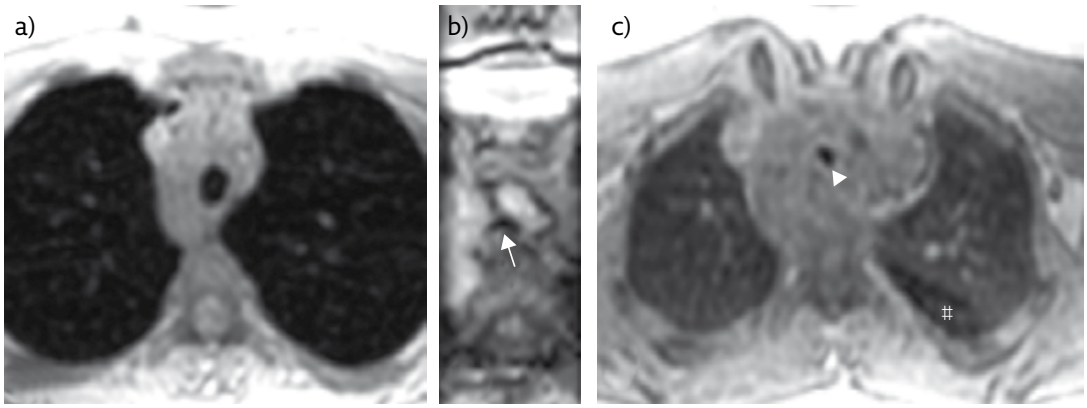

Figure 7. A 17-year-old boy with tracheomalacia. a) End-inspiratory gradient echo, isotropic 3 mm voxel, axial MRI (3D SPGR; GE). b) Reformat of cine-MRI (3D TRICKS; GE) during forced expiration. c) End-expiratory gradient echo, isotropic 3 mm voxel, axial MRI (3D SPGR). Note severe collapse of the trachea during forced expiration (arrow) and at the end of expiration (arrowhead) with an area of air trapping in the left lower lobe (#).

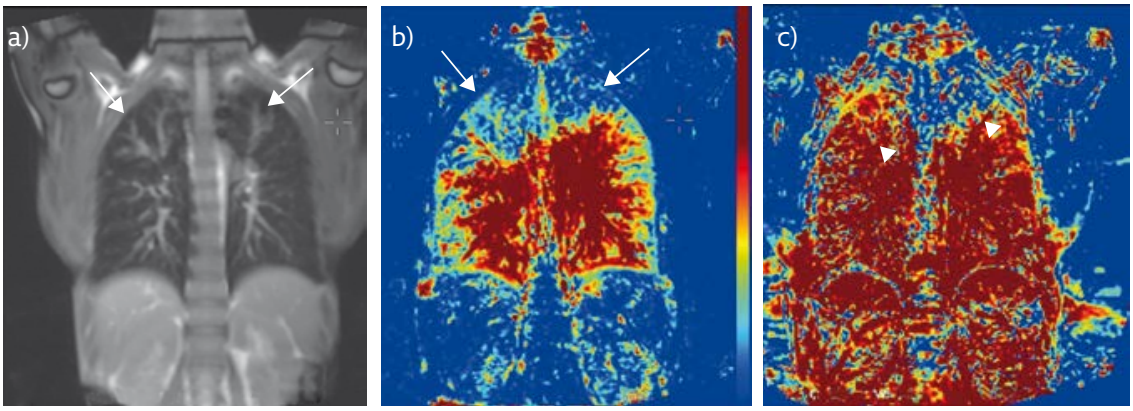

Figure 8. FD in an 18-year-old girl with CF during pulmonary exacerbation. a) Free-breathing original 2D TrueFISP (Siemens) acquisition, 3.75×3.75 mm² in-plane resolution, 10 mm slice, coronal MRI. b) Ventilation map. c) Perfusion map. Note the areas of hypoventilation (arrows in b) and the matching areas of hypoperfusion (arrowheads in c) in the upper lobes where there is also significant bronchiectasis with mucus plugging (arrows in a). Courtesy of G. Morana, Radiology Department, Ca'Foncello Regional Hospital, Treviso, Italy.

Cine-MRI can also be used to assess diaphragmatic function in paediatric patients with a congenital diaphragmatic hernia. As a radiation-free modality, MRI can visualise discontinuity of the diaphragm and distinguish it from eventration. MRI can also accurately characterise hernias in terms of contents, defect location and size.

Ventilation study

Ventilation can be assessed with hyperpolarised gas MRI (HP-MRI), or without gaseous contrast using FD. HP-MRI can provide exquisite image quality and high resolution with higher sensitivity to ventilation defects than the still-experimental FD technique. HP-MRI has been used in several paediatric lung diseases, including asthma, CF, congenital diaphragmatic hernia and BPD. However, its use is limited by the high cost of the hyperpolarised gases and the need for dedicated MRI scanner hardware. In contrast, the free-breathing FD technique is cheap and can provide both ventilation and perfusion images in a single acquisition. FD has been tested in paediatric CF patients, with similar diagnostic information to HP-MRI and contrast-enhanced MRI (figure 8).

Indications for chest MRI

Although chest CT and chest radiography are still considered the gold standard for paediatric thoracic imaging, chest MRI has been used increasingly in several paediatric lung pathologies. Indications for chest MRI have increased due to the general improvement in quality with the newer MRI scanners and the introduction of UTE and ZTE scanning.

The clinical and research indications for chest MRI are summarised in table 3.

Limitations of chest MRI

Chest MRI is limited by several factors. The longer acquisition times limit the use of MRI in sick patients who cannot lie for long in the scanner. MRI is prone to severe image degradation from breathing and cardiac motion, metal implants and motion of the patient. These factors limit those centres with less expertise in chest MRI. The lack of standardisation among MRI vendors causes significant differences in image quality, even when using similar acquisition scenarios, making it difficult to homogenise image quality across hospitals and to enable a broader use of chest MRI.

Table 3. Chest MRI indications

Indication	Setting
CF	Clinical
Asthma, BPD	Research
Congenital pulmonary malformation	Clinical
Airways pathology (tracheobronchomalacia)	Clinical
Cardiovascular pathology	Clinical
Mediastinal and thoracic masses	Clinical
Studies of inflammatory disease	Research
Tumour	Clinical
Pneumonia	Clinical

Summary

Chest MRI can be used in routine clinical practice for paediatric thoracic imaging. The anatomical detail provided by newer MRI sequences is similar to that obtained by CT, with the main advantage of no ionising radiation exposure. More importantly, MRI can provide functional information that can only be obtained by CT at the expense of high radiation exposure. Therefore, MRI can provide new insights into lung mechanics, perfusion and ventilation for different paediatric lung disorders, and opens up new diagnostic and therapeutic options.

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Lung isotope imaging methods

Georg Berding

Radiotracer methods allow physiological processes in the lungs to be visualised and the regional pathological changes due to disease, resulting in functional impairment, to be detected. Most frequently, ventilation and perfusion of the lungs are investigated. Inhaled nuclides of inert gases that emit gamma rays or aerosols of fine particles (<1 µm) containing technetium-99m (^{99m}Tc) are used to display the ventilated volume of the lungs. When injected intravenously, ^{99m}Tc-labelled macroaggregated albumin (MAA) is retained in the capillary bed of the lungs and thereby visualises arterial perfusion of the parenchyma (*via* the vasa publica). Other processes are investigated less frequently, such as mucociliary clearance function, which can be studied using aerosols of larger particles (>2 µm), or alveolar capillary membrane integrity, which can be measured with water-soluble radiotracers. A more recent approach focuses on the detection of florid inflammation or vital malignant tissue in the lungs/thorax using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) and positron emission tomography (PET). In addition to this, with the development of new molecular PET biomarkers, further pathophysiological processes such as fibrosis might be targeted in the future.

Indications

In children, scintigraphy to determine the ventilation/perfusion ratio (*V′/Q′*) is used to characterise primary/congenital abnormalities of the lungs and pulmonary vessels, as well as the heart and large vessels (figure 1). Generally, *V′/Q′* scintigraphy can be

Key points

- The use of radiopharmaceuticals enables information on ventilated volume and regional perfusion of the lungs to be obtained.
- Ventilation/perfusion scintigraphy enables accurate diagnosis of congenital abnormalities of the lungs, vessels and heart, as well as evaluation of patients with non-CF bronchiectasis or CF.
- Ventilation/perfusion scintigraphy is easy to perform, typically without sedation, and causes only low radiation exposure.
- A more recent method, ^{18}F-fluorodeoxyglucose positron emission tomography CT, contributes to the diagnosis of malignancies and inflammation.

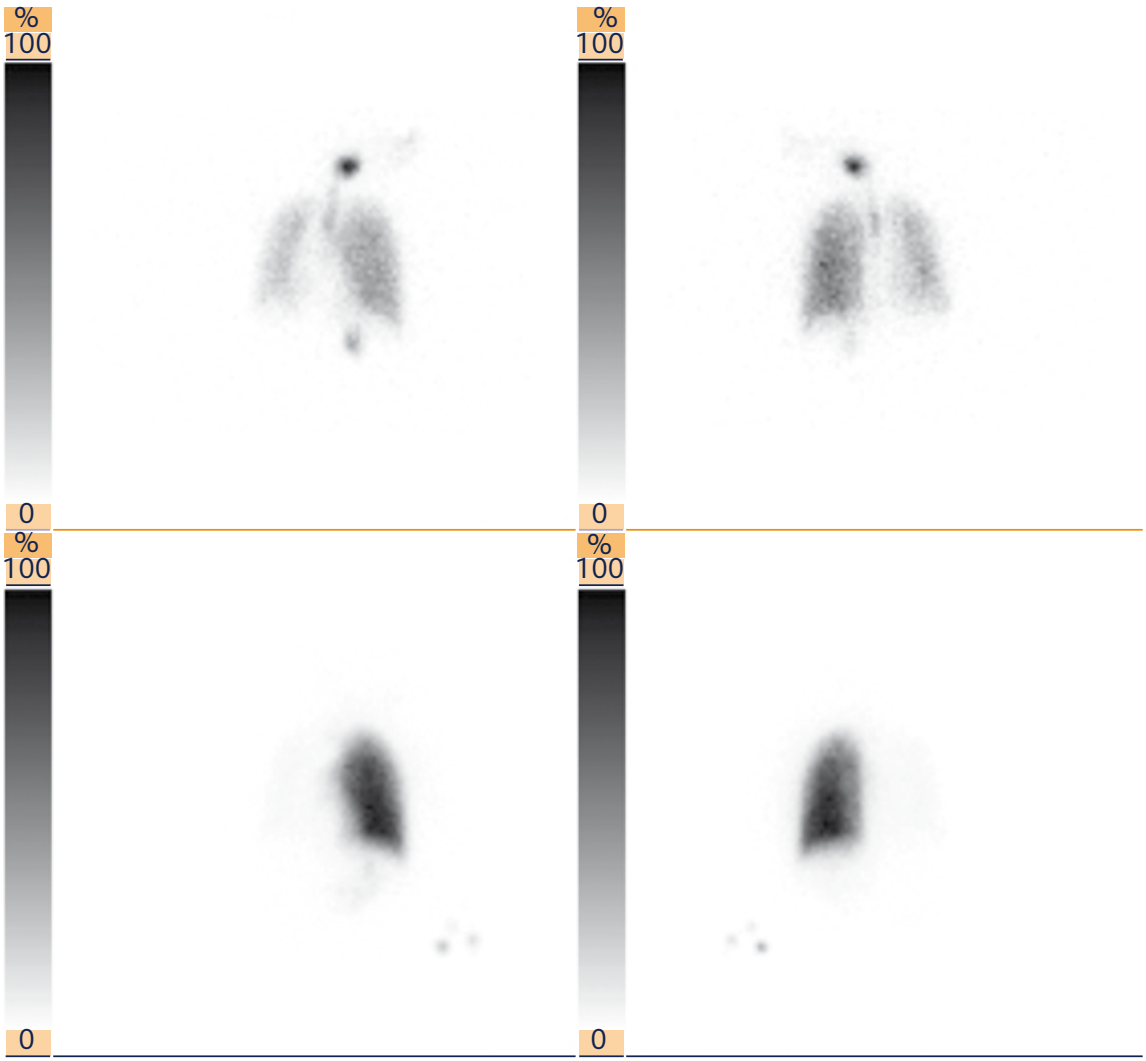

Figure 1. V′/Q′ scintigraphy in a 6-year-old boy with decreased physical capacity and recurring pneumonia of the right lung. Planar ^{99m}Tc Technegas scintigraphy showed hypoplasia of the right lung (30% versus *70%; upper row). A subsequent ^{99m}Tc MAA scan revealed a complete lack of perfusion (from the vasa publica) in the right lung (lower row). In angiographic CT, the pulmonary veins could not be detected. Angiography showed an outflow of the contrast medium from the right to the left pulmonary artery. V′/Q′ scintigraphy helped to identify a noninvasive congenital abnormality of the pulmonary vessels.*

used to quantify lung function pre- and post-intervention. In particular, essential information can be provided by perfusion scintigraphy before and after the following:

- Pulmonary arterioplasty
- Intravascular stent placement
- Coil occlusion of unwanted vascular communications
- Surgical creation of a shunt

Notable percentage fractions of *V′/Q′* in the left and right lung can be determined. In the case of right-to-left shunts, these can be measured semi-quantitatively based on kidney and brain uptake during the lung perfusion scan. These measurements can be valuable in the assessment and treatment of patients with cyanosis, for example due to the tetralogy of Fallot or arteriovenous malformations. Assessment of suspected pulmonary embolism in children is, in contrast to adults, a rare indication. Damage to lung tissue due to infection can be assessed. Regional lung function (*V′/Q′*) can be evaluated in children with non-CF bronchiectasis as well as in those with CF. Beyond this, delayed mucociliary clearance can be seen in both diseases; however, this is still

an experimental indication. The effects of foreign body aspiration (*e.g.* air trapping) can be demonstrated using *V′/Q′* scanning. In paediatric oncology with respect to thoracic masses, ^{18}F-FDG-PET is used specifically in children with lymphoma for staging, treatment response assessment and planning of radiation therapy. In inflammatory diseases, evidence provided in the literature so far suggests that ^{18}F-FDG-PET can be useful for the detection of active infective foci in children with chronic granulomatous disease and monitoring of disease activity in children with CF.

Patient preparation

There is no specific preparation that is necessary for children before *V′/Q′* scanning. However, mucus should be removed with mucolytics and chest physiotherapy to facilitate ventilation scanning. Patients must avoid moving during acquisition. In children who are old enough, this might be achieved by careful explanation of the procedure together with the parents. Neonates and infants are conveniently studied when they have fallen asleep after feeding. Sedation should be the exception. If unavoidable, at ≥7 months of age the benzodiazepine midazolam can be given *i.v.* at a dose of 0.1 mg·kg^{-1}. However, this has to be agreed upon with the referring physician, and the risk of hypoventilation has to be taken into account.

Radiopharmaceuticals

Currently, ventilation studies are performed most frequently using ^{99m}Tc Technegas. This is a pseudo-gas produced using a dedicated generator containing a graphite crucible filled with ^{99m}Tc pertechnetate in a chamber that is heated to a high temperature, producing an ultrafine aerosol of solid graphite particles with a 5–30 nm diameter, which, when inhaled, show a static alveolar deposition. Due to the much simpler logistics, Technegas has largely replaced the use of inert gases such as xenon-133 (^{133}Xe) or krypton-81m. Nevertheless, ^{133}Xe allows sequential data acquisitions and thereby identification of air trapping as a hallmark of regional obstructive airway disease. However, ^{133}Xe application to the lungs requires a bag–box spirometer system, which is rarely available. A nebuliser is required to produce aerosols of larger particles for mucociliary clearance. For perfusion studies, ^{99m}Tc MAA is injected *i.v.* This embolises a small proportion of (pre-)capillary vessels in the lung. As the number of these vessels is lower in children compared with adults, the number of injected particles has to be decreased. The radiation exposure induced by lung scintigraphy is generally relatively low. For example, in a 5-year-old child weighing 20 kg, adapted application of ~10 MBq ^{99m}Tc Technegas for ventilation scintigraphy would result in an effective dose of 0.47 mSv. In addition, the application of 46 MBq ^{99m}Tc MAA for perfusion imaging would add 1.56 mSv. Together, both scans would cause 2.03 mSv, which is below the natural annual radiation exposure in Germany.

Imaging equipment/acquisition

Lung scintigraphy is normally acquired with a dual-headed large-field gamma camera from standard projection angles (*e.g.* anterior, oblique, lateral). The use of single-photon emission computed tomography (SPECT) offers the advantage of avoiding superimposition and thereby creating the possibility of finer (subsegmental) assessment. Moreover, mismatches between ventilation and perfusion can be assessed based on the *V′/Q′* distribution. This might be of prognostic value in infants with BPD or congenital diaphragmatic hernia. However, SPECT requires more patient cooperation or anaesthesia. Furthermore, SPECT/CT allows correlation of functional and morphological findings, which can provide unique diagnostic information; however, specifically in children, the additional radiation exposure has to be balanced

against this. Regarding paediatric oncology, ^{18}F-FDG-PET/CT can be performed using specific CT parameters for children to reduce radiation exposure (ultralow-dose CT) or, in cases where a diagnostic CT investigation is required, can be performed in one session with PET, obviating the inconvenience of two separate examinations.

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Chest interventional radiology

Efthymia Alexopoulou, Argyro Mazioti and Dimitrios Filippiadis

Improvements in anaesthesiological techniques, imaging guidance and instrumentation have contributed to the evolution of several image-guided, minimally invasive, percutaneous diagnostic and therapeutic techniques, dramatically changing the role of interventional radiology in the treatment of paediatric patients.

Proper and adequate training of interventional radiologists in paediatric patients and strict local sterility measures, as well as adequate radiation protection, are prerequisites. Prophylactic antibiotics are recommended in percutaneous abscess drainage and ablation in the chest/lung; however, they are not needed in most biopsy and thoracocentesis chest interventions. Although local anaesthesia is fine for the majority of procedures, deep sedation or general anaesthesia can be required to ensure maximum cooperation and a safe environment for technique performance. Occasionally, in older children or young adults, local anaesthesia might be sufficient in certain techniques, although it is not recommended.

Preparing patients includes advising parents and, for older children, also the child on the invasive procedure itself as well as the benefits and potential risks of the

Key points

- Proper and adequate training of the operator along with extensive local sterility measures and anaesthesiological control are prerequisites for safely and effectively performed interventional radiology.
- In cases where determining a lesion's nature will alter the patient's management and benefits outweigh risks, percutaneous biopsy is indicated; core biopsy is preferred over fine-needle aspiration.
- Image-guided percutaneous drainage is a safe and efficacious technique for the treatment of pleural effusions, abscesses and empyemas; in the case of complex effusion, abscess or empyema drainage can be combined with fibrinolytic therapy.
- Tumour localisation or thermoablation can be performed in selected paediatric cases, and transcatheter embolisation is indicated for the treatment of pulmonary arteriovenous malformation or major haemoptysis in patients with CF.

technique. Pre-procedural planning includes evaluation of the patient's medical record (including laboratory and imaging studies), coagulation profile, and control of renal (in relation to intravascularly administered contrast) and cardiac function. Separate anaesthesiological evaluation should also be performed. Post-procedural follow-up includes patient monitoring, control for any delayed complications and evaluation of the overall clinical condition of the patient.

Image-guided percutaneous biopsy

Percutaneous biopsy in paediatric patients is most commonly performed for diagnosis of a focal lesion rather than for evaluation of diffuse parenchymal disease. A core biopsy is preferred over fine-needle aspiration. The absolute indication for biopsy is where management of a child will be altered according to the nature and characterisation of the lesion. Furthermore, the benefits should outweigh the risks. Contraindications of image-guided percutaneous biopsy in the chest include uncorrectable coagulopathy, lack of a safe trajectory and other comorbidities that might, for example, prohibit safe anaesthesia. Alternatives to percutaneous biopsy include transbronchial or thoracoscopic lung biopsy.

Percutaneous biopsy is performed under local sterility measures and anaesthesiological control (generally, intubation is required to control breathing). Whenever a lesion is in contact with a pleural surface, ultrasound can serve as the guiding modality of choice; advantages include the higher likelihood of a diagnostic sample, lack of ionising radiation for both the patient and the operator, low cost and wide availability. In cases where a lesion is surrounded by lung parenchyma, CT is the guiding modality of choice. The shortest trajectory that avoids fissures and blood vessels is chosen (figure 1). Biopsy can be performed using a direct or coaxial technique. Once the needle is at the lesion's periphery, the biopsy system (semi-automatic or automatic depending on the operator's choice) is fired, obtaining the sample within the trocar.

Success rates for image-guided percutaneous biopsy in children are ~85%, while complications include pneumothorax (10–15%, usually not clinically significant) and mild haemoptysis. Erect chest radiography is performed 2 h post-biopsy for evaluation of delayed pneumothorax.

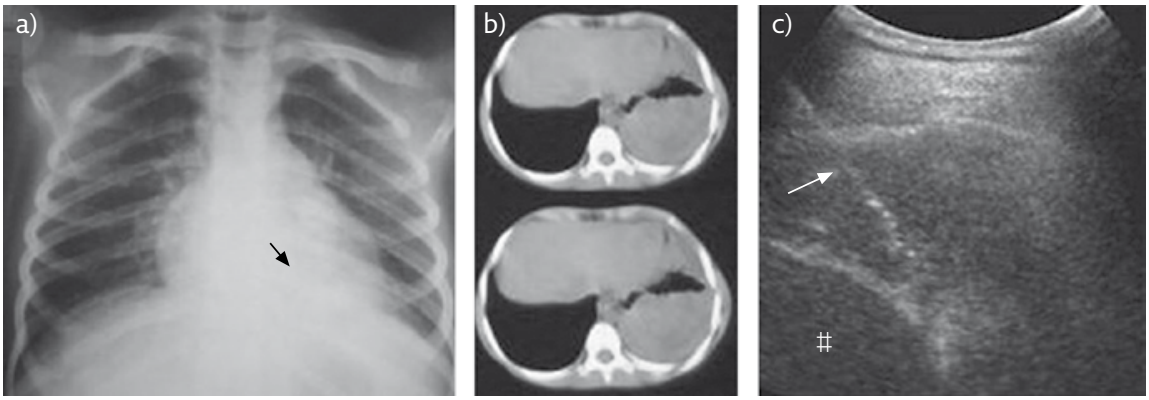

Figure 1. A 7-year-old girl with Louis–Barr syndrome, fever and cough. a) The initial chest radiograph and b) a subsequent CT scan revealed left lower-lobe consolidation (arrow). Consolidation was not resolved after persistent appropriate treatment (antibiotics), and BAL was negative for common bacteria, mycobacteria and fungi. An additional PCR test was negative for Cryptococcus, Aspergillus *and* Candida *spp. and* Pneumocystis jirovecii, *while cytology was negative for malignancy. c) The child was referred to our department for lung biopsy, which was performed under ultrasound guidance. Arrow: needle inside the lesion; #: spleen. Histology proved lymphoproliferative syndrome.*

Tumour localisation

The technique of localisation can be used in cases of a small lung nodule under the pleural surface, which will not be felt during thoracoscopic surgery. Localisation can be performed by means of image-guided percutaneous introduction of a hooked wire, needle introduction and intralesional injection of methylene blue dye, or a combination of these techniques.

Tumour ablation

Image-guided percutaneous thermoablation in the lung is most commonly performed in secondary lesions that do not respond to radiotherapy (metastatic lesions from osteosarcoma, Ewing's sarcoma and hepatoblastoma) (figure 2). For paediatric ablation, all sessions are performed under general anaesthesia, and for the first 24 h, patient-controlled analgesia is administered. Complications include pneumothorax, haemorrhage and air embolism.

Image-guided percutaneous drainage

Image-guided drainage of pleural effusions, abscesses and empyemas is characterised by high success (74–99%, with a suggested threshold of 95%) and low complication rates (1–10%, with a suggested threshold of 2–20%).

Indications for drainage include fluid sampling, the presence of large or complex accumulations, and any accumulation with symptoms warranting drainage. Whenever culture and laboratory testing are required, a sample is obtained by needle aspiration. Sedation or general anaesthesia is a prerequisite. Ultrasound is preferred

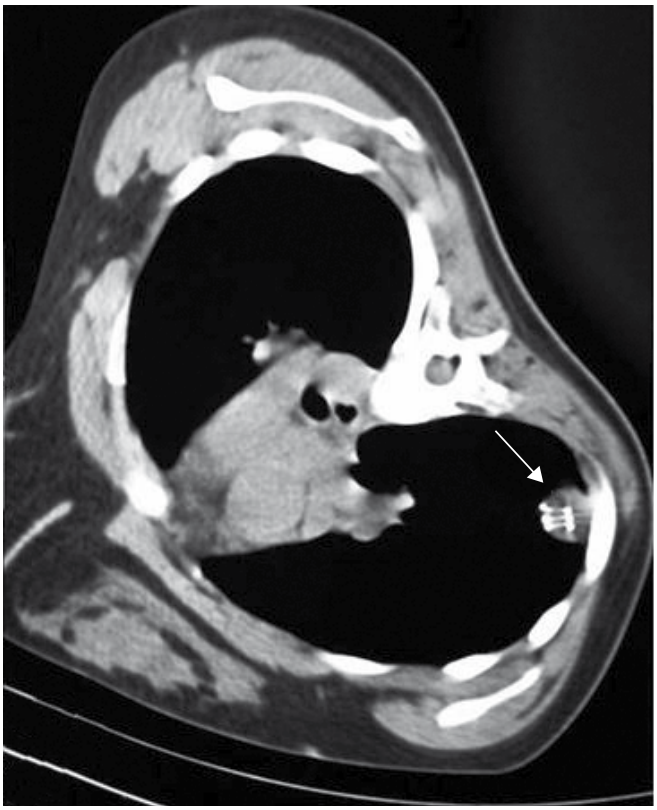

Figure 2. A 10-year-old boy (oligometastatic patient) with lung metastasis from osteosarcoma (arrow). Percutaneous radiofrequency ablation (using a multi-tined umbrella-like electrode) was performed with the patient in the lateral decubitus position under CT guidance and general anaesthesia. Courtesy of L. Thanos, Sotiria Thoracic Diseases Hospital, Athens, Greece.

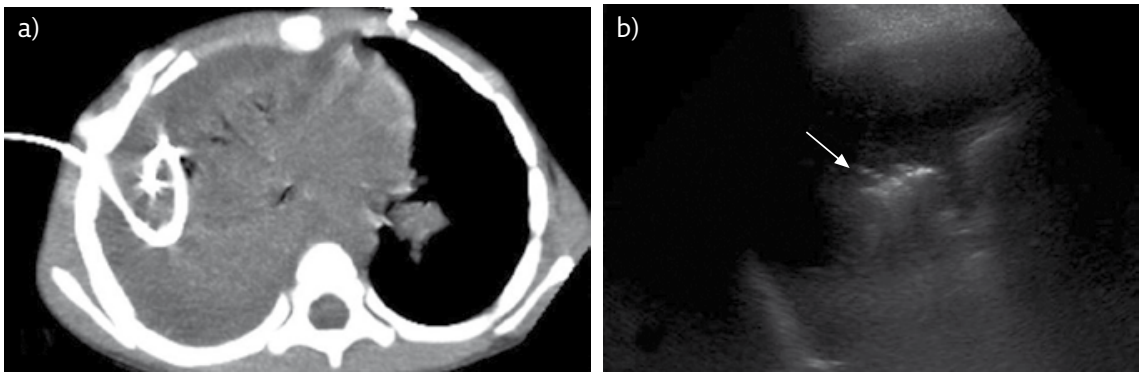

Figure 3. a) A 5-year-old boy with necrotic pneumonia and complicated right pleural effusion. A 10-French pigtail catheter was placed under CT guidance for drainage and adjuvant fibrinolytic therapy. A 10 mm multiplanar reconstruction CT image in the axial plane displays the position of the catheter. b) A 10-year-old boy with necrotic pneumonia and right pleural effusion. An 8-French pigtail catheter was placed under ultrasound guidance for drainage. Arrow: catheter inside the effusion.

as the guiding modality due to the lack of ionising radiation, low cost and wide availability. Under extended local sterility measures, a tube (6–14 French in diameter) is introduced, usually at the level of the midaxillary line with a direct or Seldinger technique, and then is connected to a water seal. Output monitoring and catheter flushing (3–10 mL of sterile 0.9% saline solution every 8–12 h) are performed to keep the tube patent. It must always be remembered that the catheter should be placed at the superior rib margin in the pleural space to avoid intercostal vessels located at the lower margin of the rib.

The technique for draining an abscess or empyema is similar; however, the need for CT guidance is higher in these indications. In any case, passage of the tube through the lung parenchyma or fissures must be avoided (figure 3).

In the case of complex effusions, drainage of abscesses and empyemas can be combined with fibrinolytic therapy with urokinase (usual dose is 40 000 U in 40 mL of 0.9% saline twice daily instilled with a 4 h dwell time) or tissue plasminogen activator (usual dose is 0.1 $mg \cdot kg^{-1}$, maximum 3 mg injected). Injection is performed through the tube, which then remains closed for some hours, and the suction is then resumed.

Drainage complications include septic shock, bacteraemia, bleeding, superinfection, bowel or pleural transgression, bronchopleural fistula, and complications associated with sedation or general anaesthesia.

Transcatheter embolisation

Transcatheter embolisation is indicated mainly for treatment of pulmonary arteriovenous malformation (AVM) or in cases of pulmonary haemorrhage. Embolic materials include coils, particles, gel foam and detachable balloons, as well as others depending on pathological substrate, vessel size/location and material availability.

Scarce data are found in the literature concerning pulmonary AVM in children and no data are found for this entity in infants. There is a clear association between pulmonary AVM and hereditary haemorrhagic telangiectasia. As transcatheter embolotherapy is associated with a 15% reperfusion rate of the AVM, it should be reserved for symptomatic children. However, pulmonary AVMs are often embolised when they are ≥3 mm due to the chance of paradoxical embolisation and stroke. Symptoms include exercise intolerance, cyanosis or clubbing, and neurological or haemorrhagic

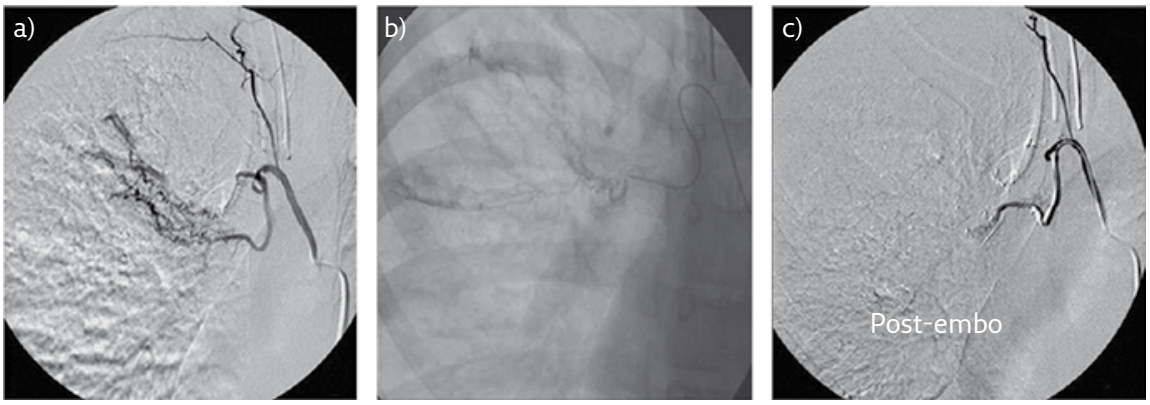

Figure 4. A teenager with CF and massive haemoptysis. a) Angiography after selective right bronchial artery catheterisation shows hyperaemia with dilated and tortuous vessels in the right upper lobe. b) Superselective catheterisation with a microcatheter was performed, and subsequent embolisation with polyvinyl alcohol particles followed. c) Final post-embolisation (post-embo) angiography revealed complete vessel obstruction.

complications (which occur mostly in cyanotic patients). The majority of pulmonary AVMs are simple, multiple and located in the lower lobes of the lungs. Complications of transcatheter embolisation include pleurisy, transient angina, severe perioral pain or leg pain, brachial plexus injury or deployment complications.

Due to the relatively low incidence of TB and non-CF bronchiectasis, in developed countries CF has become the major cause of haemoptysis in childhood. Minor bleeding in the form of blood streaking is common, while major haemoptysis occurs in ~1% of children with CF. The term major haemoptysis implies the presence of acute bleeding (>240 mL·day^{-1}) or recurrent bleeding of small volumes (>100 mL·day^{-1} over a few days or weeks). The pathophysiology of haemoptysis in CF includes erosion of enlarged thin-walled tortuous neovasculature of the bronchovascular net located in bronchiectatic areas secondary to chronic infection. Cases of minor bleeding are usually self-limited. However, cases of major haemoptysis can be self-limited or require treatment, either conservative (bed rest, intravenous antibiotics, blood transfusion, vitamin K administration, temporary postponement of positive-pressure chest physiotherapy) or transcatheter embolisation of bronchial arteries (figure 4). Complications of transcatheter bronchial artery embolisation include post-embolic syndrome (fever, thoracic pain and potential dysphagia), iatrogenic ischaemic necrosis of other organs and, very rare but severe, cases of spinal cord ischaemia.

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Upper respiratory tract infections

Rossa Brugha, Chinedu Nwokoro and Jonathan Grigg

The upper respiratory tract (URT) lies cranial to the thoracic inlet and comprises the nose (in continuity with the sinuses and lacrimal ducts) and nasopharynx, the mouth and oropharynx (in continuity with the middle ear *via* the Eustachian tube), and the larynx and laryngopharynx. The respiratory role of the URT is three-fold:

- To warm inspired air before it reaches the lungs
- To trap and remove inhaled particles that may irritate the respiratory epithelium (*e.g.* dust, smoke and organic matter such as pollen)
- To enact innate and adaptive immune responses against inhaled pathogens

The URT is also responsible for phonation and for preparing food and fluids for digestion. URT infections (URTIs) are the most common human malady. For example, in the UK, one-quarter of the population visit their doctor every year owing to respiratory infections. URTIs make up 95% of these infections. Preschool children have up to six to eight URTIs per year. The vast majority of URTIs are self-limiting viral infections, with 90% of children reporting a resolution of common cold symptoms by 15 days and earache by 7–8 days. Human rhinovirus is the most common causative agent (~40% of infections), but numerous other viruses (~200) are associated with infections throughout the URT; the most common are shown in table 1.

This chapter will outline clinical features and the management of common URTIs, alongside important rarer infections, infrequent complications of common infections and important differential diagnoses. Much of the evidence presented in the meta-analyses discussed is based on otherwise healthy populations of children, whereas in the context of significant underlying respiratory disease or multimorbidity (as is the case in many specialist respiratory clinics), a more pragmatic approach may be considered.

Key points

- The majority of upper respiratory tract infections are viral in aetiology and are self-limiting.
- Epiglottitis or bacterial tracheitis should be considered in a child with stridor who looks unwell.
- Decisions regarding antibiotics for otitis media and tonsillitis are difficult and involve pros and cons for the patients and for society; these should be openly discussed when making treatment choices.

Table 1. Common viruses in URTIs

Rhinovirus
Respiratory syncytial virus
Influenza A and B viruses
Metapneumovirus
Parainfluenza virus
Adenovirus
Coronavirus

Common cold or "viral rhinitis"

The common cold describes a group of viral illnesses involving the nasal mucosa, and is experienced annually by the majority of children.

Clinical features

Inflammation of the nasal epithelium (rhinitis) leads to a mucous or mucopurulent discharge (coryza). There may be associated sneezing, cough and/or low-grade fever. A "cold" is a diagnosis of exclusion: if the predominant symptoms are ascribed to adjacent structures (such as a sore throat or mid-facial sinus pain), then the diagnosis is ascribed to inflammation at that site (tonsillitis/pharyngitis or rhinosinusitis) as a matter of convention.

Management

Treatment is with supportive measures (antipyretics) and reassurance, once relevant negatives (allergic rhinitis/rhinosinusitus, cerebrospinal fluid leak, intranasal foreign body) have been considered or excluded. A meta-analysis of the use of antibiotics for the treatment of common colds showed no benefit in comparison with placebo and an increase in adverse events when antibiotics were prescribed in children and adults for acute purulent rhinitis (relative risk 1.46, 95% CI 1.10–1.94) (Kenealy *et al.*, 2013).

Rhinosinusitis

The term "rhinosinusitis" encompasses infection and inflammation of the sinuses as the process involves the nasal passages both for route of infection and drainage. One in every 10 childhood colds will go on to cause sinus inflammation. These infections are initially viral in aetiology, but the anatomy of the drainage means that bacteria may infect the sinuses (in approximately two per 100 cases). In the National Institute for Health and Care Excellence (NICE) guidelines, acute rhinosinusitis is defined as an increase in symptoms after 5 days, or persistence of symptoms beyond 10 days, but less than 12 weeks, whereas chronic rhinosinusitis in children is defined as the presence of nasal blockage (obstruction/congestion) or nasal discharge (anterior/posterior nasal drip) with facial pain/pressure and/or cough (daytime and night-time), lasting for longer than 12 weeks. Symptoms of 4–12 weeks' duration can be described as "subacute sinusitis". Plain radiography of the sinus should not be performed.

Clinical features

These are similar to those of the common cold (coryza, cough and fever), and in younger children (where the sinuses are still developing and the child may not communicate symptoms), sinusitis may be missed. The frontal sinuses can be demonstrated on plain radiographs in 20–30% of children by 6 years of age. Older children and young adults may experience facial "congestion" or "heaviness" alongside focal pains. The sinuses may be tender to gentle percussion. Acute bacterial sinusitis should be considered in

children with "double sickening" (*i.e.* a cold that becomes worse around day 6–7, with nasal congestion, purulent discharge or daytime cough, having previously been seen to be improving), or in those with a severe onset of symptoms from the beginning of a cold with high fever and purulent discharge from the nose.

Management

There is no evidence for the use of nasal or oral decongestants, antihistamines, humidification/steam, mucolytics or saline irrigation in acute childhood rhinosinusitis. Analgesia should be used for pain or fever. It is important to explain this clearly to parents/carers. There is modest evidence that antibiotics (phenoxymethylpenicillin or amoxicillin as the first line, amoxicillin-clavulanic acid as the second line, or an appropriate substitute if allergic) are efficacious, although most episodes are self-limiting. Antibiotics should therefore be reserved for those children at risk of complications; this group has been defined as "children with persistent acute bacterial sinusitis who received antibiotic therapy in the previous 4 weeks, those with concurrent bacterial infection (*e.g.* pneumonia, suppurative cervical adenitis, group A streptococcal pharyngitis, or acute otitis media), those with actual or suspected complications of acute bacterial sinusitis, or those with underlying conditions" (Wald *et al.*, 2013). A suggested approach is to give an antibiotic course that continues for 7 days after the resolution of symptoms. In young adults, intranasal corticosteroids may be of use as an adjunct to antibiotic therapy. Foul-smelling or bloody discharge should prompt consideration of a foreign body high in the nasal cavity.

Chronic rhinosinusitis is less common in children, and management may require otolaryngology input. A chronic sinus infection should lead the treating physician to consider an underlying diagnosis; allergic rhinitis, GOR, asthma, dental disease, immunodeficiency, CF and PCD are all associated with chronic rhinosinusitis in children, with nasal polyps a feature of CF and PCD. Complications may include pre-septal or orbital cellulitis, sinus thrombosis or osteomyelitis; the presence of significant central nervous system symptoms should trigger consideration of a subdural empyema, meningitis or encephalitis.

Acute otitis media

Acute otitis media (AOM) is extremely common in childhood, with a peak incidence between 6 and 15 months of age. Viral infections are the most common cause, although secondary bacterial infection may coexist or develop subsequently.

Clinical features

Younger children will display nonspecific features of illness; fever, vomiting, minor irritability and poor feeding are all common, and young children with these symptoms should always have their ears examined. Older children may complain of dizziness and pain in the ear or pain when eating. Examination of the ear should demonstrate an inflamed erythematous bulging tympanic membrane, which may be opaque or cloudy if there is an associated middle ear effusion. The tympanic membrane may rupture, and there may be pus in the ear canal on examination. The lymph nodes draining the area may be inflamed.

Management

The mainstays of management are adequate doses of antipyretics and analgesia in the form of paracetamol (acetaminophen) and a nonsteroidal anti-inflammatory agent. AOM is usually a self-limiting viral infection. Bacterial infection may rarely spread to the mastoid

air cells with an associated risk of osteomyelitis, intracranial infection and/or venous thrombosis, while more common complications include middle ear effusion and hearing impairment. These varied risks must be balanced against the adverse consequences of antibiotic use, for both the individual and the wider population, and can be approached *via* shared decision making, with delayed antibiotic prescribing approaches.

A meta-analysis of 13 trials using antibiotic *versus* placebo in AOM in children (using pain as an outcome measure) demonstrated no benefit at 24 h but some benefit at 2–3 days (30% fewer had pain in the antibiotic group), although most children's symptoms are improved at this point (Venekamp *et al.*, 2015). There was one case of mastoiditis (in a child treated with penicillin) in almost 3000 trial subjects. The number needed to treat to prevent one child experiencing ear pain was 20, and the number needed to harm (antibiotic side-effects such as vomiting, diarrhoea and rash) was 14. The authors concluded that antibiotics should be given to children with AOM who are <2 years old and to children with bilateral AOM or with AOM plus otorrhoea. The current NICE guidance is to prescribe a 5–7-day course of amoxicillin. Recent randomised controlled trial data suggest that 5 days of co-amoxiclav is inferior to 10 days in children <2 years of age.

Otitis media with effusion

Otitis media with effusion, or "glue ear", occurs when there is serous fluid in the middle ear without symptoms of acute infection. It occurs in association with Eustachian tube dysfunction, which may in turn be secondary to AOM. Over time, this fluid may become tenacious. One in three affected children has a culture-positive retrotympanic effusion. Otitis media with effusion can lead to impaired hearing (conductive deafness), and antibiotics have been trialled to aid its resolution. A meta-analysis of 25 studies did not demonstrate any substantial improvement in hearing or the need for grommets following antibiotic administration (Venekamp *et al.*, 2016). Neither decongestants nor nasal steroids change the course of the illness.

Chronic suppurative otitis media

Chronic suppurative otitis media is present when otitis media with effusion is associated with tympanic perforation and persistent (usually bacterial) discharge occurs. In children, this may be a sign of underlying disease, such as immunodeficiency or PCD.

Pharyngitis and tonsillitis

Pharyngitis, or inflammation of the pharynx, is predominantly viral in aetiology and may coexist as a common pathology in many URTIs (such as a cold and a sore throat). Posterior pharyngeal wall inflammation is readily observed on depression of the tongue. Treatment is supportive with analgesia and antipyretics.

Waldeyer's ring of lymphoid tissue includes the tonsils, adenoids and lymphoid aggregates in the pharynx, at the base of the tongue and in the pharyngeal walls. Tonsillitis is inflammation of the palatine tonsils and is most common in children aged 3–9 years, after which age tonsillar regression occurs. Tonsillitis may occur secondary to both viral and bacterial infections.

Clinical features

Younger children may have nonspecific features of fever, poor feeding, coryza, irritability and a rash (either a viral exanthema or a rash secondary to streptococcal infection in scarlet fever). There may also be vomiting and diarrhoea. Older children

and young adults may have similar symptoms plus localising throat pain, especially on eating or drinking. Local lymph nodes may be enlarged.

A range of suppurative and nonsuppurative complications of group A *Streptococcus* tonsillitis/pharyngotonsillitis occurs and includes the following:

- Peritonsillar abscess (quinsy), a unilateral purulent collection in the peritonsillar fossa, which presents with pyrexia, ipsilateral otalgia (ear pain), odynophagia (pain on swallowing) and often trismus (pain on opening the jaw). Examination shows a deviated uvula and swelling of the soft palate.
- Retropharyngeal abscess, which should be considered in children who present with fever, stiff neck, dysphagia and other symptoms related to inflammation or obstruction of the upper aerodigestive tract. A rare complication of retropharyngeal abscess is thrombophlebitis of the internal jugular vein (Lemierre syndrome), which is often due to infection with the anaerobic bacterium *Fusobacterium necrophorum.*
- Rheumatic fever and glomerulonephritis, previously associated with streptococcal tonsillitis but now rare outside the developing world.

Management

Acute management options include analgesia, antipyretics and in some cases antibiotics. As with AOM, conflict exists between the risks of antibiotic resistance and side-effects on the one hand, and acute and subacute post-infectious complications and morbidity on the other. Clinical scores have been developed for assessing the probability of streptococcal aetiology (Centor and FeverPAIN), albeit with low sensitivity and specificity. Of these, the Centor score is the most widely used, although it was not developed in a paediatric setting. The McIsaac score (figure 1) adjusts the Centor score for patient age. Rapid antigen detection tests for group A *Streptococcus* are reported to have 70–90% sensitivity and 95% specificity compared with throat culture.

β-lactam antibiotics are first-line drugs against the bacteria that commonly cause tonsillitis. Standard therapies include amoxicillin and penicillin. Amoxicillin was previously advised against due to concerns that it causes rashes in children who have sore throats caused by Epstein–Barr virus (infectious mononucleosis and glandular fever), but this is now thought unlikely to be clinically relevant and should not prevent treatment of possible group A *Streptococcus* tonsillitis in a child who cannot or will not take phenoxymethylpenicillin.

Tonsillectomy

Tonsillectomy prevents recurrent tonsillitis but does not prevent recurrent sore throats, as only the tonsillar or adenotonsillar lymphoid aggregates are removed. Tonsillectomy causes a sore throat for 5–7 days and exposes a child to the risk of anaesthetic and surgical complications (infection and haemorrhage), despite

Centor score items (1 point for each)
Fever
Absence of cough
Tonsillar exudates
Anterior cervical lymphadenopathy
Aged <15 years (McIsaac adjustment)

Score	Guidance
0–1	Do not prescribe antibiotics
2	Treat if the rapid antigen test is positive
3	Treat if the test is positive or treat empirically
4–5	Treat empirically

Figure 1. Centor score and McIsaac adjustment for assessing the likelihood of streptococcal infection in tonsillitis/pharyngitis.

uncertainty over the likelihood of recurrence without surgery. A meta-analysis of tonsillectomy or adenotonsillectomy for recurrent or chronic tonsillitis in childhood found that severely affected children benefit from fewer episodes of sore throat in the first year following surgery (3.6 *versus* three episodes including one surgery-associated episode) (Burton *et al.*, 2014). The review concluded that "It is clear that some children get better without any surgery, and that whilst removing the tonsils will always prevent 'tonsillitis', the impact of the procedure on 'sore throats' due to pharyngitis is much less predictable." Newer techniques such as coblation tonsillectomy are purported to reduce post-operative pain, but this is not currently supported by a recent systematic review (Pynnonen *et al.*, 2017). Children and families should be invited to consider the relative risks and benefits of intervention in comparison with a "wait and see" approach when considering surgery for recurrent sore throats.

Diphtheria

Diphtheria is a bacterial pharyngitis caused by *Corynebacterium diphtheriae*. Mortality varies between 5% and 10%. Affected children will have a fever and a sore throat; in addition, there may be malaise, weakness, neck swelling and a characteristic posterior pharyngeal grey, adherent pseudomembrane that can progress to airway obstruction, in which case urgent expert paediatric airway management is required. Diphtheria is prevented by mass immunisation; suggestive symptoms in an area of low immunisation should prompt consideration of diphtheria in the differential diagnosis. Russia, North Africa, the Middle East and East Asia all experienced diphtheria outbreaks in the 1990s. Treatment is isolation, airway management, antitoxin treatment, and parenteral penicillins or erythromycin.

Croup (laryngotracheobronchitis)

Infection of the larynx causes characteristic changes in cough and phonation. Croup is a viral infection of the larynx and adjacent structures; causative organisms include rhinovirus, respiratory syncytial virus and (most commonly) parainfluenza virus types 1 and 2.

Clinical features

The illness often begins with rhinitis, as the upper airway is infected initially. Distal progression of infection irritates the larynx, resulting in a cough. With subsequent vocal cord oedema, the cough becomes harsh or "barking", and inspiratory stridor will develop. Airway obstruction is progressive with limitation of airflow until the condition begins to resolve or anti-inflammatory measures are instigated. The onset of stridor usually occurs over 6–12 h; the Westley croup score is described for use in children <6 years of age to help calculate severity. Sudden onset of stridor should prompt consideration of an inhaled foreign body or anaphylaxis.

Management

Management aims to maximise airflow through the larynx. Risk factors for significant hypoxia include diffusion limitation (*e.g.* BPD) or pre-existing airway compromise (*e.g.* subglottic stenosis). It is imperative to keep the child as pain free and relaxed as possible, as anxiety (*e.g.* from unwelcome or unwarranted interventions) may worsen airflow; paracetamol and a nonsteroidal anti-inflammatory analgesic should be offered to the child to see if they will take them. Steroids reduce vocal cord oedema, facilitating respiration; dexamethasone is favoured. Steroids can be nebulised or delivered orally. More severely affected children (*e.g.* with reduced oxygen saturations

or showing signs of becoming tired/disoriented) may gain temporary benefit from nebulised epinephrine, with doses repeated as necessary due to the short half-life; there may be a rebound effect. Supplemental oxygen (which can be administered by a parent with the child on their lap) may be required alongside steroids and analgesia. Decreasing the viscosity of inhaled gases results in improved large airway flow, and in severe cases a heliox mixture may be helpful.

Whooping cough (pertussis)

Whooping cough is an upper airway infection caused by *Bordetella pertussis* and *Bordetella parapertussis*; it occurs in all countries and increased nine-fold in incidence in the USA between 1980 and 2010. The increase was thought to be multifactorial, but improved diagnosis (using PCR techniques) and a change to acellular vaccines (for diphtheria, tetanus and pertussis (DTaP)) were implicated. Infants aged <2 months are most at risk from severe infection as there is little transplacental transfer of immunity. Recent antipertussis strategies include maternal vaccination with the DTaP vaccine during pregnancy.

Clinical features

Children present with a coryzal, feverish illness that mimics a self-limiting URTI. At this stage, the coryzal infant is highly infectious to nonimmune close contacts. The classic, paroxysmal cough follows this stage and lasts for weeks or months; in China, whooping cough is known as "the 100-day cough". The cough has a characteristic rise in pitch and may or may not be followed by a "whoop" or episodes of vomiting in younger infants. There may also be episodes of cyanosis, apnoea or bradycardia in infants. A very high leukocyte count is associated with a poorer prognosis. Older children may simply present with a persistent cough that has not responded to bronchodilators or inhaled corticosteroids; if suspected, it is important to test for pertussis to guide local public health responses. The cough may occasionally result in petechiae in the superior vena cava distribution, subconjunctival haemorrhages, nosebleeds, rib fractures and pneumothoraces. Otitis media may occur.

Management

Accurate diagnosis with culture by pernasal swab or PCR analysis of nasopharyngeal aspirate is key, although microbial cultures take up to 1 week and decline in sensitivity the longer the illness continues. Serology may aid diagnosis. Children requiring hospitalisation (for supplementary oxygen and/or feeding support) should be isolated and subject to barrier nursing. A macrolide antibiotic (conventionally 14 days of erythromycin) is the first-line treatment, although shorter courses of newer macrolides may be considered as they may improve adherence; treatment of infants <14 days of age with macrolides is associated with an increased risk of hypertrophic pyloric stenosis. Macrolides do not change the course of the illness but do reduce infectivity; therefore, early identification and treatment are crucial. Supportive treatment including mechanical ventilation may be required. Post-exposure prophylaxis should be offered to asymptomatic household contacts within 21 days of onset of cough in the index patient as this can prevent symptomatic infection.

Epiglottitis

Haemophilus influenzae type b (Hib) causes epiglottitis, a severe swelling of the epiglottis that leads to airway obstruction. The incidence of epiglottitis has fallen considerably since the introduction of the conjugate Hib vaccine.

Clinical features

Features of infectious airway obstruction (fever, cough, stridor and recessions) occur rapidly (onset over hours) in a toxic-appearing child, without a clear viral prodrome. The child sits upright with the head held forwards to extend the neck and hold the larynx open. As airflow obstruction progresses, breathing becomes quieter and the child may become cyanosed with decreasing consciousness.

Management

Suspected epiglottitis is an airway emergency and children should be managed in cooperation with anaesthetic and otolaryngology teams. Examination of the throat may precipitate acute obstruction (*via* distress causing laryngospasm) and should be avoided until measures are in place to secure a definitive airway at the point an intervention is required. The epiglottis typically appears swollen and "cherry red" in appearance. There may be systemic features of sepsis, and treatment includes fluid resuscitation and a third- or fourth-generation cephalosporin. Intravenous access should only be obtained once the airway is secure.

Bacterial tracheitis

Since the advent of the Hib vaccine and the widespread use of steroids for croup, bacterial tracheitis is now the most common, although still rare, URTI cause of respiratory failure in children. Bacterial infection of the trachea with *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Streptococcus pyogenes* can result in erythema, oedema and purulent exudates in the trachea. There may be pseudomembrane formation. Viral tracheal infection may coexist.

Clinical features

Children present with fever, cough, hoarseness, stridor and recessions. Diagnosis is usually made at bronchoscopy where the differential diagnosis includes severe croup or epiglottitis.

Management

The majority of children require admission to intensive care, intubation and systemic antibiotic therapy. Aspiration of exudates and breakdown of membranes may be performed at bronchoscopy.

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Acute lower respiratory tract infections

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Pneumonia is defined as an inflammatory disorder of the lung characterised by consolidation due to the presence of exudate in the alveolar spaces and, as a result, associated inflammation in the surrounding interstitial tissues. In classic lobar pneumonia, watery exudates and pus filling the alveoli flow directly into adjacent zones, which extend to create a confluent and confined area of infection, generally within the affected lobe; spread of infection occurs predominantly *via* the lumen of the airways (figure 1). Invasive disease involves organisms penetrating the interstitial tissues and, more importantly, adjacent capillaries, leading to bacteraemia. Bronchopneumonia is characterised by inflammation primarily in the terminal and respiratory bronchioles with exudate often resulting in a number of discreet foci. A wide range of organisms including viruses, bacteria, "atypical organisms" and fungi are capable of creating a pneumonic illness.

The limited response repertoire of the lungs ensures that many of the clinical features of pneumonia, such as fever, cough, respiratory distress and tachypnoea, are also features of other clinical entities, such as acute bronchiolitis, "wheezy bronchitis" and viral exacerbations of asthma. Guidelines tend only to advocate the use of chest radiographs in patients with a more severe or atypical clinical course. This may lead to overdiagnosis of pneumonia, which is reflected in the use of the significantly less specific term "lower respiratory tract infection" (LRTI) in certain guidelines, which includes pneumonia and other clinical entities.

Key points

- The introduction of the pneumococcal conjugate vaccine has had a significant effect on the mortality and morbidity caused by pneumonia worldwide.
- Most children can be treated for community-acquired pneumonia with oral antibiotics unless they have severe and/or atypical disease or cannot tolerate oral therapy.
- Risk factors for hospital-acquired pneumonia include intensive care, immunosuppression and admission of infants to paediatric wards containing patients with lower respiratory tract infections.
- Following recommended infection control policies significantly reduces the rates of nosocomial infections.

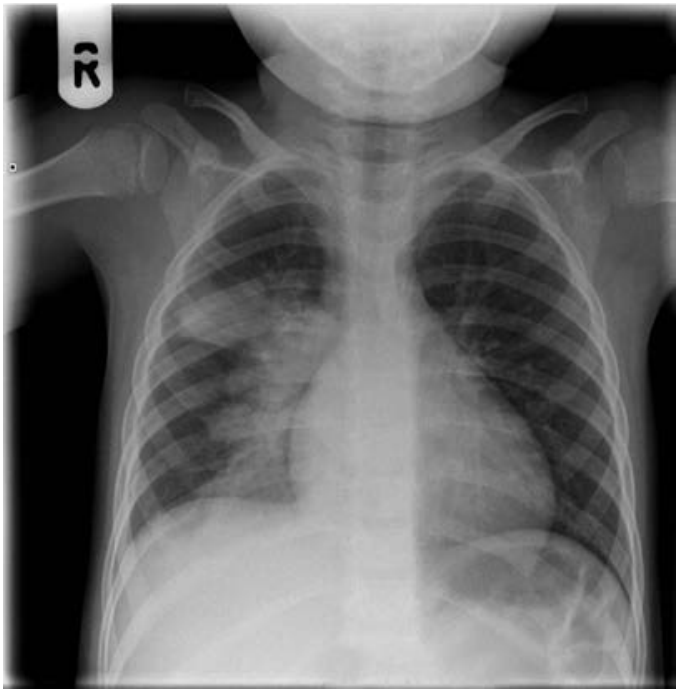

Figure 1. Lobar pneumonia.

Pneumonia can be classified as community acquired or hospital acquired. The location in which the child develops the illness can have a large impact on investigations, causative organisms and subsequent management, and therefore community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) will be approached separately in this chapter.

Community-acquired pneumonia

CAP usually refers to a pneumonia developing in a generally well individual who has acquired the organism outside a healthcare setting. Worldwide, CAP remains the leading killer of children and thus is a major health issue. It has been estimated that approximately 1 million deaths per year in children <5 years of age are attributable to pneumonia, accounting for one-sixth of all deaths in this age group. This is likely to be an underestimate, as most deaths probably occur without interaction with healthcare professionals, although it does reflect a considerable decrease from 2000 to 2013 as measured by the Global Burden of Disease study, with the widespread use of the pneumococcal conjugate vaccine (PCV) and international health promotion interventions in low- and middle-income countries being attributed to this significant improvement. Epidemiological studies indicate that the prevalence of CAP is significantly higher in developing countries, which would account, in part, for the higher mortality in these countries. However, the true incidence of pneumonia is difficult to define without confirmation of the diagnosis by chest radiography, with many LRTIs being labelled "pneumonia" on clinical grounds. Studies assessing the accuracy of a clinical diagnosis of pneumonia when compared with chest radiographs have confirmed that there is significant overdiagnosis, as well as underdiagnosis.

Aetiology

Studies aimed at determining the causative organisms in children with CAP have been hampered by difficulties in obtaining samples from the site of infection in the distal lung. This is because:

- Young children rarely expectorate sputum
- Positive blood cultures resulting from invasive disease occur in only a minority of bacterial infections
- Rapid antigen tests can be misleading due to false-positive results
- Sampling of the upper airways for viruses and bacteria may not be directly relevant to the organisms replicating in the alveoli

It is believed that most episodes of pneumonia commence with colonisation of the mucosa of the nasopharynx, with subsequent spread to the lower respiratory tract. Less commonly, persistent bacterial bronchitis may precede an acute exacerbation with associated pneumonic changes. Persistent bacterial bronchitis is usually defined as the presence of a wet cough for >4 weeks that resolves with antibiotics in the absence of an alternative specific cause of chronic cough.

A wide range of organisms including bacteria, viruses and so-called "atypical organisms" cause CAP. Mixed bacterial and viral infections are also common.

Bacteria

Streptococcus pneumoniae (pneumococcus) is the most commonly identified bacterium in CAP and is frequently considered to be responsible for the classic pneumonic illness (table 1). It is also the most common bacterium found in the analysis of parapneumonic effusion/empyema, although a large number of organisms, including viruses, may be associated with a parapneumonic effusion. Associated invasive disease, such as bacteraemia and meningitis, contributes to the poor outcome in untreated children. The current PCVs target the *S. pneumoniae* serotypes most likely to cause invasive disease, and a decrease in CAP and *S. pneumoniae* invasive disease has been demonstrated since their introduction, although the longer-term effect of serotype replacement remains to be seen.

Other bacteria that cause pneumonia include:

- *Haemophilus influenzae* type b (Hib) and nontypeable species, although Hib is now very rare in developed countries; when it occurs in a vaccinated child, it is an indication to look for an immune defect
- Group A streptococci (mainly *Streptococcus pyogenes*), with increased risk of infection after varicella-zoster virus infection (chickenpox)
- *Staphylococcus aureus*, especially during influenza A virus epidemics, if the strain produces Panton–Valentine leukocidin (PVL) toxin, or after chickenpox

In addition to these bacteria, atypical bacteria such as *Mycoplasma pneumoniae* may account for 20% of cases. This is classically considered to be a cause of pneumonia in school-age children but is capable of causing a severe pneumonia in the younger child (table 1).

Viruses

A wide range of respiratory viruses can cause pneumonia, particularly in infants and, to a lesser extent, preschool children. As with any clinical syndrome from rhinitis through to bronchitis and bronchiolitis to pneumonia, any of the respiratory viruses, including respiratory syncytial virus (RSV), parainfluenza virus, influenza virus and human metapneumovirus, may be responsible. In general, viruses cause less severe illnesses than bacteria but remain an important cause of severe disease and death. Viral LRTIs tend to affect the airways more diffusely than bacterial pneumonias, and it is not uncommon for infants with clinical acute bronchiolitis characterised by widespread crackles to have evidence of collapse and/or consolidation on a chest radiograph. Moreover, with increasingly sensitive diagnostic techniques, it is clear that

Table 1. Bacteria and CAP

Organism	Predisposing factors	Suggested first-line treatment	Comments
Streptococcus pneumoniae	Previously well	Amoxicillin (oral) Benzylpenicillin if *i.v.* therapy is required	In empyema, consider adding clindamycin
Streptococcus pyogenes	Chickenpox	Benzylpenicillin and clindamycin	Invasive group A *Streptococcus* is notifiable to the CCDC in the UK; contact tracing is indicated
Mycoplasma pneumoniae	Outbreaks every 5–7 years	Clarithromycin	Often mild; *M. pneumoniae* has no cell wall so cannot be treated with penicillin
Staphylococcus aureus	Influenza A, PVL toxin	Linezolid, clindamycin and rifampicin	Follow Health Protection Agency guidelines in the UK; contact tracing is indicated
Haemophilus influenzae	Immune defect if Hib isolated from vaccinated individual	Co-amoxiclav or cefotaxime/ ceftriaxone	Rare

CCDC: consultant in communicable disease control.

many cases of bacterial pneumonia are preceded or accompanied by infection by one or more of these viruses.

In general, studies have found that the more severe illnesses are associated with bacterial infection, but this is not necessarily the case, and this is changing with the widespread introduction of vaccines to *S. pneumoniae* and Hib. However, it should be remembered that the mortality of patients with viral LRTIs, such as acute bronchiolitis due to RSV and other viruses, in the absence of good supportive care and oxygen therapy in particular, is significant.

While it is widely stated that most pneumonias in very young children are viral, this is also the peak age for severe bacterial infections and death caused by organisms such as *S. pneumoniae*.

Clinical assessment and diagnosis

When assessing a child who may have pneumonia, it is important to make a diagnosis, assess the severity and consider comorbidities that might contribute to the development of the pneumonia or to the severity of the episode.

Diagnosis

The recommendations of the World Health Organization (WHO) are aimed at resource-poor countries and are based on simple clinical criteria. They suggest that pneumonia should be suspected in children with a cough and/or difficulty breathing with age-adjusted tachypnoea of:

- >50 breaths·min^{-1} for infants aged 2–11 months
- >40 breaths·min^{-1} for preschool children aged 1–5 years
- >20 breaths·min^{-1} for children aged >5 years

One study found that this approach had the highest sensitivity (74%) and specificity (67%) for radiographically defined pneumonia. Associated factors are used to determine severity, with recession, grunting and nasal flaring being indicative of severe pneumonia, while cyanosis, persistent vomiting, severe respiratory distress and confusion suggest a very severe illness. This pragmatic approach serves the needs of healthcare systems faced with a huge burden of disease and associated morbidity where clear, unambiguous direction in relation to management is required in order to optimise outcomes.

A similar approach is observed in several developed countries, as highlighted by the British Thoracic Society (BTS) guidelines, which again advocate a clinical approach to diagnosis. The guidelines do not have clear recommendations regarding making a definitive diagnosis but state that "bacterial pneumonia should be considered in children when there is persistent or repetitive fever >38.5ºC together with chest recession and a raised respiratory rate". They make no recommendation regarding the use of chest radiographs other than to state that they should not be considered to be a routine investigation in children thought to have CAP. Once again, this is likely to be associated with misdiagnosis, both false positives and false negatives. It is known that chest radiograph changes lag behind the clinical picture and an early chest radiograph may miss a developing pneumonia.

Cough is not a key feature, and it is known that for classic bacterial lobar pneumonia, cough may be infrequent until lysis occurs, as there are few, if any, cough receptors in the distal lung. Of other symptoms that might be present, the most predictive is wheeze, which has a very strong negative predictive value. Conversely, the absence of wheeze in a known asthmatic with respiratory distress and fever may indicate bacterial pneumonia, which generally does not cause an exacerbation of the asthma. Other auscultatory findings are considered to be unreliable, but if localised crackles are present, they increase the likelihood of a lobar consolidation, and dullness to percussion is a good predictor of an associated effusion/empyema. Widespread crackles in an infant are consistent with a diagnosis of bronchiolitis rather than pneumonia. While tachypnoea is perhaps the most important symptom, this is less specific and sensitive than noted earlier during the first few days of the pneumonia. It is likely that many children with pneumonia are treated inadvertently in primary care with antibiotics prescribed for conditions such as tonsillitis or ear infections.

Extrapulmonary symptoms are relatively common. These may be nonspecific symptoms such as diarrhoea and vomiting, headaches and myalgia. Of note is the fact that pneumonias may cause abdominal pain and should be considered in the differential diagnosis of an acute abdomen, even in the absence of coughing. Organisms such as *S. pneumoniae* and Hib may cause serious invasive disease such as septicaemia and meningitis, with or without an obvious pulmonary focus.

Comorbidities

While CAP is generally considered to develop in the community in previously well children, it is important to obtain a full history in order to try and determine whether there may be predisposing factors. These would include possible chronic aspiration associated with neuromuscular conditions, pneumonia caused by opportunistic infections such as fungi in the immunocompromised, inhalation of a foreign body, influenza and recent chickenpox.

Severity

As described earlier, features reflecting the severity of the pneumonic illness have been outlined by the WHO. These provide a guide to a stepwise approach to treatment,

escalating from oral antibiotics to intravenous antibiotics in severe disease. The BTS guidelines suggest that any of the following would advocate that admission of a child to hospital is indicated:

- S_{pO_2} ≤92% in air
- Apnoea or grunting
- Significant difficulty in breathing
- Poor feeding or dehydration
- Concerns regarding appropriate supervision

Pulse oximetry is an important parameter influencing the use of oxygen therapy and, indeed, antibiotic therapy.

Investigations

Chest radiography

Current guidelines have concluded that for most cases of pneumonia a presumptive diagnosis can be made on the basis of the clinical criteria outlined earlier and that treatment can be initiated empirically. A definitive diagnosis would require a chest radiograph with changes consistent with consolidation, although it should be remembered that the chest radiograph changes may lag behind the clinical picture, during both the evolution of infection and the resolution. The WHO and North American and European guidelines do not recommend the use of chest radiography in the majority of cases for a number of reasons. These include the apparent inability to distinguish bacterial and viral infections on the basis of chest radiograph appearances, and studies that suggest that, although in those with a clinical diagnosis obtaining a chest radiograph leads to a change in management in a minority of cases, it does not influence outcomes in the vast majority of cases. Furthermore, interobserver agreement regarding interpretation of chest radiograph changes is poor, even with clear guidance. There is certainly a consensus that they are not required in the vast majority of ambulatory patients treated in the community. The BTS guidelines suggest that a chest radiograph could be considered in those with fever >39ºC, in children aged <5 years, and in those not responding rapidly and in whom complications such as an effusion may have developed.

Microbiology

Making a positive identification of the causative organism(s) is clearly desirable, as therapy can then be tailored more accurately. However, obtaining microbiological samples from the sites of infection (the distal airways) is challenging, and invasive investigations such as bronchoscopy or lung aspirates are rarely indicated. Sputum cultures may be helpful if present, but most young children do not expectorate sputum. Blood cultures are positive in only a minority of patients, partly because many clinical pneumonias are not due to bacteria and partly because bacteraemia is often not present or is present intermittently. The likelihood of conventional microbiological approaches identifying bacteria in such samples is significantly reduced in the presence of prior antibiotic use.

Samples can be obtained from the nasopharynx and oropharynx and may reflect the cause of infection in the distal airways, but inevitably there are false positives and false negatives. This is particularly true for bacteria that are frequently present as transient "commensals" in the upper respiratory tract of infants and young children, and hence bacterial culture of the upper airways is not recommended. Viral PCR may be helpful, but a positive result does not exclude a bacterial pathogen, and it is increasingly recognised that more than one organism may be involved. Paired

serology is useful in epidemiological studies but contributes little to the clinical care and outcomes. The value of rapid antigen tests for *S. pneumoniae* is compromised by relatively low sensitivity and specificity, especially in young children where false positives are common. A negative test in older children may be valuable.

For all of these reasons, it is widely recommended that no investigations are required in those ambulatory patients with suspected pneumonia treated in the community. In those admitted to hospital, blood cultures, viral PCR on nasopharyngeal aspirates or nasal swabs, and paired serology for atypical organisms may all be of value. Where pleural fluid is obtained, culture, PCR and pneumococcal antigen detection should be undertaken.

Other investigations

Evidence suggests that acute-phase reactants are not helpful in distinguishing between viral and bacterial infection and hence are not indicated in the management of uncomplicated pneumonia. Clinical experience, however, suggests that they can contribute to the management of children who do not follow the expected clinical course, and they can be used to guide the investigation and treatment of those with a pneumonia complicated, for example, by an empyema or necrosis.

Treatment

Treatment involves both supportive and therapeutic components. There is no question that children with hypoxia should be treated with supplemental oxygen, although there is some debate as to whether an S_{pO_2} of 90% or 92% is the appropriate cut-off value, and altitude may need to be taken into account. Studies in Zambia and other countries have indicated the importance of oxygen therapy in reducing mortality. General supportive care including fluids, possibly restricted to 80% of maintenance, is indicated in those who are vomiting or unable to tolerate oral fluids. In the most severe cases, intensive care may be required.

Specific treatment in the form of antibiotics should be given to all patients with a clinical diagnosis of pneumonia as there is no reliable means of distinguishing viral and bacterial infections. It is clear that this approach will result in many children with viral LRTIs being treated with antibiotics, but the risk of mortality and adverse outcomes in untreated bacterial pneumonia is such that this is indicated. There is clear evidence that oral amoxicillin results in outcomes comparable to those of parenteral penicillin and is therefore appropriate for the vast majority of children with pneumonia, a recommendation supported by a Cochrane review of children in hospital with severe CAP (Rojas-Reyes *et al*., 2006). Intravenous therapy should generally be reserved for those with a severe illness or those who cannot tolerate oral administration.

Oral amoxicillin is the recommended antibiotic in the UK. It is effective against the majority of bacterial pathogens and there are low levels of *S. pneumoniae* resistance to penicillin compared with mainland Europe, although a BTS audit found that in a hospitalised cohort, co-amoxiclav was used more commonly. In older children where an atypical infection is suspected or where there is a poor response to therapy after 48 h, a macrolide may be used or added. Current recommendations are that co-amoxiclav is appropriate for influenza A virus-associated bacterial pneumonia. The optimal duration of treatment is unknown, with most courses lasting 5–7 days. For streptococcal pneumonia in the presence of lysis and fever, shorter courses may be appropriate, but evidence is lacking and normal course lengths are used. Benzylpenicillin is generally appropriate for *i.v.* therapy, although co-amoxiclav or a second- or third-generation cephalosporin may be used in severe disease.

Antibiotic resistance patterns vary among and within countries. For this reason, the choice of antibiotic should be based on local guidelines developed as part of a multidisciplinary approach. In children with neurodisability or a history of recent intubation, an antipseudomonal agent (*e.g.* piperacillin/tazobactam) is a good empirical choice.

Prevention

Vaccines against Hib and *S. pneumoniae* have had a significant impact on CAP. The Hib vaccine has largely eliminated this organism from the list of likely pathogens. The PCV currently covers up to 13 of the more than 80 serotypes of *S. pneumoniae*, and worldwide uptake into routine schedules, as recommended by the WHO, has occurred in 68% of countries. The Global Burden of Disease study has demonstrated a significant impact on worldwide deaths due to pneumonia, although factors such as improved nutrition will also have contributed to this effect. Disease resulting from infection with other serotypes continues, however, which may in part be due to serotype replacement.

Another benefit of the widespread introduction of PCVs is that they are effective against both antibiotic-susceptible strains and those such as serotype 19A, which is resistant to antibiotics. Furthermore, the herd immunity effect has led to an impact on incidence in the elderly, as well as in the very young.

Complications

The most common complication of CAP is the development of pleural effusion and empyema (figure 2a), and the frequency and severity of these complications appear to be decreasing with the introduction of the PCV. Small uncomplicated effusions do not need draining. Ultrasound can determine the size and distribution of the collection and its consistency. Current evidence suggests that in patients developing an empyema, drainage with a small-calibre catheter and intrapleural fibrinolytics (figure 2b) is as effective as a mini-thoracotomy and video-assisted thoracoscopic surgery (VATS). Some 10–15% of empyemas resolve relatively quickly with antibiotic therapy alone, and thus their size and consistency in conjunction with clinical parameters need to be considered. Up to 15% of patients treated with drainage and fibrinolytic therapy might subsequently require further intervention, such as VATS or decortication, although fever alone is not an indication of failed therapy. Whichever approach is used, outcomes are generally good, with complete clinical and radiological resolution.

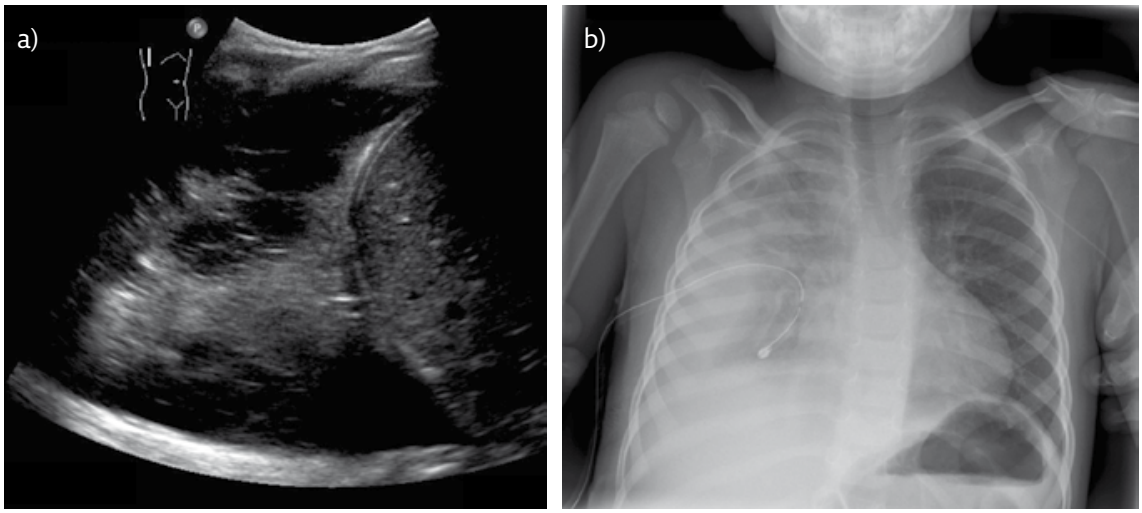

Figure 2. a) Ultrasound showing empyema with septations secondary to pneumonia. b) Empyema with a chest drain with urokinase.

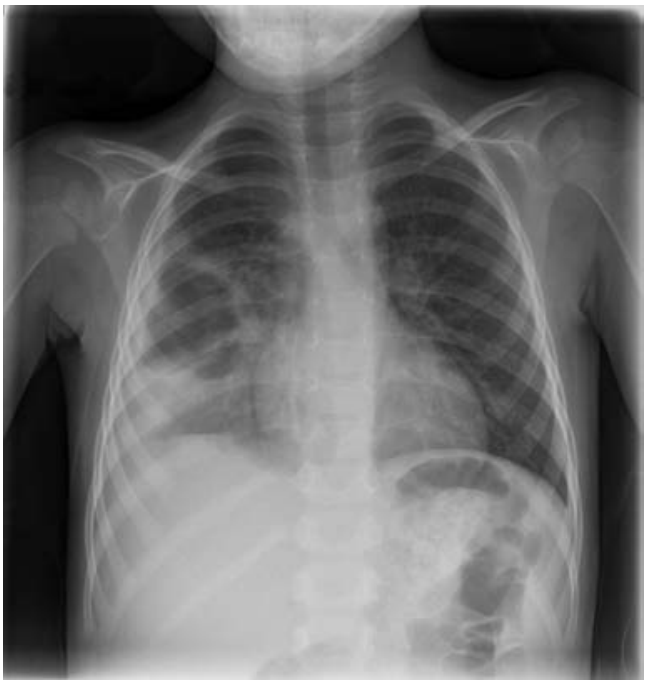

Figure 3. Pneumatocele developing during pneumonia.

Pneumatoceles are seen most commonly in patients with *S. aureus* infection but may develop in pneumonia due to almost any of the common bacteria (figure 3). The vast majority regress spontaneously, and surgical management is rarely required. Lung abscesses developing in the course of necrotising pneumonia are often associated with an empyema and are most commonly treated with a prolonged course of *i.v.* antibiotics, although radiological placement of a drain has been suggested as a way of more rapid resolution. Surgical resection should be avoided. Bronchopleural fistulae may also develop in necrotising pneumonia; these are usually peripheral and generally resolve with continuous chest drainage.

Children with empyemas, necrosis, lobar collapse and round pneumonias require a follow-up radiograph and a clinical review. Repeat imaging is not necessary for those with an uncomplicated pneumonia who recover fully.

Summary

CAP remains a major healthcare issue, although the development of vaccines directed against two of the major bacterial pathogens has had a significant impact on the incidence and the frequency of complications. A clinical diagnosis based on fever and tachypnoea is associated with improved clinical outcomes, particularly in the developing world, but inevitably results in large numbers of patients receiving antibiotics for nonbacterial infections. While the majority of pneumonias in infants and young children are viral, this is also the peak age for serious life-threatening bacterial infections. Most pneumonias can be treated effectively using appropriate oral antibiotics, with *i.v.* antibiotics being reserved for those with severe infections or who are not tolerating oral therapy. Supportive care remains a vital aspect of care for those with serious infection.

Hospital-acquired pneumonia

Hospital-acquired infections, also known as nosocomial infections, are infections that are not present and that lack evidence of incubation at the time of admission to hospital. Pneumonia and other LRTIs account for a large proportion of these potentially

serious complications of hospitalisation. Such infections can be transmitted to the patient from another source or may be due to an organism already carried by the patient. Interventions, such as endotracheal intubation or the use of broad-spectrum antibiotics, may compromise host defences and increase the patient's predisposition to infection. HAP is generally defined as pneumonia that presents with signs and symptoms that occur after, and not originating before, 48 h in hospital. A European Centre for Disease Prevention and Control survey demonstrated a 4.2% prevalence of healthcare-associated infections in the paediatric population, with HAP in neonates and children being the second most common cause of nosocomial infection after sepsis (Zingg *et al.*, 2017). HAP accounted for over one-fifth of cases and occurred most commonly in infants. In the 5–10-year age group, HAP was the leading nosocomial infection.

HAP poses the greatest risk to those undergoing mechanical ventilation, in which case it is termed ventilator-associated pneumonia (VAP). VAP is generally defined as the development of a pneumonia >48 h after intubation, although most HAPs occur outside the paediatric intensive care unit (PICU). Attempting to define HAP and VAP has been challenging for those designing epidemiological and intervention studies. Variations in definition probably contribute to differing reports of incidence, which can be up to 12% of ventilated children and differs among intensive care unit (ICUs), reflecting a variation in patient morbidity.

HAP in neonatal intensive care units (NICUs) poses an even greater challenge as it is difficult to distinguish between hospital-acquired and vertically transmitted infections. This uncertainty is compounded by the early intervention in suspected sepsis, often prior to chest radiograph changes, a feature usually integral to the definition of VAP.

Risk factors

HAP can be thought of as an endogenous disease, in which autoinfection occurs when the patient's own microbes breach the usual protective barriers and become pathogenic, or an exogenous disease, in which external factors lead to the acquisition of new pathogens that proceed to cause infection. Certain factors in the host lead to this becoming more or less likely to occur, and it is these risk factors that form the basis for interventions to limit HAPs.

Paediatric intensive care

Mechanical ventilation poses the biggest risk in this setting, as it is generally used in those with the greatest illness severity and is an invasive intervention that circumvents the normal upper and lower pulmonary antimicrobial defences. In this group of patients, HAP is usually synonymous with VAP and causes a prolongation of mechanical ventilation, as well as an increase in mortality and morbidity.

Patients, in particular those who are critically ill and require PICU admission, can become colonised with new organisms during hospitalisation. These newly colonising organisms may differ among institutions, and the rate of their establishment increases with acidosis, intubation, hypotension and broad-spectrum antibiotic use, and in those at risk of clinical or subclinical aspiration. Intubation poses the greatest risk for the establishment of HAP, as the endotracheal tube facilitates movement of organisms from the upper to the lower airways. Endotracheal tubes also impair mucociliary transport and, along with suctioning, can cause trauma that impairs host defences. Tracheostomies have an even greater effect, and in this population, nosocomial infection rates are higher. Neuromuscular blockade in all groups has a negative impact on rates of pneumonia.

In addition to the use of endotracheal tubes, ICU patients frequently have a nasogastric tube, which is likely to facilitate reflux and lead to aspiration of gastric contents into an artificially patent airway.

Neonatal intensive care

Neonatal intensive care shares many of the problems outlined for paediatric intensive care but in addition has factors unique to its population that increase the likelihood of HAP. Low birthweight, poor nutrition, a greater permeability of skin and mucous membranes, and hypogammaglobulinaemia due to a restriction in the time available for the placental translocation of maternal IgG all contribute to a greater risk of infection. In the NICU, as in the PICU, the effect of hand hygiene, local equipment practices and ward design also impact on infection rates.

Post-surgical patients

The post-operative period, with the risk of ventilation and the impact of pain or sedation, predispose to HAP. Thoracic and abdominal surgery are particularly high-risk situations, as coughing may be painful and adequate mucus clearance difficult.

Chronic disease

Immunodeficiency (primary and secondary), CF, cardiac disease, low birthweight and malnutrition all contribute to increasing rates of HAP. In addition, those with GOR, swallowing difficulties and neurological disorders are all at risk of aspiration and subsequent HAP.

Hospital factors

Nosocomial infection rates vary among institutions, and the impacts of staffing, ward design, local hygiene practices among staff and management of equipment have been shown to have a significant effect on infection rates, including pneumonias. The impact of acquiring an organism such as RSV in hospital is frequently overlooked in discussions about HAP, but studies have reported that ICU patients who acquire the virus after admission may have a mortality rate approaching 25%. Acquisition during an admission to the paediatric ward for an unrelated problem is associated with substantial increases in the duration of stay and readmission rates, as well as significant morbidity.

Antibiotic usage

Antibiotic resistance varies among countries and sometimes among healthcare establishments. Empirical guidelines are usually available, but the results should always be kept under review. Antimicrobial stewardship guidelines should be followed by all prescribers.

Aetiology

Viruses

Viruses are responsible for the majority of HAPs, being highly contagious and having the ability to infect all children, from those who are relatively well to those who are deemed high risk. The epidemiology of these HAPs reflects epidemic patterns and is, in the most part, attributable to RSV, influenza virus and parainfluenza virus, with RSV, by virtue of its high infectivity, being the most common. Other implicated viruses include cytomegalovirus, Epstein–Barr virus and adenovirus, although these occur less often and tend to be of most importance in the immunocompromised.

Bacteria

Gram-negative organisms including *Pseudomonas aeruginosa*, *Klebsiella* spp., *Enterobacter* spp. and nontypeable *Haemophilus influenzae* are the most common Gram-negative

isolates. *Streptococcus pneumoniae* and *Staphylococcus aureus* are the most common Gram-positive isolates.

Antimicrobial resistance poses a significant problem in exogenous bacterial HAP. Although less common, methicillin-resistant *S. aureus* (MRSA) infections do pose a therapeutic challenge, and third-generation cephalosporin resistance and extended-spectrum β-lactamase-producing organisms can cause significant morbidity and mortality.

Fungi

The immunocompromised are at highest risk of fungal lung infections, particularly if exposed to broad-spectrum antibiotics for suspected bacterial sepsis. Building work is a risk factor for the acquisition of *Aspergillus* spp., while endogenous *Candida* and *Aspergillus* spp. are a particular risk for neutropenic patients. Thus, in patients with neutropenic sepsis, antifungal agents tend to be used early in those not responding to first-line antibacterial agents. A high-efficiency particulate air-filtered positive-pressure air supply to single rooms is recommended for children in the period immediately after bone-marrow transplantation to reduce the risk of aerosolised fungal infection.

Pneumocystis jirovecii

This organism, previously classified as a protozoan, is an opportunistic organism with a high infection mortality rate, and its isolation should increase the suspicion of an underlying immunodeficiency. This, as well as infections with cytomegalovirus, Epstein–Barr virus and adenovirus in immunocompromised children, tends to reflect endogenous rather than exogenous acquisition and can be life-threatening.

Mycobacteria

Mycobacterium tuberculosis should not be overlooked in HAP. Although all children may be susceptible to *M. tuberculosis*, the immunosuppressed child is at greatest risk, with spread from undiagnosed adults posing a threat in the ward setting.

Prevention

Prevention of hospital-acquired infection, including HAP, should be at the forefront of the clinician's approach to the care of patients. There is a substantial body of evidence that HAP is associated with increased morbidity, mortality and healthcare utilisation, and a similar body of evidence that the implementation of programmes designed to prevent such infections can be very effective, both in the ICU and in paediatric wards. Attention to detail is the key to implementing well-known infection control measures, including rigorous hand hygiene, the use of disposable aprons and gloves, and isolating infectious patients. Ensuring that healthcare workers are immunised against influenza virus and that those with respiratory viral illnesses do not look after at-risk patients are also important aspects of preventing nosocomial infection. Care bundles, including the previously mentioned precautions, together with recommendations such as nursing ventilated patients with their head elevated where possible, minimising changes in ventilator circuits, comprehensive oral hygiene programmes and avoiding re-intubation where possible, in addition to ongoing education of staff, have been shown to have a significant impact in lowering rates of VAP. Not only does attention to detail significantly improve clinical outcomes for the patient, it also reduces healthcare costs and leads to much lower use of broad-spectrum antibiotics.

Diagnosis and surveillance

As noted earlier, the diagnosis of HAP and indeed VAP can be problematic. Common to all definitions is a deterioration in respiratory status >2 days after admission or intubation that does not appear to be attributable to infection apparent at the point

Table 2. Antimicrobial treatment for HAP in children

Clinical setting	Probable organisms	Appropriate "first-guess" treatment	Comments
Post-operative, previously healthy	*Streptococcus pneumoniae* *Haemophilus influenzae* *Moraxella catarrhalis*	Co-amoxiclav[#] or cefuroxime	If genuine penicillin allergy, discuss oral switch with a microbiologist; maximise physiotherapy
Post-viral (*e.g.* deterioration in bronchiolitis)	*Streptococcus pneumoniae* *Haemophilus influenzae* *Moraxella catarrhalis* *Staphylococcus aureus*	Co-amoxiclav[#] or cefuroxime	If genuine penicillin allergy, discuss oral switch with a microbiologist
VAP	*Pseudomonas aeruginosa* *Staphylococcus aureus*	Piperacillin/tazobactam[#] or ceftazidime plus teicoplanin	Usually requires full *i.v.* course
Neutropenic/ post-transplant/ immune deficient	Wide variety of potential organisms: bacterial, fungal and viral Consider possibility of *Mycobacterium tuberculosis*	Follow local protocols; consider antifungal and antiviral treatment in addition to antibacterial	Discuss with microbiology, infectious diseases, radiology and oncology; may need invasive diagnostic tests

Treatment should be guided by local protocols and sensitivity patterns. Consider an *i.v.* to oral switch as soon as clinically appropriate. [#]: these agents are penicillins and should be avoided in cases of genuine penicillin allergy.

of admission or intubation. New chest radiograph changes associated with fever and leukocytosis or leukopenia, together with clinical features such as increased cough or airway secretions on suctioning, strongly support the diagnosis, although it is clear from *post mortem* and other studies that over- and underdiagnosis occur, as is the case with CAP. Hospital-acquired LRTIs, caused by viruses such as rhinovirus or RSV, are often not classified as HAP as they develop after discharge and if the patient is re-admitted are frequently assumed to be community acquired.

Diagnostic approaches include sampling the lower airways in those being ventilated with simple endotracheal aspirates, blind protected brushings and BAL. Identifying the bacteria responsible enables more focused antibiotic prescribing and reduces the use of broad-spectrum antibiotics. None of the sampling techniques is ideal in terms of sensitivity and specificity, with the sensitivity increasing with combinations of techniques. For nonventilated patients, obtaining samples from the lower airways is rarely undertaken other than in immunosuppressed patients, although sampling of the upper airways for respiratory viruses can be valuable.

Treatment

Ideally, treatment should be tailored to the specific organism. As noted previously, this is not possible for many patients with HAP, and empirical treatment is frequently used based on probable organisms. The choice of antibiotic should be based on local guidelines developed as part of a multidisciplinary approach. A suggested approach is outlined in table 2.

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Acute viral bronchiolitis

Fabio Midulla, Greta Di Mattia and Laura Petrarca

Bronchiolitis is an acute viral respiratory infection involving the terminal and respiratory bronchioli in infants, resulting in small airways obstruction. Bronchiolitis is a clinical diagnosis, but, despite its high frequency, its definition is still controversial. The American Academy of Pediatrics (AAP) subcommittee defines bronchiolitis as a disorder in infants <24 months of age that is most commonly caused by a viral lower respiratory tract infection characterised by wheezing. In contrast, European guidelines define bronchiolitis as a seasonal viral illness in infants <12 months of age characterised by nasal discharge, cough, tachypnoea, retractions and bilateral crackles. These definitions reflect differences in how the disease is interpreted, and the North American definition, in particular, might engender an overlap between bronchiolitis and early wheezy bronchitis.

Epidemiology

Bronchiolitis is the most common cause of acute viral lower respiratory tract infection in infants <1 year of age and is the leading cause of hospitalisation in this group of children. Bronchiolitis is epidemic during the winter months. Annually, 11 out of every 100 infants develop bronchiolitis and 11–13% of patients require hospitalisation. Each year, 150 million new cases of bronchiolitis are reported worldwide. Only 1–3% of infants require admission to intensive care, mainly those in whom risk factors are present.

Key points

- Bronchiolitis is defined as the first episode of acute viral infection of terminal and respiratory bronchioli in infants <1 year of age.
- Moderate-to-severe respiratory distress with rales at auscultation and dehydration peak between 3 and 7 days of disease.
- Supportive therapies aim to keep the upper airways clear and the infant oxygenated and hydrated.
- Nebulised salbutamol can be tried but should be continued only if it achieves a documentable clinical benefit.

Aetiology/risk factors

Bronchiolitis is caused by viruses. The most common viruses responsible are respiratory syncytial virus (RSV), human bocavirus, rhinovirus, human metapneumovirus, influenza A and B viruses and parainfluenza viruses 1–3.

Risk factors for severe bronchiolitis are age <3 months, male sex, low socioeconomic conditions, maternal smoking and RSV infection. Other risk factors for severe bronchiolitis are prematurity with BPD, and coexisting comorbidities, such as cardiovascular diseases, immunodeficiency and chronic respiratory diseases. The only known protective factor is maternal breastfeeding.

Pathophysiology

Viral respiratory infection results in respiratory epithelium necrosis, loss of epithelial cilia, collection of desquamated airway epithelial cells, lymphocyte and neutrophil infiltration within terminal and respiratory bronchioli, and oedema around the airway. Cellular debris, inflammatory cells and fibrin cause airway obstruction. Mucus plugs can partially or totally occlude the bronchioli. When the bronchioli are completely occluded, atelectasis develops; if the bronchioli are only partially occluded, diffuse air trapping occurs (figure 1).

The elevated airway resistance and reduced dynamic lung compliance increase the work of breathing. Atelectasis and air trapping result in hypoxaemia and increased carbon dioxide levels due to an altered ventilation/perfusion ratio. Tachypnoea, increased work of breathing and reduced feeding can cause dehydration with metabolic acidosis.

Diagnosis

Bronchiolitis is commonly diagnosed on clinical grounds alone without help from diagnostic tests. The criteria for the diagnosis of bronchiolitis include exposure to other children or adults with respiratory viral infection, age <12 months, preceding upper respiratory illness and signs of acute lower respiratory illness (respiratory

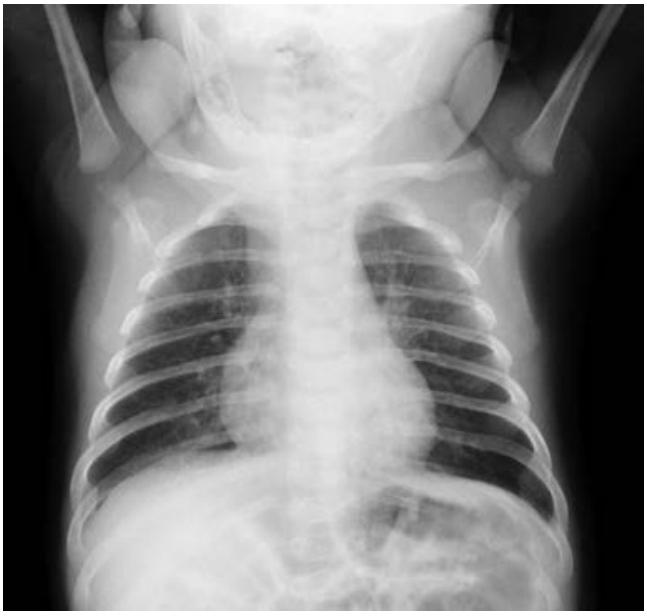

Figure 1. Chest radiograph of an infant with severe acute bronchiolitis showing diffuse air trapping and peribronchial thickening.

distress, low S_{pO_2}, rales and, rarely, wheezing). Chest radiographs and blood tests are required only if suggested by clinical indications; blood gas analysis is recommended only in more severe cases. Rapid virus detection could reduce antibiotic use and is important for cohorting.

Symptoms

The incubation period is usually ~5 days, after which the infant starts to present clinical symptoms of an upper airway infection that usually lasts 3 days. Although fever can be present during the coryza period, it is normally absent when the child starts to have symptoms of a lower respiratory tract infection. In evaluating an infant with bronchiolitis, it is important to know that the risk of a reduction in food intake with possible dehydration and of severe respiratory symptoms usually peaks between 3 and 5 days after the onset of rhinitis and cough. Bronchiolitis is a "dynamic disease" and its clinical characteristics can change quickly.

High fever during the respiratory distress period is rare and is reported in only 30% of patients. In the presence of high fever, the child should be evaluated carefully to rule out other causes of fever. A proven secondary bacterial infection is present in only 1.2% of infants with bronchiolitis and should be suspected if the child presents a new fever and the clinical status worsens. A urinary tract infection is reported in 1–2% of febrile infants with bronchiolitis. Particular attention should be paid to infants <30 days of age with high fever (>39ºC) and localised fine crackles at lung auscultation because a bacterial pneumonia may be present. Another important point to consider when evaluating an infant with bronchiolitis is that the first clinical sign that manifests before the respiratory status worsens is a reduction in food intake during the previous 24 h, and this change should be evaluated carefully. Severe dehydration with metabolic acidosis and SIADH (syndrome of inappropriate antidiuretic hormone secretion) is common in infants with severe respiratory distress and can cause hyponatraemia and accidental fluid overload.

Admission criteria include respiratory distress, apnoea, tachypnoea, oxygen requirement, poor feeding, dehydration, a requirement for continuous clinical assessment of airway clearance, underlying chronic disease, and inappropriate social and family conditions.

The major discharge criteria are S_{pO_2} that remains stable at 94% in room air in the absence of respiratory distress for 4 h including during sleeping, and adequate daily oral intake (>75% of usual intake) at a level to prevent dehydration, followed by adequate parental care and family education about the potential duration of acute symptoms.

Indications for intensive care unit consultation and admission include failure to maintain S_{pO_2} >92% with oxygen therapy, deteriorating respiratory status with exhaustion and recurrent apnoea.

Supportive therapy

The key to managing infants with bronchiolitis is supportive treatment (figure 2). This consists of minimal handling, control of feeding, nasal suctioning and oxygen therapy. Physiotherapy has no role in infants with bronchiolitis unless the infant has a chronic disease. Heart rate, respiratory rate and S_{pO_2} should be monitored for at least the first 24 h. A small minority of patients with severe bronchiolitis need airway support by either CPAP or mechanical ventilation.

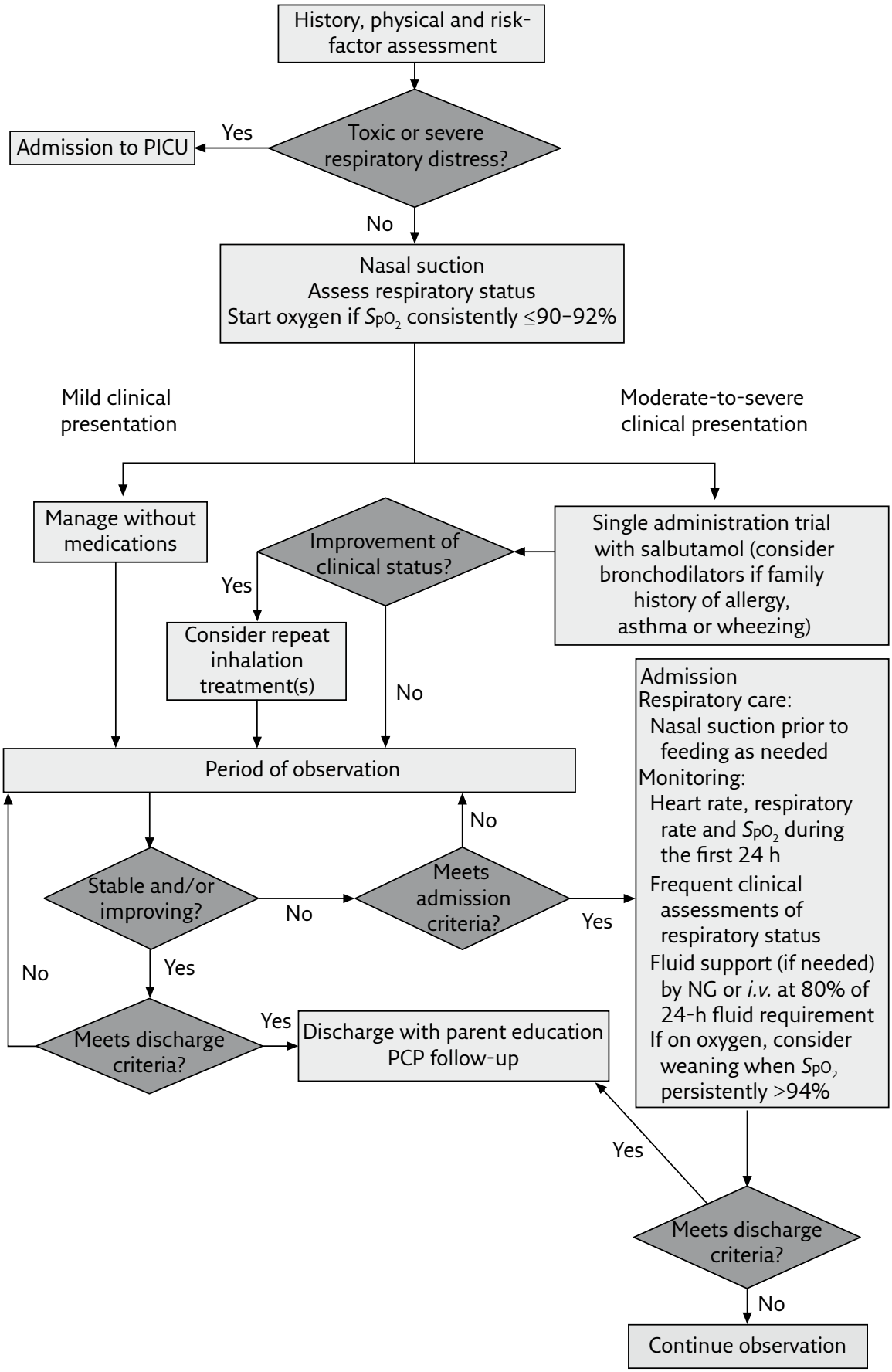

Figure 2. An algorithm for the management of bronchiolitis in the emergency department. PICU: paediatric intensive care unit; NG: nasogastric feeding; PCP: primary care physician.

In infants with mild bronchiolitis, breastfeeding should be supported and small volumes and frequent feeding should be encouraged. Nasogastric feeding or intravenous hydration should be considered in infants with severe bronchiolitis and dehydration. The amount of fluid to be given should cover the fluid loss and prevent dehydration and should not be >80% of the daily requirement to avoid fluid overload.

Cleaning the upper airways with saline is an important step in the initial management of infants with bronchiolitis. Nasal cleaning is recommended before feeding and when a child has difficulties in breathing and has apnoea episodes, but frequent deep nasal suctioning should be avoided.

According to the AAP, oxygen should be administered only when S_{pO_2} at room air is <90% in the absence of respiratory distress, while the National Institute for Health and Care Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN) guidelines recommend the use of oxygen when S_{pO_2} remains permanently <92%. Pre-warmed and humidified oxygen is usually administered with low-flow systems such as *via* a nasal cannula or head box. Recent evidence shows that oxygen can be given efficaciously with a heated humidified high-flow nasal cannula; its presumed role is reduction of the work of breathing, prevention of dynamic airways collapse and improvement of gas exchange by administering humidified, pre-warmed oxygen at a known inspiratory oxygen fraction (F_{IO_2}) and with a flow that should be a little higher than the infant's peak inspiratory pressure, usually 1–2 $L \cdot kg^{-1}$ of body weight. Several studies have demonstrated that while this technique does not shorten the disease course, it improves the work of breathing, thus reducing the need for intensive care and mechanical ventilation.

Indications for CPAP include severe respiratory distress, a need for an F_{IO_2} >0.5 or the presence of apnoea. It is hypothesised that the addition of heliox to CPAP, transforming turbulent into laminar gas flow, could improve the washout of carbon dioxide as well as oxygenation in the newly recruited airways, with a consequent decrease in the work of breathing. Unfortunately, the potential benefit of CPAP in preventing mechanical ventilation has not been evaluated.

Pharmacological therapy

Although bronchiolitis has a well-known pathogenesis, no effective medical treatment is yet available for this disease. Current clinical evidence shows that bronchodilators produce small short-term improvements in clinical scores. A trial with salbutamol is justified in infants with severe respiratory distress, but inhaled salbutamol should be continued only if clinical examination documents a significant clinical response (*e.g.* a decreased respiratory rate or an improvement in S_{pO_2}).

With regard to other bronchodilator agents, there is not enough evidence to justify the use of nebulised ipratropium bromide in infants with bronchiolitis, but nebulised racemic adrenaline has been demonstrated to provide better short-term improvements in the clinical score than placebo, particularly in the first 24 h. Clinical trials comparing adrenaline *versus* salbutamol found no admission differences for outpatients, but inpatients receiving adrenaline had a shorter hospital stay than those receiving salbutamol. Inhaled adrenaline should be continued only if clinical examination documents a significant clinical response.

Two recent multicentre randomised double-blind studies showed that 3% hypertonic saline did not change the length of hospital stay and duration of oxygen administration in hospitalised infants with bronchiolitis (Everard *et al.*, 2014; Teunissen *et al.*, 2014). Conversely, a recent Cochrane review of 28 trials showed that nebulised 3% hypertonic

saline alone or together with a bronchodilator reduced the length of hospitalisation among infants with nonsevere acute viral bronchiolitis and improved clinical severity scores in outpatient and inpatient populations (Zhang *et al.*, 2017). At present, there is insufficient evidence to recommend the use of hypertonic saline in hospitalised infants with bronchiolitis.

Current evidence provides no support for a clinically beneficial effect of systemic or inhaled glucocorticoids.

The use of antibiotics in bronchiolitis should be avoided because affected infants rarely undergo bacterial superinfection. Antibiotic treatment should be recommended only in infants with severe bronchiolitis requiring intubation, a group in whom bacterial superinfection is more common. Studies conducted on macrolides in infants with bronchiolitis do not suggest the use of these antibiotics.

Nebulised DNase and montelukast are not indicated in the treatment of bronchiolitis. In infants with a history of prematurity with episodes of apnoea, caffeine appears to be a rational choice of treatment.

Prevention and prophylaxis

Preventative measures include adequate healthcare professional education about epidemiology and control of viral infection, such as washing hands before and after caring for patients with viral respiratory symptoms and single rooms for infected patients. Equally importantly, adequate local policies should restrict hospital visiting by those with symptoms of respiratory infections.

Palivizumab is a humanised monoclonal anti-RSV antibody licensed for preventing the development of severe diseases arising from an RSV infection. Palivizumab prevents hospital admission for RSV infections but does not decrease the length of stay or oxygen requirements for those who are hospitalised. Palivizumab is a useful therapeutic option in infants <12 months of age who have severe comorbidity (extreme prematurity with or without BPD, significant congenital heart disease and, although not licensed for, congenital or acquired lung diseases, neuromuscular disease, Down syndrome and immunodeficiency).

Recently, a single injection of a new monoclonal antibody, nirsevimab, has been shown to reduce RSV-associated lower respiratory tract infections and hospitalisations in preterm babies.

Prognosis and follow-up

Mild respiratory symptoms may last for ~3 weeks after bronchiolitis. About 50% of children with bronchiolitis may have episodes of wheezing in later years. The most important risk factors for recurrent and persistent wheezing after bronchiolitis are rhinovirus infection and a positive family history for atopy.

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Pleural infection, necrotising pneumonia and lung abscess

Fernando Maria de Benedictis, Roberto Guidi and Giovanni Cobellis

Pleural infection

In childhood, pleural infection is usually a complication of community-acquired pneumonia. A parapneumonic pleural effusion (PPE) is present in up to 40% of pneumonia cases, and up to half of these may complicate further. Pleural infection is a continuum, but classically it has been divided into three stages according to the evolution of the inflammatory process: exudative (simple PPE), fibropurulent (complicated PPE) and, eventually, overt pus in the pleural space (empyema). In our setting, the term empyema is used generically to describe an advanced stage of PPE.

Streptococcus pneumoniae, *Staphylococcus aureus* and *Streptococcus pyogenes* are the main pathogens involved. Despite a declining incidence of childhood pneumonia after introduction of the seven-valent pneumococcal conjugate vaccine (PCV) into immunisation programmes, population rates of complicated pneumonia increased, mainly due to serotypes that were not contained in that vaccine. However, after introduction of the 13-valent PCV, rates of complicated pneumonia including empyema fell consistently.

Key points

- Rates of complicated pneumonia including empyema have fallen consistently after introduction of the 13-valent pneumococcal conjugate vaccine.
- The most common pathogens associated with empyema, necrotising pneumonia and lung abscess are *Streptococcus pneumoniae* and *Staphylococcus aureus*. Real-time PCR is significantly more sensitive than culture in identifying pathogens, in both pleural fluid and blood.
- Chest ultrasound is a useful tool in identifying complicated pneumonia. It can also be useful to guide chest drain insertion and to follow the evolution of the disease. Chest CT should be considered in selected cases (*e.g.* when there is diagnostic doubt).
- Pleural infection, necrotising pneumonia and lung abscess are serious conditions in children and deserve a systematic, multidisciplinary approach. Therapeutic choices should be evaluated individually. The long-term outcome of complicated pneumonia is usually good.

Mycoplasma pneumoniae and *Pseudomonas aeruginosa* are less common causes of PPE. In areas with a high prevalence of TB, *Mycobacterium tuberculosis* has increasingly been associated with presentation with acute pneumonia and pleural effusion.

Clinical features

The features of empyema can closely resemble those of an uncomplicated pneumonia, but pleural complication should be suspected in children who remain pyrexial or unwell 48 h after starting antibiotic therapy. Dull percussion and decreased breath sounds may be found. Judicious use of appropriate investigations can clarify what is often a difficult clinical diagnosis.

Imaging

Imaging studies help to confirm the clinical suspicion and to follow the evolution of the infectious process.

Chest radiography

Chest radiography is usually the first investigation that confirms the presence of PPE. Early signs include blunting of the costophrenic angle and a rim of fluid ascending the lateral chest wall (meniscus sign) (figure 1a). Large effusions may appear as a complete "white out" of the lung field, making it impossible to differentiate between pleural fluid and consolidated lung. Lateral chest radiographs are not necessary in most cases.

Chest ultrasound

Chest ultrasound offers several benefits such as wide availability, no need for sedation, low cost and no radiation exposure. It is a useful tool in identifying PPE and can differentiate pleural fluid from consolidated lung, estimate the size of the pleural effusion, and reveal fibrinous septations and fluid loculations. Chest ultrasound can also be useful to guide chest drain insertion and to follow the evolution of the disease.

Chest CT

Chest CT does not appear to be able to reliably distinguish the stage of pleural collection or to predict the outcome of pleural infection. While unnecessary for most cases of empyema, CT may be considered when there is diagnostic doubt (*i.e.*

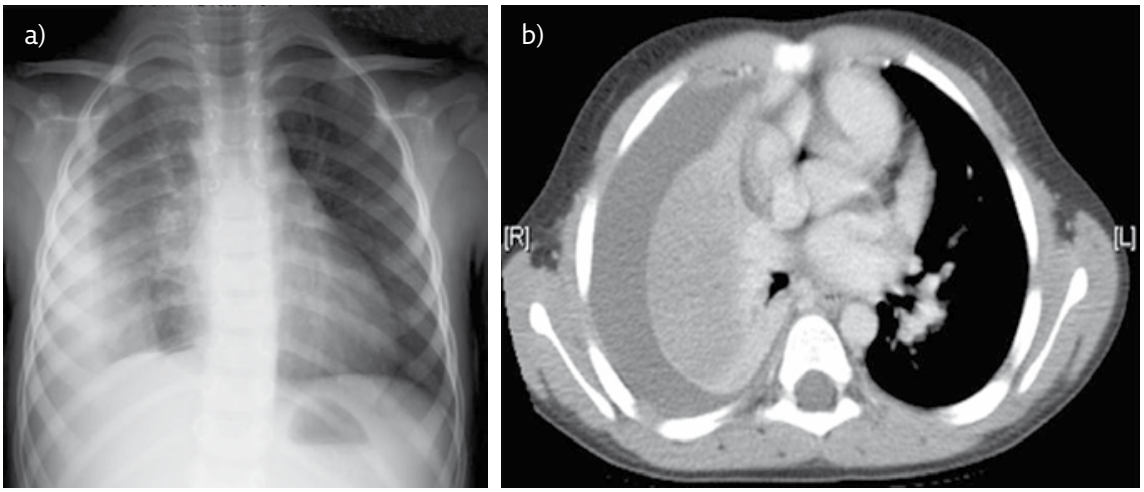

Figure 1. a) Pleural effusion, with blunting of the right costophrenic angle and a rim of fluid ascending the lateral chest wall. b) Empyema, showing a consistent amount of infected fluid in the right pleural space and a totally collapsed right lung.

blood-stained pleural fluid) or clinical improvement is not obtained after appropriate treatment (figure 1b). Many surgeons require chest CT to be performed before surgical intervention in order to delineate the anatomy further.

Laboratory tests

Acute-phase reactants

Acute-phase reactants such as white cell count, C-reactive protein, erythrocyte sedimentation rate and procalcitonin are unhelpful in distinguishing bacterial from viral pneumonia. However, an initial evaluation of acute-phase reactants should be obtained to provide supportive evidence for an infective aetiology of PPE. Serial measurements can be helpful in monitoring the progress of infection.

Blood cultures

Blood cultures provide a low isolation rate in PPE but occasionally may be positive when pleural fluid culture proves sterile.

Molecular tests

Real-time PCR of blood and respiratory specimens has become widely available, enabling rapid identification of pathogens. Real-time PCR was found to be significantly more sensitive than culture in identifying pathogens in paediatric empyema, in both pleural fluid (79.7% *versus* 12.5%) and blood (17.8% *versus* 7.4%) (Azzari *et al.*, 2019). Therefore, this technique should always be considered in the diagnostic approach, when available.

Sputum

Any available sputum should be sent for culture, as microbiological isolation is likely to represent the infecting organism from the lower airways. However, the low quality of specimens often obtained from children and the inability to distinguish colonisation from infection of the respiratory tract limit the usefulness of this analysis.

Pleural fluid

Any sample of pleural fluid should undergo biochemical (glucose, pH, lactate dehydrogenase and proteins), cytological (cell count and cell differential) and microbiological (Gram stain, acid-fast bacilli stain, culture, real-time PCR and antibiotic sensitivity testing) analysis.

Other analyses

In children, rapid detection of pneumococcal C polysaccharide antigens in urine has been shown to produce false-positive results, making this test unhelpful for diagnostic purposes. Mantoux testing and microbiology for *M. tuberculosis* should be performed if there is a predominance of lymphocytes in the pleural fluid or risk factors for TB are present.

Management

Despite empyema having been recognised for >2000 years, its management in childhood remains controversial, mainly because of the paucity of evidence-based studies at this age. The goals of treatment are sterilisation of the pleural cavity and drainage of excessive pleural fluid to allow re-expansion of the lung and restoration of the normal pleural fluid circulation. As management is harder in those with an advanced process, prompt recognition and treatment remain important. Preferably, children with empyema should be referred to a tertiary paediatric respiratory unit, particularly if the effusion is large or the child is unwell. The therapeutic choices should be evaluated individually and shared within a multidisciplinary team.

Antibiotics

There is undoubtedly a role for antibiotic treatment alone in children with mild PPE and no respiratory compromise. Most PPEs will respond to antibiotics without the need for further intervention. Decisions on empirical antibiotic therapy should be based on pneumonia treatment guidelines and should take into consideration whether the infection was community or hospital acquired, the local antibiotic resistance patterns and whether the child has any underlying medical problems (*i.e.* CF or immunodeficiency). Antibiotics should be modified accordingly once the causative pathogen and sensitivity are known. If culture results are negative, the adjustment may depend on the response of clinical, laboratory and imaging parameters.

Given evidence from epidemiological studies, it is imperative that initial antibiotics provide good *S. pneumoniae* cover, pending culture results. If there is radiological evidence of pneumatoceles, adequate staphylococcal cover is required. Anaerobic cover should be added if the child is at risk of aspiration. A second- or third-generation cephalosporin (cefuroxime, cefotaxime or ceftriaxone) or amoxicillin-clavulanate is often used empirically intravenously. In areas where there is a high prevalence of methicillin-resistant *S. aureus*, clindamycin or a glycopeptide can be used as an additional first-line agent. In children with a known allergy to penicillin, clindamycin should be considered. When *M. pneumoniae* infection is documented, treatment should also include a macrolide. Children with PPE caused by *M. tuberculosis* should be treated according to standard guidelines. Intravenous antibiotic therapy should be continued until there is definite evidence of clinical improvement and resolving fever, or at least until the chest drain is removed. While there is no evidence to guide the duration of treatment, oral antibiotics, such as amoxicillin-clavulanate or a second-generation cephalosporin, are generally continued for 2–3 weeks following discharge.

Thoracentesis

Thoracentesis is not recommended in children, unless there is a suspicion of a noninfectious aetiology. Unlike adults, the clinical relevance of the biochemical analyses of pleural fluid in children is modest. In addition, obtaining a sample of pleural fluid is technically challenging in children, requires sedation and results in a significantly higher re-intervention rate when compared with insertion of a pigtail catheter as the primary procedure.

Chest drain alone

Following the introduction of appropriate antibiotics, the decision to proceed to drainage should take into consideration a number of factors, including the clinical and laboratory response to antibiotic therapy at 48–72 h and evidence of an enlarging effusion on repeated ultrasound. Chest drain insertion alone can be effective in children with empyema, but the length of hospital stay is prolonged and the failure rate is higher than for a chest drain with intrapleural fibrinolytics.

Chest drain with fibrinolytics

The aim of instilling a fibrinolytic agent into the pleural cavity is to break down fibrin strands in order to improve drainage and re-establish pleural circulation. Urokinase is the preferred agent for the treatment of empyema, but alteplase is used in some countries. The most widely used dosage regimen of urokinase is 10 000 U in 10 mL of normal saline for children <1 year of age or 40 000 U in 40 mL of normal saline for children >1 year of age, which is administered every 12 h for 3 days. After instillation, the chest drain is clamped for 4 h and the child is encouraged to mobilise; the drain is left on a negative suction pressure of 10–20 cmH_2O until the next dose. There is some evidence that smaller catheters may reduce the time of drainage, the number of

days that the patient is febrile and the length of hospital stay. Possible complications such as bleeding are rare.

Video-assisted thoracoscopic surgery

Video-assisted thoracoscopic surgery (VATS) is a minimally invasive surgery technique that achieves debridement of fibrinous material, breakdown of loculations and drainage of pus from the pleural cavity under direct vision. The role of VATS *versus* a chest drain with fibrinolytics in the primary management of childhood empyema is a controversial area. A recent systematic review and meta-analysis of 10 studies in children with empyema showed that VATS and a chest drain with fibrinolytics had a similar incidence of perioperative complications, but VATS seemed to be associated with a reduced incidence of re-intervention and a shorter length of hospital stay (Pacilli *et al.*, 2019). However, the American Pediatric Surgical Association guidelines recommended that nonoperative intervention through chemical debridement should be the first-line therapy in childhood empyema, owing to decreased resource utilisation. It should be noted that both local policies and professional experience may affect the management, as in some settings VATS is preferred over a chest drain with fibrinolytics.

Open thoracotomy

Open thoracotomy enables removal of the thickened pleural rind and irrigation of the pleural cavity. Potential drawbacks include a large scar and the risk of wound infection, persistent air leaks and bleeding. Mini-thoracotomy involves a similar procedure through a small incision. A number of retrospective studies have compared VATS with open thoracotomy for rescue treatment, demonstrating less post-operative pain, better cosmetic results and, in some cases, a shorter length of hospital stay in children undergoing VATS. Open thoracotomy procedures should be reserved for late-presenting empyema with significant pleural fibrous rind.

A pathway for the evaluation and management of PPE in children is shown in figure 2.

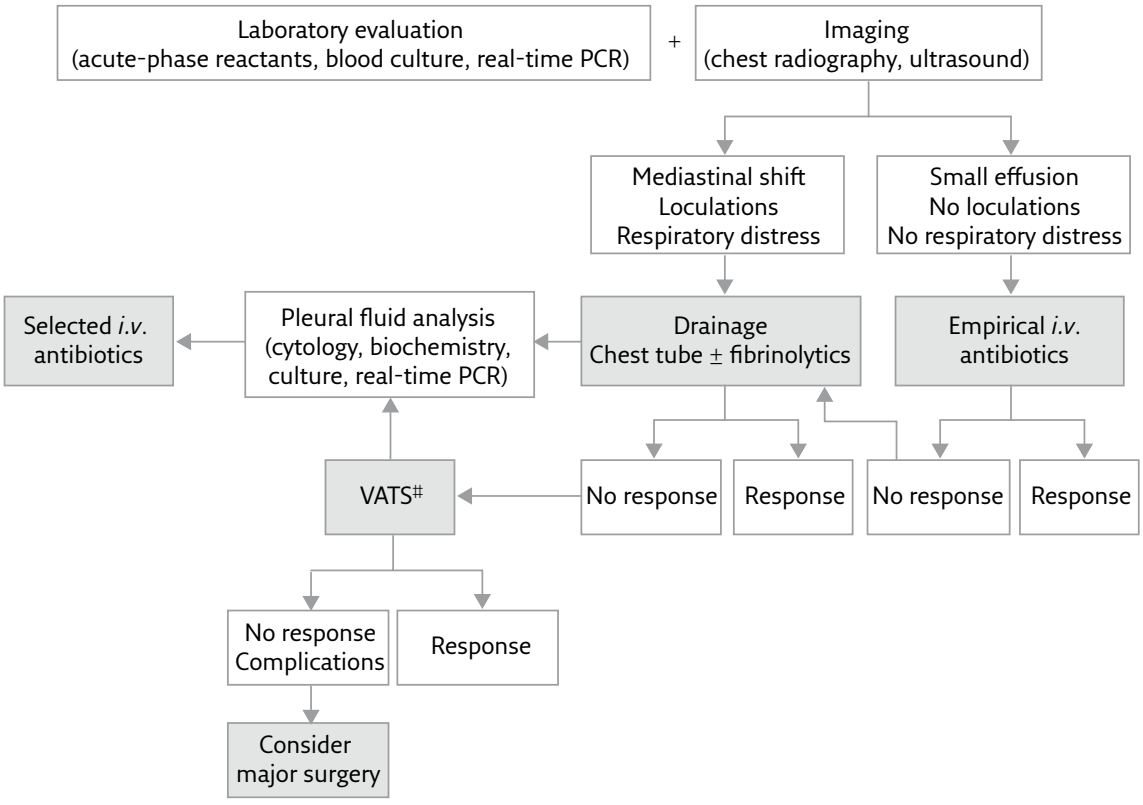

Figure 2. Pathway for the evaluation and management of PPE in children. #: occasionally consider VATS as the primary option (in place of a chest tube plus fibrinolytics).

Prognosis

The prognosis of childhood empyema is usually good. Unlike adults, empyema in children is associated with a low mortality (<0.5%), with the majority of children eventually making a complete recovery. Follow-up studies have shown that chest radiographs return to normal in almost all patients by 6 months and that lung function returns to normal or shows only minor abnormalities in the long term.

Pneumatoceles are generally complications of a staphylococcal pneumonic process; they may be associated with empyema and are more common in infants and young children. They usually regress spontaneously with improvement of the infectious process but may require surgical intervention when they become taut or infected, or break in the pleural cavity, thus inducing pneumothorax or pyopneumothorax. A bronchopleural fistula may occasionally be present.

Necrotising pneumonia

Necrotising pneumonia (NP) is a severe complication of community-acquired pneumonia and is characterised by extensive destruction and liquefaction of the lung tissue and loss of the pulmonary parenchymal architecture; cavitation of the lung and pleural effusion are frequent. In the last few years, increasing numbers of cases of NP in previously healthy children have been reported with a special emphasis on clinical, laboratory, pathological and radiological aspects. There are no recent data on the epidemiology of NP. However, there is consistent evidence that routine immunisation with the 13-valent PCV has reduced the global burden of complicated pneumonia without increasing pneumonia due to other bacteria and without pneumococcal serotype shift.

S. pneumoniae is the most frequent aetiological agent of NP, as in empyema. *M. pneumoniae* and *S. aureus* strains, often methicillin-resistant and producing the cytotoxin Panton–Valentine leukocidin, have also been involved in the genesis of NP. Other bacteria less frequently reported include *S. pyogenes*, *Streptococcus viridans*, *P. aeruginosa* and anaerobes. Influenza virus and other viruses may occasionally be responsible agents.

The pathogenic mechanisms of NP are not clear, but it is commonly believed that tissue necrosis is the result of the inflammatory response due to toxins produced by the invasive pathogen or the associated vasculitis with thrombotic occlusion of alveolar capillaries. Lung consolidation and fluid-filled cavitary lesions are typical of the initial stage. Lung necrosis rapidly progresses to parenchymal destruction and development of intraparenchymal bullae, irrespective of antibiotic therapy. Cavitary lesions are generally limited to a single lobe, but multilobular involvement may also be present. Due to tissue liquefaction, multiple small cavities may coalesce and form larger cavities, including air-filled pneumatoceles. The process may extend further to the pleural space and create bronchopleural fistulas, especially when the necrotic segment is adjacent to the pleural surface.

Clinical features

Children with NP usually present with symptoms of severe pneumonia, such as high fever, cough and tachypnoea, lasting for several days. NP should be suspected when a patient with pneumonia develops progressive respiratory distress, haemoptysis or septic shock, despite appropriate antibiotic treatment. Pleural effusion is often detectable on physical examination.

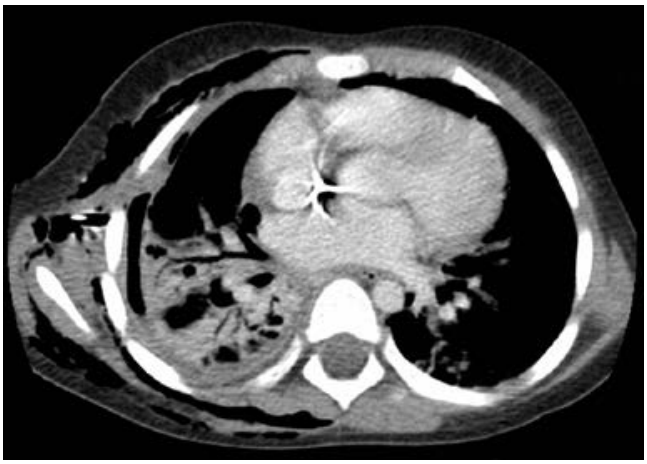

Figure 3. Necrotising pneumonia, with multiple cavitary lesions and an air bronchogram in the consolidated right upper lobe.

Imaging

Chest radiography

Chest radiography underestimates the degree of parenchymal destruction. In the initial phase, fluid-filled cavitary lesions have the same density as adjacent consolidated lung and are unlikely to be identified using this technique.

Contrast-enhanced CT

Contrast-enhanced CT can reveal early changes in lung parenchyma. The CT criteria for NP include loss of the normal lung architecture and the presence of areas of decreased parenchymal enhancement, representing liquefaction, which are progressively replaced by multiple air- or fluid-filled cavities (figure 3). Although CT is sensitive in terms of identifying parenchymal complications, clinical management is not changed in most cases, and routine use is therefore not justified.

Chest ultrasound

This is effective for early detection of parenchymal lesions and may also be useful for follow-up.

Laboratory tests

Increased acute-phase reactants, a low haemoglobin level and hypoalbuminaemia are observed in most patients. Almost 50% of cases of NP have no identified aetiological cause using common microbiological methods. However, the use of real-time PCR has greatly increased the diagnostic yield.

Management

The optimal management of NP remains controversial, with options ranging from a conservative approach to radical surgery with lung resection.

Antibiotics

Exclusive treatment with high-dose antibiotics is frequently successful in children, with unexpected parenchymal conservation and lung re-expansion over time, even in cases of severe pulmonary involvement. As with empyema, the choice of initial antibiotics should be directed at broad coverage of commonly implicated pathogens and modified accordingly once the causative agent and sensitivities are known. Penicillins or cephalosporins may be administered initially, while clindamycin or

metronidazole can be added to cover possible involvement of *S. aureus* or anaerobes, especially if aspiration is suspected.

Interventional procedures and surgery

Complicated PPE is frequently associated with NP. When pleural effusion is present, treatment generally reflects that of empyema, but some caution should be maintained. Due to the high risk of fistulation, a chest drain should be positioned by expert hands and removed as soon as possible.

Intrapleural fibrinolytics should be avoided, as breakdown of the fibrinous sealing reaction may favour air leaks from necrotic peripheral areas of the lung. The indication and timing for VATS in NP are not clear, but the illness severity and nature of the pleural effusion can guide the choice. The risk of fistulation due to intrapleural manoeuvring should, however, be taken into consideration.

Lung surgery is rarely necessary and should be reserved for particularly severe bronchopleural fistulas or large pneumatoceles resistant to conservative treatment.

Prognosis

The long-term outcome of NP in childhood is usually good. Follow-up imaging studies have shown almost complete normalisation of pulmonary parenchyma within months of hospitalisation. This pattern of improvement suggests that the lung damage caused by NP in children is transient, and no or minimal functional sequelae are expected.

Lung abscess

A lung abscess is a thick-walled cavity containing purulent material that results from suppuration and necrosis of the lung parenchyma. It is an uncommon paediatric condition with a paucity of quality data in the literature.

There is usually a single lung abscess, but multiple abscesses may be present less frequently. Classically, lung abscesses are divided into primary and secondary, based on the existence of predisposing comorbidities, such as neurocognitive disability, immunodeficiency, CF or congenital lung malformation (*e.g.* pulmonary sequestration). Lung abscesses may develop in any area of the lung but are more frequent in the lower lobes.

A lung abscess may be the consequence of a primary infection of the lung, often due to aspiration of infected or noninfected fluid (*i.e.* gastric content), or may arise from haematogenous spread of septicaemia in the lung. Alternatively, it may represent the local extension of an infection from a contiguous organ, such as an abdominal collection. The time course for progression from initial involvement to abscess formation is usually slow.

S. aureus, group B *Streptococcus*, *Escherichia coli* and *Klebsiella pneumoniae* are common pathogens in young children. In older children, the likelihood of aspiration increases, and oral anaerobic bacteria (*e.g. Peptostreptococcus and Fusobacterium* spp.) or mixed flora may be found. More rarely, *M. pneumoniae* or fungi such as *Candida albicans* or *Aspergillus* spp. can cause lung abscesses in children.

Clinical features

Children may present for several days with a low-grade cough and mild fever. Less commonly, chest pain, dyspnoea, sputum production and haemoptysis are present. The clinical history is important in revealing predisposing conditions. A physical examination may reveal normal chest auscultation or signs of consolidation.

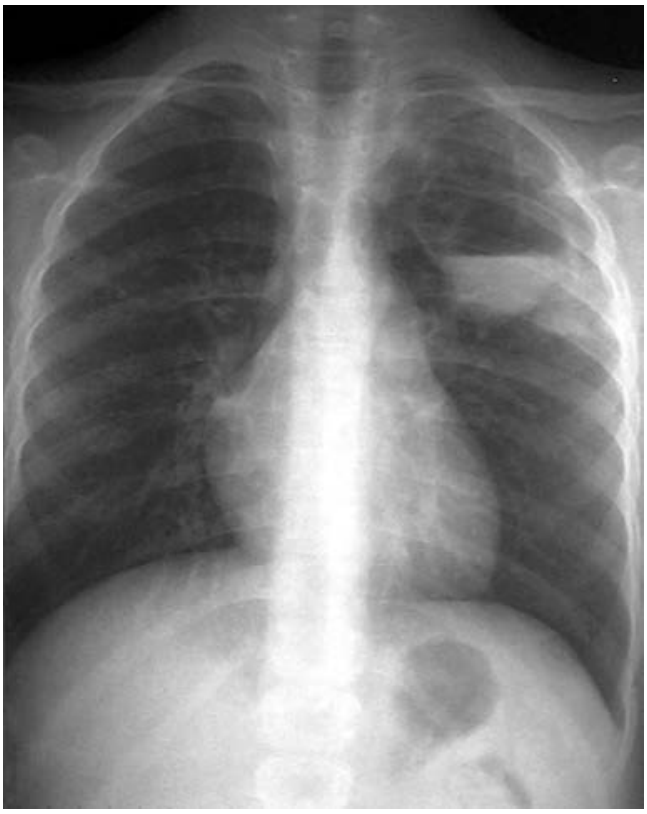

Figure 4. Lung abscess, visible as a well-circumscribed shadow containing an air–fluid level in the left upper lobe.

Imaging

Traditionally, the diagnosis of lung abscess is based on chest radiography, which will reveal a well-demarcated shadow often containing an air–fluid level (figure 4). Ultrasound is effective in revealing the characteristics of lung abscesses and the distinction between parenchymal abnormalities and pleural collections, and in assessing the response to treatment. CT may be reserved to resolve diagnostic doubt or to visualise the lung for surgical planning.

Laboratory tests

Image-guided aspiration and drainage of the abscess cavity through a percutaneously placed pigtail catheter are often used for diagnostic purposes. This interventional procedure, combined with new microbiological techniques such as real-time PCR, has increased the yield of pathogens identified from abscess fluid samples.

Management

Antibiotics

Treatment with a course of high-dose, *i.v.* antibiotics will successfully treat a lung abscess in most cases. The choice and duration of antibiotic therapy will be guided by the type of abscess (primary or secondary) and the ability to isolate the aetiological agent. Antibiotics should cover *S. aureus*, *Streptococcus* spp. and Gram-negative bacilli that are usually found in the upper respiratory tract. Treatment may include cephalosporins, vancomycin, clindamycin, aminoglycosides, quinolones and carbapenems. If anaerobic infection is suspected, metronidazole should be considered. Generally, a 2–3-week course of *i.v.* antibiotics is sufficient to induce clinical and radiological improvement of the lesion. Once the child has improved, oral antibiotics may replace the *i.v.* route to complete a 4-week treatment course.

Interventional procedures and surgery

Image-guided drainage of the abscess cavity through a pigtail catheter may be used in combination with antibiotic therapy. Occasionally, thoracoscopic drainage may be obtained concurrently with treatment of empyema. Major surgery should be limited to the few patients who are refractory to medical treatment.

Prognosis

Complications of a lung abscess may include pneumothorax, bronchopleural fistula, lung compression and mediastinal shift with progressive respiratory compromise. The existence of underlying conditions will influence the prognosis. The long-term outcome of lung abscesses in immunocompetent children is generally favourable, and most recover uneventfully with no pulmonary sequelae.

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Mycobacterial infection and disease

James Paton

TB is a bacterial infection caused by *Mycobacterium tuberculosis*. This is the main pathogen within the *M. tuberculosis* complex of organisms, a genetically related group of slow-growing *Mycobacterium* spp. that can cause TB in humans and other animals. Mycobacteria are slender, nonmotile rods with lipid-rich cell walls that are identified as acid-fast by Ziehl–Neelsen staining.

Burden of TB infection and disease in children

In children, TB occurs most commonly in those <5 years of age. Pulmonary TB is the main form in most populations, but occurrence at body sites other than the lung (extrapulmonary TB) is also common (~30–40% of cases).

The World Health Organization (WHO) estimated that in 2017 there were at least 1 million new active TB cases in children (<15 years) and around 250 000 TB-related deaths, amounting to ~10% of total cases and 15% of deaths.

Children who develop TB disease usually develop it within 1 year of infection. Childhood TB therefore provides a marker of recent transmission in the community and hence of wider TB control in the population. However, TB in children has been called a "hidden epidemic" because poor ascertainment and under-reporting of cases have hindered accurate estimates of the burden of TB in children. The WHO estimated that in 2016 only 40% of the ~1 million children with TB were notified to national TB programmes.

Reasons for underestimating TB in children include the following:

- Nonspecific symptoms, which often occur in children with TB.
- Difficulties in confirming a case of childhood TB. Children <10 years develop paucibacillary types of TB and are usually not infectious in comparison with

Key points

- Globally, TB remains a major but often unrecognised cause of disease and death in children.
- Children with TB are usually not infectious.
- TB in children generally reflects active disease in the adult population.
- Diagnosing TB in children remains a challenge, and their treatment is not straightforward.

adults with caseating pulmonary TB. Because cough is also less effective, young children are often unable to produce sputum, and the combination of ineffective sputum production and the low concentration of organisms in children makes bacteriological confirmation challenging. Fewer than 30% of paediatric cases will have bacteriological confirmation of TB.
- TB/HIV coinfection. Children are also susceptible to the dual epidemic of TB/HIV, with HIV infection increasing the incidence of TB in children by a factor of ~8, rising with the degree of immunosuppression. However, children who have TB and who are HIV positive when they die are classified internationally as having died from HIV.
- A lack of awareness of multidrug-resistant (MDR) TB in both adults and, particularly, children.

In Europe in 2017, children (<15 years) accounted for 4.4% of all new and relapsed TB cases, with a notification rate of 2.9 per 100 000 of the population. While rates in children in Europe have been declining over the last 5 years, many children still suffer from TB, with wide variations in rates within and among countries.

Natural history in children

The natural history and presentation of *M. tuberculosis* infection in children is different from that in adults, being strongly influenced by age and immune status.

Infection following exposure

M. tuberculosis infects almost all children *via* respiratory tract inhalation of aerosolised particles that are released into the air by an index case with active TB. This is usually an adult in close contact with the child, usually in their household environment, who is coughing and infectious. A number of factors influence the clinical outcomes following infection:

- Closeness of contact with an infectious (especially a smear-positive) case of pulmonary TB: the WHO defines a "close contact" as a person who shares an enclosed space such as a social gathering place, workplace or facility with the index case for extended daytime periods during the 3 months before the start of a treatment episode
- Age: children <2 years have the highest risk of developing TB
- Impaired immune status (*e.g.* due to HIV infection)
- Poor nutritional status
- Bacillus Calmette–Guérin (BCG) vaccination status
- Genetic susceptibility
- Microbial virulence

In the pulmonary alveoli, *M. tuberculosis* organisms are immediately ingested by resident phagocytes including alveolar macrophages and dendritic cells, and may be killed without causing further problems (figure 1).

Organisms that survive initiate a localised granulomatous inflammatory process in the mid- to upper zones of the lung. In most cases, the centre of this focus undergoes caseous necrosis (the Ghon focus). *M. tuberculosis* bacilli, either free or within phagocytes, drain into the main regional, mediastinal lymph nodes (hilar, paratracheal and subcarinal), which also often caseate. Enlarged regional lymph nodes along with the Ghon focus and the local tuberculous lymphangitis constitute the "primary complex". These enlarged regional lymph nodes can be seen in 50–70% of children on good-quality plain radiographs.

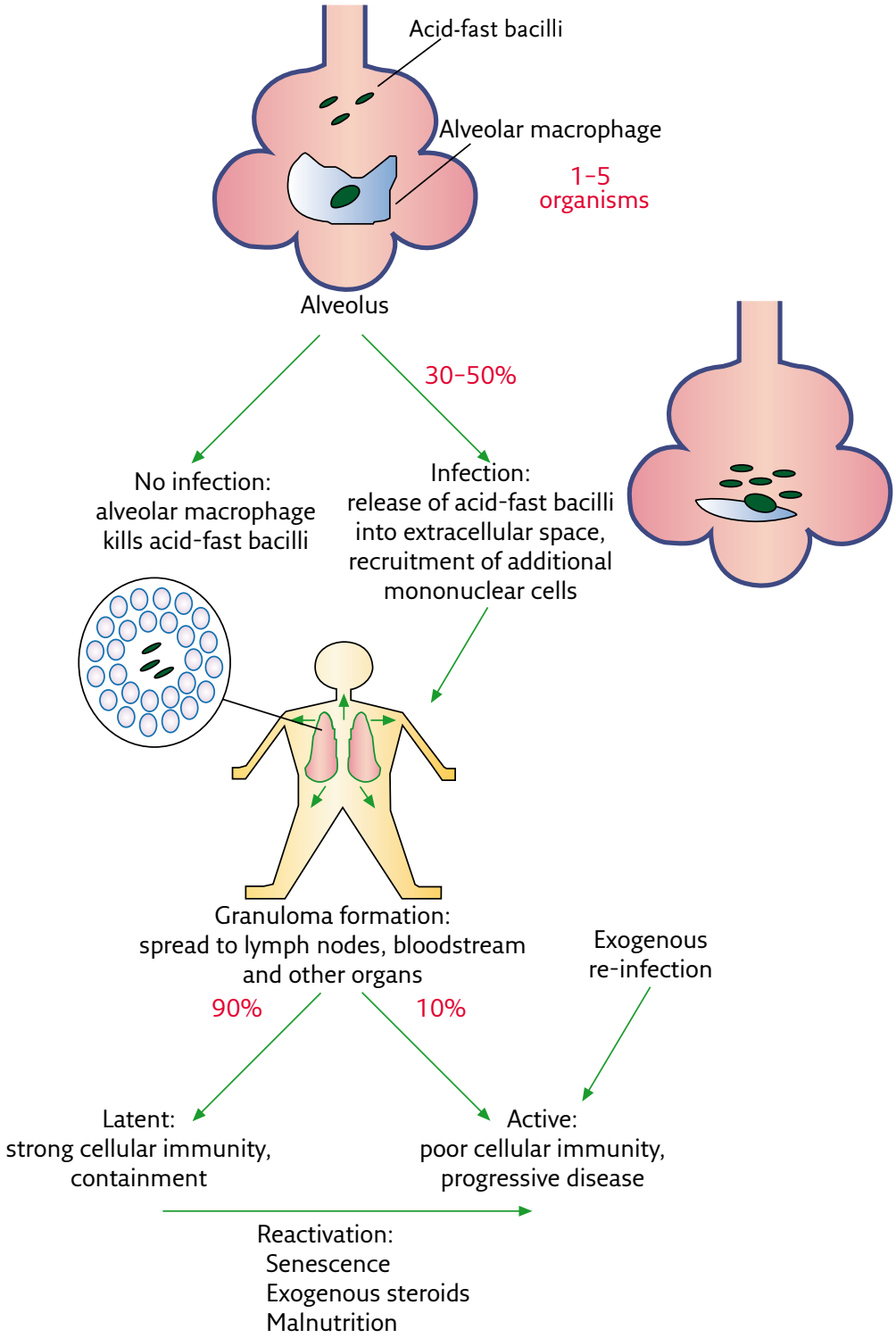

Figure 1. Outcomes following exposure to M. tuberculosis. *The percentages in red are typical of outcomes in older children and adults. Reproduced and modified from Manabe* et al. *(2000) with permission.*

From the regional lymph nodes, bacilli enter the systemic circulation. Occult haematogenous spread can occur before an immune response develops and contains the disease. The disseminated bacilli can then survive in target organs for long periods.

Development of an immune response

The immune response, as indicated by the development of a positive tuberculin skin test (TST), develops ~3–8 weeks after primary infection and usually stops the multiplication of *M. tuberculosis*.

In the terminal alveoli, activated macrophages infected with *M. tuberculosis* induce the synthesis and secretion of chemokines and cytokines, which recruit other inflammatory cells to the site of infection. The dendritic cells, which are the major antigen-presenting cells in the lung, migrate to regional lymph nodes where they present processed *M. tuberculosis* antigens to naïve $CD4^+$ T-cells *via* major histocompatibility complex class II molecules. The antigen presentation by dendritic cells with the aid of costimulatory molecules such as CD80 and polarising cytokines such as interleukin (IL)-12 promote the priming, proliferation and differentiation of naïve $CD4^+$ T-cells into *M. tuberculosis*-specific $CD4^+$ T-cells with T-helper type 1 (Th1) effector function. These cells produce classical Th1 cytokines including interferon (IFN)-γ, tumour necrosis factor-α and IL-2. IFN-γ produced by the *M. tuberculosis*-specific $CD4^+$ T-cells is critical for the optimal activation of infected macrophages into cells that are microbicidal and can kill the phagocytosed bacilli and thus protect against TB.

Clinical progress following infection

The end of the asymptomatic incubation period and the development of an immune response may be marked by immune hypersensitivity reactions. These include nonspecific, self-limiting, viral-like symptoms such as fever or, more rarely, florid reactions such as erythema nodosum. In most cases, a child will have no symptoms.

In the majority of children, the primary complex heals completely and the organisms are contained by the cell-mediated immune response within the tissues. In up to 50% of children, the regional lymph nodes calcify within 12–24 months, indicating that the disease is quiescent. However, *M. tuberculosis* can persist in calcified lymph nodes, and dormant organisms may reactivate to cause TB later in life. The proportion of people who continue to harbour potentially viable pathogenic *M. tuberculosis* bacteria has been debated, but recent estimates suggest it is between 1% and 10% of people with evidence of TB immunoreactivity.

Following primary infection, a parenchymal pulmonary lesion sometimes continues to enlarge and spread, resulting in focal pneumonitis and pleural involvement (primary progressive TB).

Enlarged mediastinal lymph nodes do not usually cause problems, but they can compress the airways, producing ventilation disturbances and, occasionally, complete bronchial obstruction and distal atelectatic changes in the affected segment.

If caseating lymph nodes liquefy, there may be local extension and distant haematogenous spread of *M. tuberculosis*. If the lymph nodes are subcarinal, infection can spread to adjacent structures such as the heart, causing pericarditis. Haematogenous spread seeds *M. tuberculosis* into other tissues and organs. Disseminated TB appears when multiple foci develop in the lungs or other organs.

Time course following infection

The natural history of primary TB in children follows a typical time course. The risk of disease progression and extrapulmonary dissemination is highest within the first 2 years of life, with the risk of progression estimated at 40–50% in the absence of BCG vaccination or prophylactic therapy (table 1). The very young (0–4 years) and the immunocompromised are most at risk. Pulmonary disease accounts for the majority of cases (figure 2). Lymphohaematogenous dissemination leading to miliary or another disseminated disease is uncommon and occurs overall in 0.5–2% of cases, usually between 3 and 39 months after lymph node involvement (table 1). Bone and joint TB develop later, usually a few years after infection.

Table 1. Average age-specific risk for disease development following primary infection

Age years[#]	Disease[¶]	Risk of disease %
<**1**	No disease	50
	Pulmonary disease (Ghon focus, lymph node or bronchial)	30–40
	TBM or miliary disease	10–20
1–2	No disease	70–80
	Pulmonary disease (Ghon focus, lymph node or bronchial)	10–20
	TBM or miliary disease	2–5
2–5	No disease	95
	Pulmonary disease (lymph node or bronchial)	5
	TBM or miliary disease	0.5
5–10	No disease	98
	Pulmonary disease (lymph node, bronchial, effusion or adult-type)	2
	TBM or miliary disease	<0.5
>**10**	No disease	80–90
	Pulmonary disease (effusion or adult-type)	10–20
	TBM or miliary disease	<0.5

TBM: tuberculous meningitis. [#]: at primary infection; [¶]: in immunocompetent children (dominant disease entity indicated in parentheses). Reproduced and modified from Marais *et al*. (2004) with permission of the International Union Against Tuberculosis and Lung Disease. Copyright © The Union.

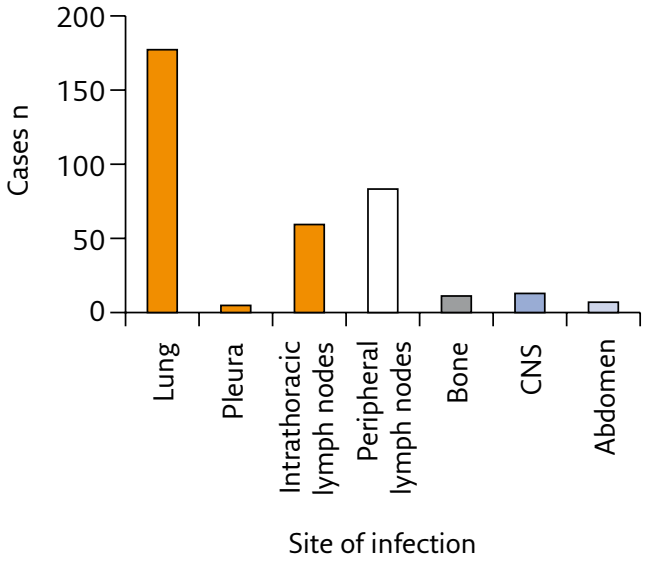

Figure 2. Sites of disease in children with TB in the UK, 1988–1998. Orange bars indicate pulmonary disease. CNS: central nervous system. Data from Balasegaram et al. *(2003).*

Around puberty, the risk rises again, and there is a switch in disease phenotype to adult-type cavitary disease. Adult-type disease can follow recent primary infection in children >10 years, particularly in girls around the age of menarche.

Only a small proportion of children with TB develop post-primary TB, due to either re-activation or re-infection.

Role of age-related and impaired immune responses in clinical manifestations of TB

It is well established that less mature or impaired immune responses contribute to the disseminated forms of TB seen in children and immunocompromised hosts.

A number of studies have reported an age-related functional impairment of both innate and adaptive immune responses in children. The current paradigm in TB immunology is the crucial importance of *M. tuberculosis*-specific $CD4^+$ T-cells and key cytokines such as IFN-γ produced to protect against *M. tuberculosis*. However, *M. tuberculosis*-specific IFN-γ responses alone are not an absolute correlate of protection against the development of TB. Specifically, it has been reported that alveolar macrophages in children show diminished phagocytosis, cellular recruitment and microbial killing when compared with those of adults, which could allow delayed initiation of antigen-specific T-cell responses and promote disease progression. These immunological differences may reflect the immaturity of the immune response and might explain the high rate of disease progression seen in young children.

Apart from intrinsic deficiencies in cell-mediated immune responses in children, there are other primary and acquired causes of immunosuppression that could further increase the risk of TB disease progression in children.

Genetic susceptibility to TB

Further evidence of the importance of the cell-mediated immune response and the IFN-γ-mediated Th1 response in protection against *M. tuberculosis* infection has come from genetic studies reporting an increased risk of progressive disease related to specific genetic defects affecting the IL-12/IFN-γ pathway.

Mendelian susceptibility to mycobacterial diseases is a familial inherited disorder particularly associated with an increased susceptibility to severe disseminated mycobacterial diseases that often manifests in childhood. Affected children have a diminished ability to induce activation and upregulation of the killing mechanism of *M. tuberculosis*-infected macrophages because of a number of specific mutations in the genes encoding major components of the IL-12/IL-23–IFN-γ axis of the Th1 cytokine pathway. A number of mutations have been identified in autosomal genes including *IFNGR1* (encoding IFN-γ receptor 1), *IFNGR2* (IFN-γ receptor 2), *STAT1* (signal transducer and activator of transcription 1), *IL12P40* (IL-12 p40 subunit), *IL12RB1* (IL-12 receptor β1 chain), *TYK2* (tyrosine kinase 2) and *NEMO* (NF-κB essential modulator).

Acquired susceptibility to TB due to HIV infection

The most compelling evidence for the crucial role of $CD4^+$ T-cells in protection against mycobacterial infection is the increased risk of infection, re-activation and progression to TB disease in individuals with HIV coinfection. A number of studies have reported a higher risk of TB and worse survival among HIV-infected children compared with HIV-negative children with TB, while the reported risk of disseminated BCG disease (so-called BCG-osis) in HIV-infected children has prompted the WHO to recommend avoiding BCG vaccination in newborns with a known HIV-positive status.

Although the attributable effect of the HIV epidemic on the burden of TB in children is less well defined than in adults, the HIV epidemic has resulted in a shift of TB disease burden to younger adults, resulting in increased exposure of both HIV-infected and -uninfected children at a very young age. HIV infection is known to be a strong risk

factor for TB, a risk that is further increased in HIV-infected children by their younger age and underlying immune status as defined by the $CD4^+$ count and viral loads.

Transplant-related immunosuppression

Impairment of immune control of *M. tuberculosis* can also result from immunosuppression, as a result of disease and/or treatment in solid-organ transplants and/or haematopoietic stem-cell transplants. Lung transplantation has the highest risk of such donor-derived transmission and of post-transplant TB. As such, the incidence of TB and its associated mortality is higher in transplant recipients than in the general population and the incidence is directly proportional to the endemicity of *M. tuberculosis* infection in the general population. These risks are further amplified in paediatric transplant recipients due to immunosuppression. Efficient pre-transplant risk assessment and screening of both the transplant recipient and the donor or donor organ is an important part of the management of recipients, allowing preventative intervention in the pre- and/or post-transplant period.

Helminth infestation

Several studies have suggested that helminth infection could downregulate the protective immune response against *M. tuberculosis*, thereby facilitating progression to active TB disease. Heavy helminth infection in humans has been shown to be associated with a generalised state of immune hyporesponsiveness, probably facilitated through immunoregulatory pathways that are also involved in mycobacterial control.

Malnutrition

Evidence of an association between malnutrition and the risk of TB is derived largely from observational studies in humans, experimental studies in animal models and *in vitro* studies. However, it is still unclear whether malnutrition facilitates TB or whether TB leads to malnutrition. Similarly, the effects of different forms and degrees of malnutrition or micronutrient deficiencies and the population-attributable risk due to malnutrition in communities where both TB and malnutrition are endemic remain to be defined.

Vitamin D deficiency

Vitamin D deficiency is associated with TB among children and immigrants in low-endemic settings, as well as in people in TB-endemic settings, regardless of HIV status. A seasonal variation in the notified cases of TB related to exposure to ultraviolet light and vitamin D deficiency has also been reported from several populations. Vitamin D, through its active metabolite 1α,25-dihydroxyvitamin-D3, contributes to the host immune protection against TB through "nonclassical" mechanisms including upregulation and activation of antimicrobial peptides such as cathelicidins, promoting IFN-γ-induced activation of *M. tuberculosis*-infected macrophages, and maturation and activation of dendritic cells.

Sites of disease

Pulmonary TB

The chest is the most common site of involvement in children, with the lungs most frequently affected, followed by the intrathoracic nodes and the pleura (figure 2).

More than half of children with chest radiographic changes of TB will have no symptoms or clinical signs of disease and are identified only through contact tracing. Infants may have more intensive symptoms of TB, while school-age children may have disease that is not clinically apparent. Adolescents develop adult-type TB and can present with parenchymal destruction and cavity formation, leading to them becoming sputum smear positive and able to transmit infection.

Extrapulmonary TB

Extrapulmonary TB is also common in children. It develops by lymphohaematogenous spread of *M. tuberculosis* from a primary pulmonary focus, or from contiguous spread from infected lymph nodes or direct inoculation with the development of foci in various organs. The risk of both disease progression and extrapulmonary TB is highest in the first 2 years of life (table 1).

Lymph node TB

Superficial tuberculous lymphadenitis is the most common site of extrapulmonary infection (figure 2).

Typically, lymphadenitis presents 6–12 months after initial TB infection as nontender, nonerythematous solid masses 2–4 cm in diameter, with the anterior cervical lymph nodes being most frequently affected. They may become matted together and develop into a chronic discharging sinus. Constitutional symptoms such as fever, fatigue and failure to thrive are observed in >50% of children. Infants are rarely affected.

Central nervous system TB

Central nervous system (CNS) TB constitutes ~13% of all cases of extrapulmonary TB in children and complicates the clinical course of TB in 0.5–2% of cases. CNS TB develops 3–6 months after primary infection, usually in children <2 years of age.

Tuberculous meningitis (TBM) is the most common form of CNS TB (~95% of cases); tuberculomas and cerebral abscesses are less common. The spinal cord is rarely involved. TBM is very rare in countries with a low TB prevalence.

TBM is a devastating illness. It may develop acutely but more commonly evolves more slowly than other forms of bacterial meningitis. Serious neurological sequelae develop in almost 50% of cases and overall mortality is ~13%.

Miliary TB

Classic miliary TB refers to millet seed-like nodules (1–5 mm) of TB bacilli in the lung that are visible on chest radiography. Very young and/or immunocompromised children, such as those who are HIV infected or severely malnourished, are usually affected.

Miliary TB tends to develop soon after primary infection. Progressive symptoms similar to other forms of pulmonary TB develop over days or weeks. The illness can progress rapidly and the prognosis is poor. Typical miliary changes on chest radiography take ~1–3 weeks to develop (figure 3).

Pleural TB

Pleural TB is reported in 2–38% of cases in children and may be a manifestation of primary or re-activation disease. Primary pleural TB results from a hypersensitivity reaction to bacilli in the pleural space. The effusion usually develops 6–12 weeks after infection. Pleural effusions are rare in children <5 years and are most common in adolescent boys. Effusion is usually unilateral and more common on the right.

Other forms of extrapulmonary TB

Pericardial TB, bone and joint TB (mainly monoarticular involving the spine, hip or knee) and abdominal TB affect ~1–2% of children with TB.

Congenital TB

M. tuberculosis infection may be acquired before birth during intrauterine life, perinatally or post-natally. In a pregnant woman with active TB, *M. tuberculosis* can

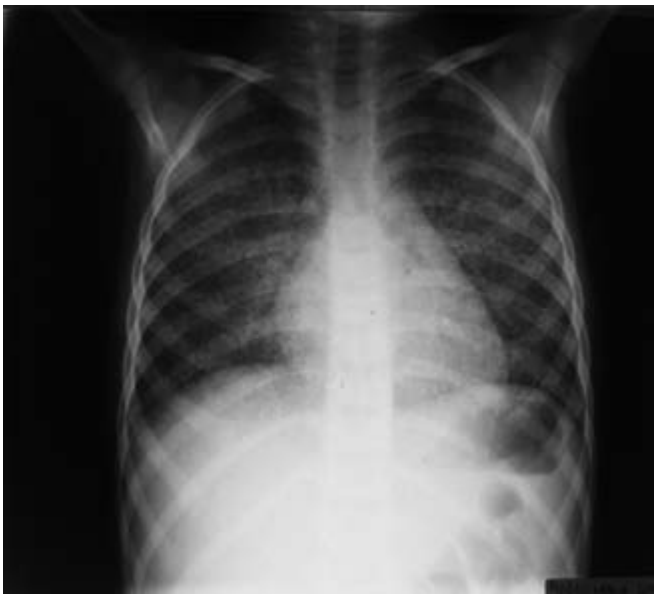

Figure 3. Chest radiograph of a 2-year-old boy with miliary TB, showing a bilateral distribution of miliary nodules.

be transmitted transplacentally from the bloodstream of the mother to the fetal blood. Once in the fetal circulation, the organisms spread *via* the umbilical veins to the tissues and organs, mainly to the liver and spleen. Symptoms (failure to thrive, jaundice and hepatosplenomegaly) develop within a couple of weeks after birth.

A newborn infant may also acquire *M. tuberculosis* infection during delivery or soon after through close contact with an infectious case, such as a breastfeeding mother. In this situation, nonspecific respiratory symptoms develop after 3–4 weeks. Chest radiography is not diagnostic, and a test of TB immunoreactivity (*e.g.* TST) may be negative.

Diagnosing TB

History and examination

Children are usually evaluated for TB either after presenting with symptoms or signs suggestive of TB (passive case finding) or, most commonly in low-prevalence countries, as a result of contact investigation or new entrant immigrant screening (active case finding). Children detected through active case finding often have either TB infection or TB disease in a very early phase.

History of close exposure

A history of close exposure to an infectious index case is a key piece of diagnostic information. The WHO defines close contact as living in the same household as, or being in frequent contact with, a sputum smear-positive pulmonary TB case. Cases of smear-negative TB that are sputum culture positive are also infectious but to a much lesser degree.

The infection risk from close household contact is greatest for infants and young children <5 years (table 1). Young children are particularly likely to have contracted TB at home. The contact is commonly recent, because children usually develop TB within 1 year of infection.

Symptoms consistent with TB

In children identified through active case finding who have radiographic changes indicative of pulmonary TB, more than half will have no symptoms or signs of disease.

In children, well-defined symptoms of recent onset that are persistent and nonremitting are typical of TB, *i.e.* symptoms that persist for >2 weeks without sustained improvement or resolution after treatment of other possible diagnoses (*e.g.* antibiotics for pneumonia). The five most relevant symptoms in a community study in South Africa were cough, chest pain, weight loss, fatigue and fever (Marais *et al.*, 2005). Both persistent cough and/or persistent fatigue of recent onset were highly sensitive and specific markers of TB. A persistent nonremitting cough in childhood was almost exclusively associated with TB. As a result, in this setting, clinical follow-up was a useful diagnostic tool because a nonremitting cough lasting >2–4 weeks was uncommon other than with TB, and no child whose symptoms spontaneously resolved was diagnosed with TB in the following 6 months.

Clinical examination including growth assessment

There are no specific identifying physical signs that unequivocally establish that a child has TB. Some signs are highly suggestive of extrapulmonary TB (*e.g.* gibbus deformity of recent onset, painless cervical adenopathy with fistula), while others require investigation to exclude extrapulmonary TB (*e.g.* pleural effusion, phlyctenular keratoconjunctivitis, erythema nodosum). Clinical examinations should include an assessment of growth and nutrition and a review of a child's growth chart if available.

Tests of adaptive immunity

Tuberculin skin test

For >100 years, the TST was the only test available to detect whether a person is or was infected with *M. tuberculosis*. It measures TB immunoreactivity but gives no information on whether mycobacteria are present or not.

The test involves the intradermal injection of purified protein derivative (PPD) comprising tuberculin derived from *M. tuberculosis*. A PPD solution contains dozens of TB antigens, with the exact composition varying among batches. Many of these antigens are also present in environmental nontuberculous mycobacteria (NTM).

The WHO recommends using the Mantoux method, which involves the intradermal injection of 5 tuberculin units (TU) of PPD or 2 TU of PPD-RT23 (a purified form of PPD). Those administering it must be trained in performing and reading the test.

A child who mounts a cell-mediated immune response to PPD has a delayed-type hypersensitivity skin reaction, usually within 48–72 h, causing measurable induration at the injection site. This response can be due to infection with *M. tuberculosis*, receipt of the BCG vaccine or previous exposure to NTM. Interpretation of the TST depends on the clinical situation.

The TST can be used in the assessment of children with suspected TB because it indicates that a child has been infected at some point. It cannot distinguish between TB infection and TB disease, but it may help in diagnosing TB when used along with signs and symptoms and other diagnostic tests. It can also be used in screening children exposed to TB.

The current WHO guidance is that in children who are immunosuppressed (including HIV-positive and severely malnourished children), induration of >5 mm should be regarded as positive; in all other children (whether they have had a BCG vaccination or not), induration >10 mm is considered positive.

The TST has problems with both false-positive and false-negative results. Populations with exposure to environmental NTM typically have reactions <10 mm. The largest source of false positives arises because some of the antigens in PPD are also found in *Mycobacterium*

bovis, an attenuated form of which is used in the BCG vaccine. The consequence is that in some children, induration in response to TST reflects previous BCG vaccination.

When the TST is used in subjects lacking risk factors for TB, the vast majority of positive results are false positives, a problem more common in children who have received the BCG vaccine. False negatives can also arise in children with an impaired ability to mount a delayed response, such as those who are immunosuppressed by HIV or immunosuppressive treatments, or following live viral vaccination. The most effective way to avoid false positives is to avoid testing children who lack risk factors for TB infection.

Interferon-γ release assays

The problems with the TST have led to the development of peripheral blood T-cell-based IFN-γ release assays (IGRAs). IGRAs measure IFN-γ production *ex vivo* by circulating T-lymphocytes when incubated in the presence of the highly specific *M. tuberculosis* antigens ESAT-6 (early secreted antigenic target 6) and CFP-10 (culture filtrate protein 10). These proteins are encoded within the region of difference locus 1 of the *M. tuberculosis* genome. This region is not encoded in the genome of *M. bovis* (BCG vaccine) or most species of NTM, and particularly not in *Mycobacterium avium* complex organisms, which are the most ubiquitous pathogenic environmental NTMs. Hence, IGRAs are more specific than the TST and can distinguish a positive TST due to BCG vaccination or to environmental atypical mycobacterial (NTM) infection from a positive TST test due to infection with *M. tuberculosis*. However, despite their greater specificity, IGRAs cannot differentiate between active and latent TB, and neither test should be used for the diagnosis of active TB. A negative IGRA result does not exclude TB.

Two commercially available IGRA platforms are available: a whole-blood IGRA (QuantiFERON-TB Gold In-Tube assay; Cellestis, Melbourne, Australia) and an enzyme-linked immunospot assay (T-SPOT TB; Oxford Immunotec, Oxford, UK).

TST or IGRA?

At present, the WHO recommends that for children in low- and middle-income countries, IGRAs should not be used in place of the TST for the diagnosis of latent TB.

The role of IGRAs in children, particularly in young children <5 years, is still being evaluated because the rates of indeterminate/invalid results seem to be higher in infants and toddlers than in older children. A positive IGRA in a young child probably indicates infection, but a negative result does not rule it out. TSTs and IGRAs may be complementary, and doing both tests may improve the sensitivity of the assessment in specific clinical circumstances.

Radiography and other imaging (if available)

The majority of children with pulmonary TB will have chest radiography changes, typically hilar and mediastinal lymphadenopathy (figure 4a and b). Extraluminal compression by the enlarged lymph nodes may cause partial luminal obstruction of the airway leading to radiographic signs of hyperinflation and "air trapping". Caseous lymph nodes may ulcerate into the airway, closing the lumen completely and causing distal atelectasis. Persistent pulmonary opacification, especially if there is no improvement with antibiotics, along with prominent hilar or subcarinal adenopathy is highly suggestive of TB.

Adolescents may have a radiographic appearance more typical of adult cases, with apical lung disease and cavity formation.

A chest CT may be very useful in demonstrating early cavitation and bronchiectasis. However, while chest HRCT offers excellent visualisation of mediastinal lymph nodes,

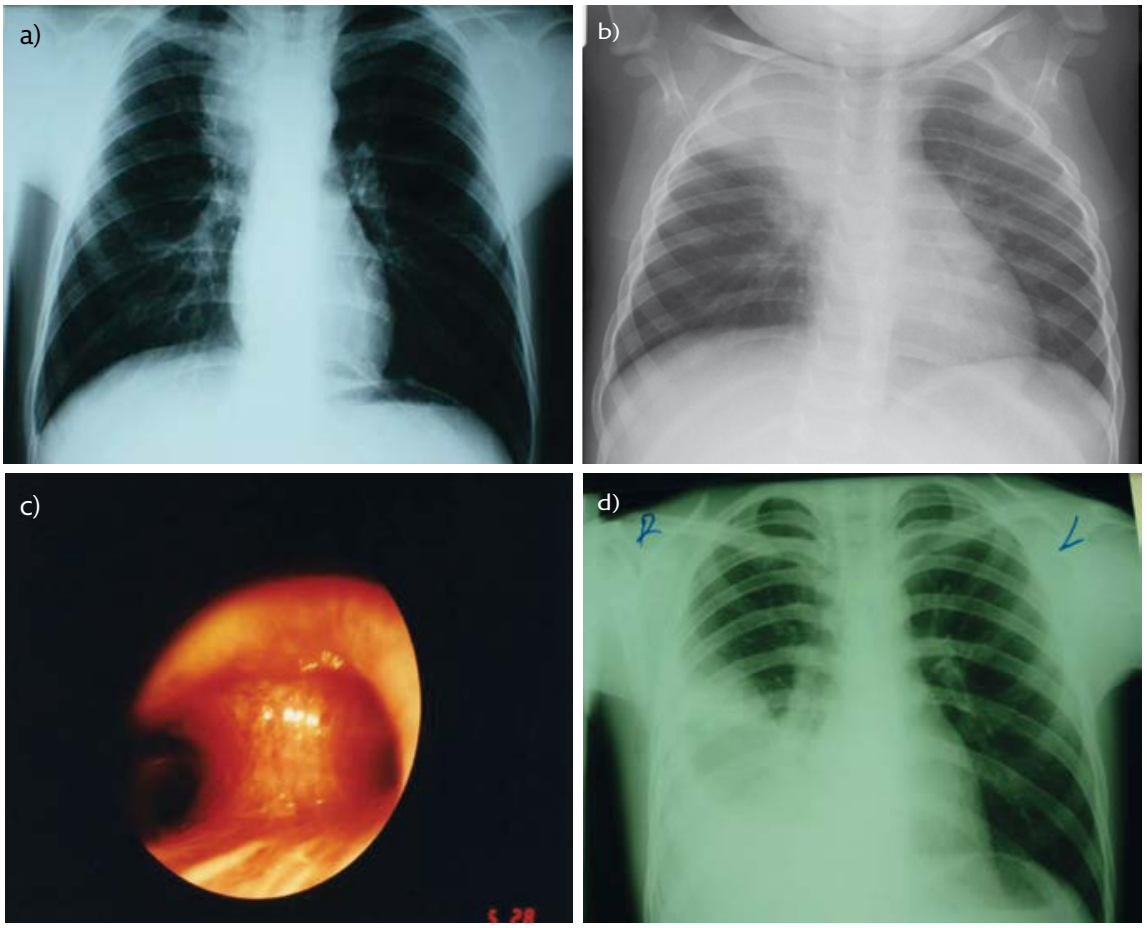

Figure 4. a) Right mediastinal lymphadenopathy in a child with TB. b) Right upper lobe atelectasis and hilar adenopathy in a child with TB; chest radiograph courtesy of Ernst Eber (Medical University of Graz, Graz, Austria). c) Extramural compression demonstrated on bronchoscopy with broadening of the main carinal bifurcation due to subcarinal lymphadenopathy. d) A 15-year-old boy with TB with right lower lobe atelectasis and pleural effusion.

treatment algorithms for latent TB and pulmonary TB in children have been based on plain radiography. Accordingly, chest CT is usually reserved for more complex cases.

Bronchoscopy may be useful in children with areas of atelectasis where compression by lymph nodes or caseating material ulcerating through an airway can be visualised (figure 4c).

Ultrasound can identify and guide drainage of pleural (figure 4d), pericardial or abdominal effusions and help in guiding fine-needle aspiration of lymph nodes.

Microbiological diagnosis

Children generally have paucibacillary disease, and respiratory secretions, particularly in young children, are difficult to collect. This makes microbiological diagnosis of TB in children more difficult than in adults. Microbiological confirmation is frequently not achieved, and in many cases is not even attempted. Nevertheless, a positive culture for *M. tuberculosis* remains the gold standard for the diagnosis of TB. Microbiological confirmation is increasingly important because of the increase in drug-resistant TB (DR-TB). The WHO recommends that bacteriological confirmation should be sought wherever possible.

Appropriate samples from suspected sites of involvement should be obtained for microscopy, culture and, if appropriate, histopathology.

Conventional culture can take weeks and is consequently unavailable to inform clinical decisions at the start of treatment. However, over the last 15 years, new techniques to confirm TB have become available. These include more rapid culture techniques and genotyping techniques that improve detection of *M. tuberculosis*. Such facilities are often not available in low-resource settings.

Molecular testing

One molecular testing system, the Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) has been endorsed by the WHO as an initial diagnostic test in adults and children suspected of having DR-TB or HIV-associated TB. The system is an automated cartridge-based system that can detect both TB and resistance to rifampicin in <2 h.

A large systematic review including 4768 respiratory samples from 3640 children found positive culture tests in 12% of children tested compared with Xpert MTB/RIF-positive results in 11% (Detjen *et al.*, 2015). Compared with culture, the pooled sensitivities and specificities for Xpert MTB/RIF for TB detection were 62% and 98% with expectorated or induced sputum and 66% and 98% with gastric lavages, respectively. Xpert MTB/RIF was ~40% more sensitive than microscopy, and the sensitivity of this test on culture-negative children started on anti-TB therapy was 2% for expectorated or induced sputum. The pooled sensitivity and specificity of Xpert MTB/RIF for detection of rifampicin resistance were 86% and 98%, respectively.

Although Xpert MTB/RIF can provide rapid confirmation of disease, its sensitivity remains suboptimal compared with culture tests. Hence, a negative Xpert MTB/RIF test does not rule out TB and has to be interpreted in the context of other clinical and radiological findings. It is not affected by whether a child has HIV infection or not. A newer, more sensitive version of this test, Xpert MTB/RIF Ultra, was introduced in 2017. However, the cost of cartridges for the Xpert system remains an important factor in most settings where TB is endemic.

The WHO now recommends that Xpert MTB/RIF should be used rather than conventional microscopy and culture as the initial diagnostic test in children suspected of having MDR-TB or HIV-associated TB. It may also be used in all children suspected of having pulmonary TB. If an initial test is negative, it should be repeated. If there is a high clinical suspicion of TB, the child should be treated, even if an Xpert MTB/RIF test is negative or not available. Xpert MTB/RIF testing can also be used in the testing of nonrespiratory specimens (*e.g.* from lymph nodes) and for testing cerebrospinal fluid (CSF) in children with suspected TBM. Again, where there is a high suspicion of TB, a child should be treated, even if the test is negative.

Collecting samples

Diagnosis of intrathoracic TB uses sputum specimens, which are difficult to collect in children. Sputum samples from spontaneous coughing may be obtainable in older children (>10 years). In younger children, particularly <5 years, sputum is more difficult to obtain because smaller amounts of sputum are produced and these are swallowed rather than expectorated. Consequently, most children are sputum smear negative, even when optimised techniques are used. As a result, sputum smear microscopy is of little value in children. Furthermore, microscopy cannot distinguish between *M. tuberculosis* and NTM, between viable and nonviable organisms, or between drug-sensitive and drug-resistant strains. Culture techniques have a greater but very variable sensitivity.

In children who cannot expectorate, bacteriological samples can be collected by a number of methods including BAL, gastric aspirate, induced sputum and nasopharyngeal aspirate. BAL is not available in many low- and middle-income

Table 2. Tests used in the diagnosis of extrapulmonary TB

Site of disease	Practical approach to diagnosis
Peripheral lymph node (especially cervical)	Lymph-node biopsy or fine-needle aspiration
Miliary TB	Chest radiograph and lumbar puncture
TBM	Lumbar puncture and CT/MRI imaging
Pleural effusion (older children and adolescents)	Chest radiograph, pleural tap for biochemical analysis including measurement of adenosine deaminase, cell count and culture
Abdominal TB	Abdominal ultrasound and ascitic tap
Osteoarticular TB	Radiograph, joint tap or synovial biopsy
Pericardial TB	Echocardiogram and pericardial tap

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countries. Gastric aspirate *via* a nasogastric tube is typically carried out in the early morning following an overnight fast. Sputum induction following nebulisation with hypertonic saline (3–5%) has been shown to be safe and effective in children of all ages, with bacterial yields as good as or better than gastric aspirate. However, the technique requires training and equipment, and staff need to follow effective infection control procedures appropriate for infectious aerosol exposure. A recent review found that detection yields for culture of childhood intrathoracic TB were 1–30% for induced sputum, 1–45% for gastric aspirate and 4–24% for nasopharyngeal aspirate (Ioos *et al.*, 2019). For Xpert MTB/RIF, detection rates were 2–17% for induced sputum, 5–51% for gastric aspirate and 3–8% for nasopharyngeal aspirate.

A tendency has been noted for better yields from induced sputum when the pre-test probability of TB is low to moderate and from gastric aspirate when it is high. Collecting a second specimen has been found to increase the cumulative yield; this often requires repeating the collection over 2 days, but using a combination of different methods on the same day is probably as effective.

The possibility of using stool samples to detect TB bacilli that are swallowed in combination with the Xpert MTB/RIF assay has shown promise as an alternative to sputum sampling in children, particularly in those with HIV infection.

For TB lymphadenitis, fine-needle aspiration of accessible enlarged lymph glands has been shown to be useful, with a high bacteriological yield (table 2). Aspiration of CSF and pleural or other fluids may also provide essential material for biochemistry, cellular analysis, microscopy and culture in appropriate situations.

All fluids (*e.g.* CSF, pleural) should be analysed with biochemistry, cell count, acid–alcohol-fast bacilli stain and culture where possible. Measurement of adenosine deaminase, an enzyme produced from lymphocytes and involved in purine metabolism, is considered an indicator of cell-mediated immunity, with raised levels supporting a diagnosis of TB (table 2). Its level is considerably elevated in patients with pleural effusion, a form of extrapulmonary TB with otherwise poor microbiological confirmation from pleural fluid analysis culture.

HIV testing

HIV testing should be offered to all children with presumptive and diagnosed TB.

Making the diagnosis

Because microbiological confirmation is commonly not available in children, the diagnosis of TB is often based on a careful assessment of the available evidence and a high index of suspicion. TB can mimic many common childhood diseases. A careful combination of clinical, radiological and laboratory findings along with a history of TB exposure and immunological evidence of *M. tuberculosis* allows an accurate diagnosis in most cases. However, every effort should be made to confirm a diagnosis of TB using whatever specimens and laboratory facilities are available.

Treatment of TB

Management of active TB

The goals of treatment are to cure the individual child, to prevent death from the disease or its late complications and subsequent relapse, to decrease transmission to others and to prevent the development of drug resistance. These outcomes should be achieved with minimal toxicity. Successful TB treatment requires more than just anti-TB chemotherapy medicines. Medications need to be provided within an appropriate clinical and social framework if an effective cure is to be achieved.

Although every effort should be made to attain a microbiological diagnosis, the threshold for starting treatment empirically is lower for children, especially young children, where potentially life-threatening conditions such as TBM or miliary TB can develop quickly. Fortunately, drug-related adverse events are rare in young children treated with first-line drugs, and they are at low risk for acquiring or transmitting drug-resistant disease.

The principles of drug treatment in children are the same as for adults: 1) TB should never be treated with a single drug, and 2) a single drug should never be added to a failing regime because of the risk of developing drug resistance.

Recommended drugs and dosages

The first-line drugs used in the treatment of TB in children are the same as those used in adults. The influence of young age on drug metabolism means that a particular dose ($mg \cdot kg^{-1}$) when given to a young child may not achieve the same blood level as in an older child or adult. To address this problem, in 2012 the WHO revised recommended doses of the main first-line anti-TB drugs upwards for children. The current WHO recommendations are listed in table 3.

In pharmacokinetic studies, these dosages achieve higher blood levels in young children, including those <2 years of age. Since their introduction, the revised doses have had an excellent safety record and have not been associated with increased

Table 3. Recommended doses for first-line anti-TB drugs in children

Drug	Dose (range) $mg \cdot kg^{-1}$ body weight	Maximum dose $mg \cdot day^{-1}$
Isoniazid	10 (7–15)	300
Rifampicin	15 (10–20)	600
Pyrazinamide	35 (30–40)	
Ethambutol	20 (15–25)	

The higher end of the dose range applies to younger children, with the lower end more appropriate for older children. Reproduced and modified from the WHO guidance (2014) with permission.

risk of toxicity, particularly risks of drug-induced hepatotoxicity with isoniazid or pyrazinamide, or of optic neuritis due to ethambutol.

Using combination regimens

Combination regimens are used to treat active disease. The aim is to eliminate both actively replicating and dormant or near-dormant mycobacteria by using a combination of drugs with different antimycobacterial actions while minimising toxicity and preventing the emergence of drug-resistant organisms.

Bactericidal drugs are used to kill actively metabolising and replicating organisms. These bring about a rapid reduction in microbial load leading to clinical improvement, preventing disease progression and stopping transmission. Isoniazid and rifampicin are the most important first-line drugs, with isoniazid having the most important bactericidal activity.

Sterilising drugs aim to eradicate organisms that are less metabolically active in order to prevent relapse. Rifampicin and pyrazinamide are important first-line sterilising agents. Protection against the emergence of drug-resistant organisms is achieved through the combination of effective bactericidal activity with effective sterilising activity and is strengthened by the addition of ethambutol.

Recommended treatment regimens for new cases of TB in children

Recommended regimens are based on guidance from national programmes for a particular country, if one exists (*e.g.* NICE, 2016), or from the WHO (table 4).

Table 4. Recommended treatment regimens for new cases of TB in children

TB diagnostic category	Anti-TB drug regimen[#]	
	Intensive phase	Continuation phase
Low HIV prevalence (and HIV-negative children) and low isoniazid resistance settings		
Smear-negative PTB	2HRZ	4HR
Intrathoracic lymph node TB	2HRZ	4HR
Tuberculous peripheral lymphadenitis	2HRZ	4HR
Extensive pulmonary disease	2HRZE	4HR
Smear-positive PTB	2HRZE	4HR
Severe forms of EPTB (other than TBM/ osteoarticular TB)	2HRZE	4HR
High HIV prevalence or high isoniazid resistance or both		
Smear-positive PTB	2HRZE	4HR
Smear-negative PTB with or without extensive parenchymal disease	2HRZE	4HR
All forms of EPTB except TBM and osteoarticular TB	2HRZE	4HR
All regions		
TBM and osteoarticular TB	2HRZE	10HR
MDR-TB	Individualised regimens	

PTB: pulmonary TB; EPTB: extrapulmonary TB; H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol. [#]: the number represents the duration of the phase (months). Reproduced and modified from the WHO guidance (2014) with permission.

HIV-infected children should receive the same dosages of anti-TB therapy as HIV-uninfected children.

In Europe, the most frequent scenario is that the *M. tuberculosis* organism is sensitive to all first-line agents. The European Centre for Disease Prevention and Control currently recommends treatment with the four first-line drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) for 2 months as an initial bactericidal regimen. After 2 months, treatment is continued with a prolonged sterilising regime of isoniazid and rifampicin for a further 4 months.

Adherence

Ensuring adherence to the long courses of treatment used for treating TB is a major problem. Poor adherence is an important factor in the emergence of resistance to TB therapy and in treatment failure.

Children, parents and families should be educated about TB and the importance of completing treatment. Patient treatment cards are recommended for documenting treatment adherence.

As a minimum, all children and families should be assessed for the risk that adherence is likely to be poor. In some settings, directly observed treatment (DOT) may be used for those at high risk of nonadherence. A healthcare worker or a trained community worker can give DOT. Children with severe disease such as TBM or with severe side-effects may need prolonged hospitalisation during the first 2 months of treatment to ensure that the treatment is successfully delivered. Newer approaches exploiting smartphone technology to improve compliance are being trialled. A recent trial of synchronous video-observed therapy using smartphones in London proved more effective than conventional DOT and was cheaper to deliver.

The WHO recommends that all children should receive TB drugs free of charge, irrespective of whether the child is smear positive at diagnosis or not. Treatment should be given daily. Regimens of three times a week are generally not recommended. They should only be considered during the continuation phase for children who are known not to be infected with HIV and are living in a setting with well-established DOT programmes, and in children who do not have extensive pulmonary or disseminated disease.

Fixed-dose combinations

Fixed-dose combinations (FDCs) of drugs should be used whenever possible. These simplify adherence and minimise the risk of developing drug resistance.

In 2015, the WHO and the TB Alliance launched child-friendly FDCs for the treatment of drug-susceptible TB in children weighing <25 kg. These were developed in line with the revised dosing published in the WHO guidance (table 3).

The available formulations are:

- Intensive phase of treatment: rifamipicin 75 mg + isoniazid 50 mg + pyrazinamide 150 mg (3FDC)
- Continuation phase of treatment: rifamipicin 75 mg + isoniazid 50 mg (2FDC)

These FDCs are water dispersible and pleasant tasting, and are likely to greatly simplify treatment and improve adherence. Detailed advice about how these FDCs should be administered based on a child's weight has been published (World Health Organization and UNICEF, 2017).

Treatment response and follow-up

Treatment outcomes are generally good in children as long as treatment starts promptly and is adhered to until the course is completed. The risk of serious adverse events in children is very low.

Regular follow-up at 2 weeks and then every 2 months is recommended, with assessment of symptoms, adherence, adverse events and weight. A child who does not appear to be responding to anti-TB treatment requires a detailed assessment. They may have developed DR-TB, an unusual complication or another disease, or they may have problems with treatment adherence.

Side-effects

Hepatotoxicity can be caused by isoniazid, rifampicin or pyrazinamide and is the major drug-related adverse event, with case reports of hepatic failure even when recommended doses of anti-TB therapies are used. However, side-effects are much less common in children than in adults. Hepatotoxicity may be detected more frequently in children who are malnourished or immunocompromised (*e.g.* with HIV infection), or who present with extensive and serious TB disease. If signs of hepatotoxicity develop (vomiting, jaundice, liver tenderness, hepatomegaly), all drugs should be stopped immediately and levels of hepatic enzymes monitored. Children should be screened for other causes of hepatitis. Re-introduction of anti-TB therapy should not be tried until the liver function is normal and should then proceed on a stepwise basis with one drug re-introduced at a time.

Ethambutol is now recommended for use in children of all ages including those <5 years. At the recommended doses and durations, review of the evidence has suggested that ethambutol is safe with a negligible risk of toxicity throughout childhood.

Other drugs and management issues

Corticosteroids

Corticosteroids are used for the management of some specific cardiorespiratory complications of TB, such as airway obstruction and atelectasis secondary to TB mediastinal lymph gland enlargement, or pericardial TB. Corticosteroids have been used in advanced pulmonary disease with clinical and radiological benefits. They are also recommended for all children with TBM where they have been shown to improve survival and reduce morbidity in advanced cases.

Prednisolone (2 $mg \cdot kg^{-1}$ daily, increased to 4 $mg \cdot kg^{-1}$ in the most seriously ill children, with a maximum 60 $mg \cdot day^{-1}$ for 4 weeks and then tapered) has been the most commonly used drug. Rifampicin induces hepatic enzymes that catabolise corticosteroids and reduces effective bioavailability by ~50%.

Immune reconstitution inflammatory syndrome

Corticosteroids are also used in the management of immune reconstitution inflammatory syndrome (IRIS; also known as a paradoxical reaction). In this situation, a temporary deterioration occurs after the start of anti-TB treatment due to restitution of the individual's capacity to mount an inflammatory immune response. This may cause fever, increased lymph node size and tuberculomas. It can occur after the start of anti-TB treatment (*e.g.* commonly as enlargement of the mediastinal lymph node on chest radiography), after improved nutrition or following the initiation of antiretroviral therapy (ART) in children with HIV infection.

Pyridoxine supplementation

Pyridoxine (vitamin B6) is used to prevent isoniazid-induced B6 deficiency and neuropathy. Supplemental pyridoxine (5–10 $mg \cdot day^{-1}$) is recommended for children

being treated with isoniazid, particularly children who are severely malnourished or HIV positive.

Nutritional support

Severely malnourished children have a greater risk of dying from TB. Regular nutritional assessment and nutritional support are important, particularly during the intensive phase of treatment.

Drug-resistant TB in children

Modelling studies suggest that DR-TB is far more common than is diagnosed, with estimates of 58 000 children with isoniazid-monoresistant TB, 25 000 with MDR-TB, and 1200 with extensively DR-TB (XDR-TB) out of an estimated 67 million children infected with *M. tuberculosis*.

Drug resistance usually originates in adults with TB who have a high bacillary load and who receive inadequate anti-TB therapy or are poorly compliant. Acquisition of resistance during treatment is rare in the paucibacillary disease that occurs in children, and the vast majority of cases result from person-to-person transmission from an adult index case. There is evidence that DR-TB strains may be more infectious but less virulent than drug-susceptible strains, with infected contacts being less likely to develop active TB. However, there is no doubt that DR-TB can cause severe disease and death.

Resistance to isoniazid and/or rifampicin is particularly important because these two drugs are the mainstays of current first-line treatment. In MDR-TB, the organism is resistant to both rifampicin and isoniazid with or without resistance to other anti-TB drugs.

DR-TB should be suspected when there is contact with a known or suspected source case. A child who is not responding to first-line treatment despite good adherence or a child who has previously been treated for TB and who presents with a recurrence may also have DR-TB. When DR-TB is suspected, every effort should be made to confirm this diagnosis by obtaining specimens for culture and drug susceptibility testing. Rapid testing for isoniazid and rifampicin resistance or rifampicin resistance alone using molecular techniques can now provide evidence of resistance within hours to 1–2 days.

While the principles of treatment are the same and the same second-line drugs are used as in adults, treatment is often complex and specialist advice should be sought. There is uncertainty about the activity and safety of the available second-line drugs in children, and suitable formulations for children are often not available. There is limited evidence on treatment of MDR-TB in children, and the optimal duration for treatment is unknown, with the intensive treatment phase often lasting ≥8 months and the total duration ≥10 months.

If an isolate from the child is not available, the best guide to treatment is the susceptibility pattern of the adult source case. In general, at least four drugs certain to be effective (and to which the child is naïve) including an injectable agent and a fluoroquinolone are given on a daily basis using DOT.

Regular monitoring during treatment is essential and should include monitoring of hearing because of the risk of ototoxicity with injectable agents such as amikacin. Adherence to therapy is critical for the success of treatment but highly problematic because of the amount and unpleasant nature of some of the drugs and the common side-effects of nausea and vomiting. Prolonged hospitalisation may be necessary if therapy is to be successful.

Close childhood contacts of DR-TB patients who develop TB usually develop DR-TB, and accordingly all close childhood contacts should be screened. Pivotal clinical trials of latent TB preventative regimens in contacts of patients with DR-TB are underway. While awaited, the WHO recommend that preventative treatment should be individualised based on a risk assessment and a sound clinical justification. This should include confirmation that the subject is positive for latent TB infection (LTBI) and is a household contact at high risk (*e.g.* due to HIV coinfection). The drugs used should be selected depending on the drug susceptibility of the source case. Those at risk should be observed closely for at least 2 years (every 2–3 months for the first 6 months and then every 6 months), regardless of whether preventative treatment is used or not.

Children with TB/HIV coinfection

Children with HIV infection have an 8-fold increased risk of developing TB, increasing with the degree of immunosuppression. ART reduces the risk by ~70%, with protection increasing over 1–2 years. The WHO published updated policy guidelines in 2012 for the collaborative management of TB and HIV infection.

The diagnostic difficulties in childhood TB are compounded in HIV/TB coinfection: the clinical presentations in both diseases are similar, and radiological features are nonspecific. The TST, which is the most widely used immunological test supporting the diagnosis of TB, is frequently falsely negative because of HIV-associated "anergy" in delayed-type hypersensitivity to PPD. Induration of >5 mm is considered positive if the child has HIV infection. Thus, diagnosis of TB in children, especially in resource-limited settings, relies on practical algorithms, which lack standard symptom definitions and adequate validations.

The WHO recommends that all children with suspected or diagnosed TB should be screened for coinfection with HIV. It is also recommended that in a TB-endemic situation, all children with HIV infection should be screened for TB at every clinical contact.

TB in HIV-infected children should be treated with a four-drug, 6-month regimen, as for uninfected children. Intermittent regimens should not be used.

Drug interactions with HIV ART and the similar side-effect profiles of the drugs involved in treating the two diseases make managing the two treatments challenging. Rifampicin, in particular, reduces the concentration of many HIV drugs.

Treatment with ART improves TB treatment outcomes in children. It is now recommended that TB treatment should be started first, followed by ART as soon as possible thereafter and within 8 weeks of starting TB treatment.

Immune reconstitution inflammatory syndrome

Immune recovery in children with HIV infection in the early months after initiation of ART, nutritional rehabilitation or sometimes just beginning anti-TB therapy may unmask subclinical disease or induce a paradoxical temporary deterioration despite adequate therapy for TB (*i.e.* IRIS). This can simulate worsening TB disease with fever and increased size of lymph nodes or tuberculomas. Treatment for TB should not be interrupted. A course of steroids may be required for severe IRIS.

Secondary isoniazid preventative therapy

The WHO now recommends an additional 6 months of isoniazid therapy after successful TB disease treatment in children with HIV infection who are living in high-prevalence areas of TB.

TB control and prevention

Latent TB infection

LTBI has been defined as "a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically manifest active TB" (WHO, 2018b). Because there is no gold standard test for LTBI, the global burden is not known with certainty, but up to one-third of the global population is estimated to be infected with *M. tuberculosis*. Overall, 5–10% of those infected will develop active TB disease, usually within 5 years of first being infected.

Preventative chemotherapy

TB preventative therapy is important in two broad categories of children: 1) those who have recently been exposed to *M. tuberculosis*, for example following close contact with an infected case, and 2) those at increased risk of progression of *M. tuberculosis* infection to TB following exposure because of age or other clinical conditions such as HIV infection.

Controlled trials have focused on preventing progression from LTBI to active disease by providing a limited course of treatment (in terms of either number of drugs or duration of treatment) to sterilise existing subclinical lesions and prevent future progression to TB disease. Primary prevention (primary chemoprophylaxis) is used to prevent primary infections from becoming established during or after a period of usually close household contact with an infectious case. In both situations, the recommended treatment is most commonly 6 months of isoniazid preventative therapy.

Preventing recurrence of TB may be achieved by "secondary chemoprophylaxis" provided after successful completion of therapy, using isoniazid therapy for an additional 6 months.

Treatment of recently infected children

Treating recently infected children and preventing progression to active TB (*i.e.* treatment of LTBI) eliminates reservoirs of *M. tuberculosis* and prevents later re-activation disease. Such treatment is particularly important in children <5 years and among people with compromised immunity due to HIV infection who are at high risk of developing TB following infection.

Current WHO guidelines recommend treatment for LTBI for: 1) all children aged <5 years (irrespective of BCG status) who are household contacts of people with bacteriologically confirmed pulmonary TB and who are not thought to have active TB, and 2) children aged ≥12 months with HIV infection who are in contact with a case of TB and in whom investigation shows no TB disease.

The WHO has recently updated the recommended treatment options for LTBI (table 5). Before treating LTBI, it is important to exclude active TB by an appropriate clinical evaluation.

All of the recommended treatment options can be self-administered, and the benefits of treatment outweigh the potential harms. Shorter regimens have higher adherence rates. Because of potential drug interactions, rifampicin- and rifapentine-containing regimens should be prescribed with caution to people living with HIV infection who are on ART.

Unfortunately, the implementation of preventative strategies has been poor because of policy-practice gaps or the unavailability of preventative treatment in many settings.

Table 5. Recommended regimens and doses for treatment of LTBI in children

Drug regimen	Dose[#]	Maximum daily dose
Daily isoniazid alone for 6 or 9 months	10 mg (range 7–15 mg)	300 mg
Daily rifampicin alone for 3–4 months	15 mg (range 10–20 mg)	600 mg
Daily isoniazid plus rifampicin for 3–4 months	Isoniazid 10 mg (range 7–15 mg), rifampicin 15 mg (range 10–20 mg)	Isoniazid 300 mg, rifampicin 600 mg
Weekly rifapentine plus isoniazid for 3 months (12 doses)	Isoniazid: ≥12 years: 15 mg 2–11 years: 25 mg Rifapentine: 10–14 kg: 300 mg 14.1–25.0 kg: 450 mg 25.1–32.0 kg: 600 mg 32.1–50.0 kg: 750 mg >50 kg: 900 mg	Isoniazid 900 mg, rifapentine 900 mg

[#]: per kg body weight, unless otherwise stated. Reproduced and modified from the WHO guidelines (2018b) with permission.

Treatment for TB-exposed children with HIV infection

In HIV-infected children, the value of post-TB exposure prophylaxis and the need for careful ongoing screening is clear. Isoniazid preventative therapy is indicated following every documented exposure to TB, particularly for the young and the immunosuppressed. The WHO now recommends that children ≥12 months with HIV infection who are not thought to have TB on the basis of symptom screening and who are not in contact with a case of TB should be offered 6 months of isoniazid preventative therapy as part of their package of HIV care if they are living in a high TB prevalence setting.

Treatment to prevent recurrence of TB

In adults, the use of secondary isoniazid preventative therapy after completion of TB treatment has reduced the incidence of recurrence. This is now recommended by the WHO for 6–36 months after the completion of TB therapy in all patients, including children, who live in areas with a high prevalence of TB.

BCG vaccination

The BCG vaccine is a live attenuated vaccine derived from *M. bovis*, prepared as a freeze-dried powder for suspension prior to injection. It was first used in humans in 1921 and is one of the most widely used of all vaccines. The BCG vaccine is currently the only available TB vaccine.

BCG vaccination is given intradermally, normally into the lateral aspect of the left upper arm at the level of insertion of the deltoid muscle (the left arm is recommended by the WHO). The correct administration technique is important to ensure the correct dosage and optimum vaccine safety and efficacy. BCG vaccination usually causes a scar at the injection site. However, scar formation is not a marker for protection, and ~10% of recipients do not develop a scar.

Vaccination with a single dose of BCG soon after birth is recommended in high TB prevalence countries or where there is a high risk of exposure to TB. Countries with low

TB prevalence use risk-based strategies targeting neonatal BCG vaccination to protect those children most at risk from exposure to TB. Such targeted approaches require careful ongoing audits to ensure that high proportions of the at-risk continue to be vaccinated.

Effectiveness in preventing progression to disease

Studies of the effectiveness of the BCG vaccine in protecting against TB have given widely varying results, ranging from no protection in some studies in India to 70–80% protection in UK school children. The reasons for the variations in efficacy in different regions of the world are not well understood.

Neonatal BCG vaccination has consistently been shown to be 70–90% effective in preventing against TBM and miliary TB, the more severe forms of disseminated disease that occur in infants and young children. Recent studies combining IGRAs and TSTs have suggested that the BCG vaccine may also protect against TB infection, producing a modest reduction in the risk of primary TB infection and the development of LTBI. However, the BCG vaccine is poorly protective against pulmonary disease in adolescents and adults, and therefore at reducing *M. tuberculosis* transmission, with the most limited protection in geographical areas such as India where TB is most prevalent.

Levels of protection from BCG vaccination decrease over time, with the best estimates suggesting protection lasting for up to 15 years, although some studies have suggested much longer levels of protection, particularly with neonatal vaccination. The vaccine is not protective if given to those already infected, and re-vaccination does not seem to offer substantial re-protection.

Side-effects

The BCG vaccine is one of the most widely administered vaccines worldwide and only a small number of children (1–2%) develop adverse effects. The most common complications are local abscesses, secondary bacterial infections, and suppurative adenitis or keloid formation. Serious adverse effects are rare.

BCG in immunocompromised and HIV-infected children

Individuals with genetic defects in key immune genes or, more commonly, infants with HIV infection are highly susceptible to developing disseminated BCG disease. Thus, use of the BCG vaccine is contraindicated in children with untreated HIV disease/AIDS or in children with congenital immunodeficiencies.

However, the WHO now recommends that children with HIV infection who are receiving ART, are well and are immunologically stable ($CD4^+$ cells >25% in children <5 years or $CD4^+$ cell count ≥200 in children ≥5 years) should receive the BCG vaccination because the benefits of preventing severe TB disease are considered to outweigh the risks of vaccination.

New developments

Intensive research is underway to develop more effective TB vaccines. Candidate vaccines are being developed for prevention of TB disease in adolescents and adults, for early-life immunisation as a BCG replacement, as BCG boosters, for vaccination of TB patients after treatment to prevent disease recurrence or as immunotherapeutic adjuncts to drug therapy intended to reduce treatment duration.

Importance of TB control programmes

Children are generally infected with TB through close contact with an infectious adult, so early diagnosis and treatment of adult infectious cases is the best way to stop children from becoming infected. A well-functioning TB control system that ensures the early diagnosis and treatment of infectious adults with TB has a key role in preventing TB in children.

Contact screening and management

The aims of contact screening and management are: 1) to identify undiagnosed TB disease in contacts of all ages of an index case, and 2) to provide preventative therapy to those contacts without TB disease who are particularly susceptible to TB disease following recent infection.

Screening and clinical evaluation of the following groups of children who are household and close contacts should be prioritised:

- Children with symptoms suggestive of TB
- Infants and children <5 years of age
- Children with known or suspected immunodeficiency, especially HIV infection
- Child contacts of index cases with MDR- or XDR-TB

Infection control: reducing TB transmission

Because of the paucibacillary nature of TB in children, the risk of infection of healthcare workers from paediatric patients with primary TB within hospitals and clinics appears to be minimal, and most children with TB do not need isolation.

However, it is important to remember that symptomatic parents or caregivers may have TB and pose an infection risk. Infection control efforts should therefore be focused on accompanying adults and adult visitors. While most infection control measures focus on diagnosed patients who should be on effective treatment, most transmission is from unsuspected or drug-resistant cases of TB. Active case finding, rapid diagnosis including for drug resistance and prompt effective therapy are now recognised as the most important interventions to stop transmission.

Nontuberculous mycobacteria infection

NTM are a large family of acid-fast bacilli that are ubiquitous in water, soil and biofilms. NTM organisms share many features with *M. tuberculosis* such as hardiness and intracellular pathogenicity. Most NTM are nonpathogenic, but some can cause disease in children.

Burden of disease

Surveillance data on NTM diseases are lacking, particularly in children, with most data on NTM infections coming from surveys of adults in developed countries. The absence of specific tests for NTM disease hinders estimation of the disease burden, particularly in low-resource settings.

Estimates of mycobacterial lymphadenitis, the commonest clinical syndrome in children, from high-income countries vary. An annual incidence of 0.84 NTM infections per 100 000 children aged <15 years was noted in an Australian study, while the incidence rate in a German study was 3.1. *M. avium* complex (comprising mainly *M. avium* and *M. intracellulare*) were the most frequently isolated NTM in these paediatric studies.

In low-resource settings, there are no data on the estimates of clinical syndromes caused by NTM, and any data tend to come from studies assessing the burden of pulmonary TB or in relation to the investigation of MDR-TB. For example, in one South African study of children being investigated for pulmonary TB as part of a TB vaccine surveillance programme, NTM were isolated in 6% of all children investigated for pulmonary TB and in more than one-third of those with a positive mycobacterial culture.

An important lack in our current knowledge is the absence of data on the frequency of NTM isolates from otherwise healthy children.

Natural history

The source of NTM infections remains unclear, but they have most commonly been associated with environmental sources such as water and soil. The presence of NTM in water supply systems has been documented, and aerosol inhalation from such sources may be one route of infection. Nosocomial outbreaks in paediatric stem-cell and bone-marrow transplant recipients have been associated with contaminated hospital water supplies.

NTM infection has been increasing in individuals with CF who are becoming infected with *Mycobacterium abscessus*, which is frequently MDR. Human-to-human transmission of MDR *M. abscessus* has been documented in patients attending a CF centre using a combination of whole-genome sequencing and detailed epidemiological analysis. The data indicated that NTM acquisition occurred *via* cross-infection, despite conventional infection control measures.

Localised lymphadenitis

NTM-associated unilateral cervical lymphadenitis is the commonest clinical presentation in otherwise healthy, immunocompetent children. The causative organisms are usually slow-growing NTM from the *M. avium* complex.

The clinical presentation is substantially identical to *M. tuberculosis*-associated lymphadenitis. Compared with *M. tuberculosis* infection, NTM lymphadenitis appeared to be unilateral, and occurred in younger children with a median age of 2.5 years in one large survey.

Pulmonary disease

Pulmonary NTM disease is rarely described in otherwise healthy children.

In adults, NTM can cause chronic pulmonary infection in patients with inflammatory lung diseases such as CF, non-CF bronchiectasis and COPD, as well as in individuals with no definable risk factors.

Many CF children with isolated NTM on respiratory culture do not progress to active disease or treatment. However, MDR *M. abscessus* has emerged as a major respiratory pathogen in individuals with CF, where it leads to an accelerated decline in lung function and can prevent safe lung transplantation. Between 3% and 10% of individuals with CF in the USA and Europe are now infected with *M. abscessus*. Because of the MDR nature of the organism, treatment is challenging, requiring extended therapy with poorly tolerated combinations of antibiotics.

Disseminated disease

Disseminated disease can occur in children due to either genetic susceptibility to mycobacterial disease or to acquired immunodeficiency from HIV infection or post-transplant. In HIV infection, NTM become a clinical problem in advanced stages with $CD4^+$ counts <50 cells·μL^{-1}.

Diagnosis

NTM and the *M. tuberculosis* complex that causes TB share microbiological attributes, induce a similar immune response and cause overlapping disease presentations, particularly in the lymph nodes and lung. Thus, diagnosis of NTM infection is challenging, particularly in regions where TB is highly endemic.

Like TB, diagnosis requires clinical, radiological and microbiological assessment. Isolation of NTM organisms from nonsterile sites (*e.g.* gastric aspirates) needs to be considered in the wider clinical context because isolation from such sites does not equate to disease.

Optimum microbiological diagnosis requires solid and liquid media and different incubation temperatures for mycobacterial culture, with confirmation of NTM culture best done using molecular techniques.

Localised lymphadenitis

NTM lymphadenitis is a paucibacillary disease that is often diagnosed without microbiological confirmation. Fine-needle aspirates of lesions have been shown to be better for microbiological sampling than biopsy, with molecular detection shown to be more sensitive than culture. A complete excision biopsy can be both diagnostic and curative.

Pulmonary disease

In children with CF, culture of NTM from respiratory secretions may be an isolated finding unassociated with clinical disease. Diagnosis of NTM disease in children with CF will usually require: 1) positive cultures from two or more sputum samples or from a single BAL sample, 2) radiological evidence of NTM-specific changes on HRCT, and 3) clinical decline or a decline in lung function despite optimum treatment of other CF organisms and morbidities. There is considerable overlap between the clinical and radiological presentations of NTM infection and CF, as well as between NTM infection and infection by other CF pathogens. In identifying which children require NTM treatment, it is essential that all non-NTM organisms are optimally treated.

Disseminated disease

Disseminated disease is diagnosed using blood culture, or staining and culture of bone marrow. Disseminated skin disease requires skin biopsy and culture.

Treatment

There are limited data on drug treatment regimens for NTM disease in children. NTM frequently become resistant to antimicrobial agents so, as for TB, combinations of drugs are used. Treatment is usually lengthy, side-effects are common and formulations suitable for children are frequently not available.

An accurate microbiological diagnosis is essential for constructing an antimicrobial regimen. Management is usually based on combinations of several antimycobacterial drugs. Macrolides are the cornerstone of treatment, with the choice of other antimicrobials generally being based on the NTM species and the clinical situation. *In vitro* sensitivities are not always a reliable guide to *in vivo* efficacy.

NTM lymphadenitis

Complete surgical excision is the usual approach in NTM lymphadenitis and, if possible, leads to a quick resolution. Partial excision combined with a drug regimen that includes clarithromycin can be an alternative if excision of the necrotised lymph nodes is technically difficult, but leads to delayed healing. A "wait and see" approach can also be effective in immunocompetent children, with total resolution taking 6–12 months.

Pulmonary disease

M. abscessus causing pulmonary disease is often MDR. Treatment usually includes a combination of a macrolide, ethambutol and a rifamycin in conjunction with an injectable aminoglycoside such as amikacin during an initial intensive phase of 3–12 weeks. Antibiotic treatment should be given until cultures have been negative

for ≥1 year. Surgical approaches may be useful if the disease is localised and there is resistance or intolerance.

Disseminated disease

Disseminated disease in children who are immunodeficient because of a genetic defect or with acquired immunodeficiency (*e.g.* HIV infection) should be treated with a macrolide and ethambutol. Rifabutin or aminoglycosides are often added in the initial treatment phase, with treatment continuing with at least two of the drugs used in a successful initial treatment phase. After successful treatment, secondary prophylaxis is recommended to prevent recurrence or until immune reconstitution.

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Protracted bacterial bronchitis and non-CF bronchiectasis

Adeline Y.L. Lim, Ahmad Kantar and Anne B. Chang

Chronic cough is a common presenting symptom highlighted by parents seeking primary healthcare for their children. Chronic (duration >4 weeks) wet or productive cough (hereafter termed wet cough) in children is associated with endobronchial suppuration and airway neutrophilia. Early diagnosis and treatment can improve the quality of life (QoL) of the child and their parents and minimise future morbidity. Protracted bacterial bronchitis (PBB) and bronchiectasis are common causes of chronic cough in children presenting to respiratory specialists (40% in one series of 346 children). PBB and bronchiectasis are extreme ends of a spectrum of chronic endobronchial suppuration.

Protracted bacterial bronchitis

PBB as a diagnostic clinical entity was first described in Brisbane (Australia) in 2006. It is now well recognised in guidelines as a cause of chronic wet cough in children, and the European Respiratory Society (ERS) has produced a task force document.

Key points

- Protracted bacterial bronchitis, a common cause of chronic wet/productive cough in children, is linked with bronchiectasis, as part of a spectrum.
- Persistent and/or recurrent chronic wet/productive cough unresponsive to prolonged antibiotic therapy should be evaluated for other possible underlying causes.
- Bronchiectasis, no longer considered rare, is the consequence of many aetiological factors. Early diagnosis of bronchiectasis, leading to appropriate and optimal clinical care, is important, as mild radiologically proven bronchiectasis is reversible in children.
- Although the evidence for the management of bronchiectasis is limited, all children with bronchiectasis should be optimally managed with personalised airway clearance techniques, appropriate antibiotics and other modalities (for comorbidities and treatable traits), monitored and regularly reviewed using a team approach.

However, decades ago, many physicians recognised PBB-like conditions as a precursor of bronchiectasis, as well as the importance of the pathogenic bacteria found in PBB, *i.e.* persistent lower airway infection.

Definition of PBB

The original definition of PBB was based on the presence of three criteria: 1) chronic wet cough, 2) lower airways bacterial infection (>10^4 colony-forming units (cfu) per mL), and 3) resolution of cough within 2 weeks of antibiotics. This original PBB definition is now termed "PBB-micro". It is not feasible to obtain lower airway samples in all children. Thus, the ERS has defined "PBB-clinical" when the following criteria are fulfilled: 1) presence of chronic wet cough (>4 weeks), 2) absence of symptoms or signs of other causes of wet cough, and 3) cough resolved following a 2-week course of an appropriate oral antibiotic (usually amoxicillin-clavulanate). In a minority of children, 4 weeks of antibiotics are required to resolve their cough (compared with the standard 2 weeks) and this is termed "PBB-extended".

Epidemiology of PBB

The true prevalence of PBB in community clinics is unknown, although a few studies from paediatric specialist clinics in Australia and Turkey found PBB to be among the most common causes of chronic cough. In an Australian multicentre study, 41% (142 out of 346) of newly referred children for chronic cough had PBB, with a higher incidence in young children (aged <5 years). In a study of 839 children (median age 2.3 years, range 0.1–14.7 years) enrolled with cough from a paediatric emergency department, 30% developed chronic cough (duration >4 weeks) in whom PBB was the most common cause (47%).

The burden of PBB is reflected in multiple doctor visits pre-diagnosis and impaired QoL. Prior to treatment, generic health-related and chronic cough-specific QoL scores of children with PBB are poor and similar to those recorded in children from other diagnostic groups (*e.g.* bronchiectasis). These QoL scores improved and normalised when the cough resolved.

Pathophysiology of PBB

Tracheobronchomalacia is common in children with PBB but whether this lower airway abnormality increases the risk of, or is a consequence of, PBB is controversial. There is, however, little doubt that children with PBB have chronic lower airways infection and neutrophilic inflammation that, unabated, can be injurious to the lung.

Microbiology

Common lower airway pathogens in PBB are nontypeable *Haemophilus influenzae* (NTHi), *Streptococcus pneumoniae* and *Moraxella catarrhalis.* When found at clinically important densities (≥10^4 cfu·mL^{-1} in BAL fluid), these organisms are considered pathogens and not commensals. Infections are often polymicrobial (multiple respiratory bacterial pathogens in 30–50%). If other bacteria such as *Pseudomonas aeruginosa* are present, diagnoses other than PBB should be considered. *S. pneumoniae* serotypes in children with PBB are somewhat dependent on vaccination history and antibiotic use, *e.g.* 100% of *S. pneumoniae* isolates from BAL samples of Greek children were serotypes available in the 13-valent pneumococcal conjugate vaccine (PCV), *versus* 28% of *S. pneumoniae* isolates from PCV-vaccinated children in the UK. Viruses are also sometimes co-present in BAL samples in children with PBB; the most common virus detected was human adenovirus (species C).

The BAL microbiota in PBB share some similarities with bronchiectasis, but are significantly different from CF and controls. Within a cohort of PBB, several microbiota profiles have been described and inflammatory markers have been significantly associated with bacterial biomass. However, inflammatory profiles did not significantly associate with alpha diversity (*i.e.* diversity of the local specimens), suggesting that inflammation in children with PBB is not driven by a single pathogenic species.

Inflammation and immunology

There are relatively few data on the pathobiology of PBB. The associated inflammation is neutrophilic (elevated neutrophils percentage, interleukin-8 and matrix metalloproteinase-9 in BAL fluid), consistent with a response to bacterial infection. Studies have described upregulation of innate immunity responses (elevated Toll-like receptor (TLR) 2, TLR 4, human β-defensin-2 and mannose-binding protein). Abnormality in apoptosis and efferocytosis (reduced alveolar macrophage phagocytic response to cells infected with NTHi) of lower airway cells has been described. This process may also contribute to the neutrophilic inflammation and NTHi infection.

Clinical features of PBB

PBB predominates in young children but is also found in adolescents. Children with PBB appear well with normal growth and development. There is no history of recurrent sino-aural disease and signs of chronic suppurative lung disease are absent (*e.g.* digital clubbing, chest wall deformity and adventitial auscultatory chest findings). Occasionally, crackles and a "rattly chest" may be heard. Although parents often (41–81%) report "wheeze", true wheeze is not usually found.

The chest radiograph is normal or near normal (peribronchial changes). The prevalence of atopic features (*i.e.* eczema, elevated IgE, positive radioallergosorbent test, or systemic and airway eosinophilia) has been found to be similar to that of children without PBB. Spirometry and respiratory system reactance and resistance are normal.

Treatment of PBB

All current guidelines, apart from one, recommend a 2-week course of antibiotics in children with PBB. With a shorter (5–7-day) antibiotic course, a relapse or incomplete resolution of the cough usually occurs. However, a longer course of antibiotics of 4 weeks may be required for a minority of children. The UK cough guidelines suggest a 4–6-week course of antibiotics irrespective of initial response, but this recommendation was produced prior to the randomised controlled trial (RCT) showing efficacy of 2 weeks of antibiotics. A shorter antibiotic course of 2 weeks should be prescribed first, to reduce antimicrobial resistance and adverse events. Antibiotics should target common pathogens based on local data. The most common antibiotic used is amoxicillin-clavulanate, as it is effective for the most common pathogens identified in BAL-based prospective data. At present, no studies have examined the role of azithromycin in the management of PBB. While some advocate airway clearance techniques (ACTs) or chest physiotherapy, these are not universally recommended (there is a lack of evidence) unless there is concurrent tracheobronchomalacia.

In an ideal setting, a lower airway specimen (*i.e.* sputum) should be obtained prior to commencing antibiotic treatment. However, as most children with PBB are very young, they are unable to expectorate, sometimes despite sputum induction, although this has been reported to be feasible in some settings. Bronchoscopy is neither necessary

nor practical in all children with PBB, but when performed, this frequently shows purulent secretions.

Prognosis of PBB

A majority of children with PBB respond well to a course of antibiotics. In patients where therapy fails, possible reasons include non-adherence or having another underlying cause for wet cough. This subpopulation of children should be referred for further evaluation for suspected bronchiectasis and other causes of chronic wet cough (*e.g.* aspiration lung disease or H-fistula).

Despite an initial response to antibiotic therapy, one prospective study of 161 children found that 43.5% of children had recurrent disease and 8% developed bronchiectasis within 2 years of PBB diagnosis. As the study was undertaken in a tertiary hospital, the group of children may have had more severe disease and not have been representative of children from the community. Major risk factors for later development of bronchiectasis were NTHi lower airway infection in BAL fluid (7.5 times risk) and recurrent PBB (>3 episodes per year; 11 times risk). Thus, parents should be counselled to seek medical attention if recurrent PBB occurs (>3 episodes per year). While prophylactic antibiotics for long-term management of recurrent PBB appear attractive, there are currently no supportive data and they cannot be recommended.

Bronchiectasis

Although once considered rare, there is a global resurgence in bronchiectasis, as highlighted in a 2018 series in the *Lancet*. Indeed, there are more people with non-CF bronchiectasis than with CF. Despite its increasing prevalence over the last 15 years and its substantial impact on morbidity and mortality, bronchiectasis remains relatively underrecognised in the general community. The diagnosis of bronchiectasis is highly dependent on case ascertainment and hence awareness is important. Prompt and accurate detection of bronchiectasis is pivotal, so that treatment is started and early disease can be reversed.

Definition and diagnosis of bronchiectasis

Childhood bronchiectasis is a clinical syndrome defined by persistent or recurrent (>3) episodes of chronic wet cough (>4 weeks) with persistent coarse crackles and, in severe cases, digital clubbing. This is confirmed radiographically using the broncho–arterial ratio (BAR) measured on a chest CT scan (inner diameter of bronchus to outer diameter of artery, within 5 mm in a non-tangential plane). The pathognomonic CT finding of bronchiectasis is the signet-ring appearance (figure 1) and an abnormally increased BAR. The old BAR diagnostic threshold of 1.0 was derived decades ago from adult studies using now outdated CT protocols and applied to all ages, despite large differences in mean BAR between young children and the elderly. Based on data from two studies (in the USA and Australia) of children without cardiorespiratory disease, the recommended diagnostic threshold for bronchiectasis is a BAR of >0.8. When bronchiectasis is more severe, the BAR increases and its morphological appearance is reflected in cylindrical (mild), varicose and cystic (most severe) forms. Other non-pathognomonic CT features are 1) bronchial wall thickening, 2) lack of bronchial tapering (from central to periphery), 3) bronchial structures present in the lung periphery, 4) mucus plugs, and 5) mosaic perfusion reflecting air trapping.

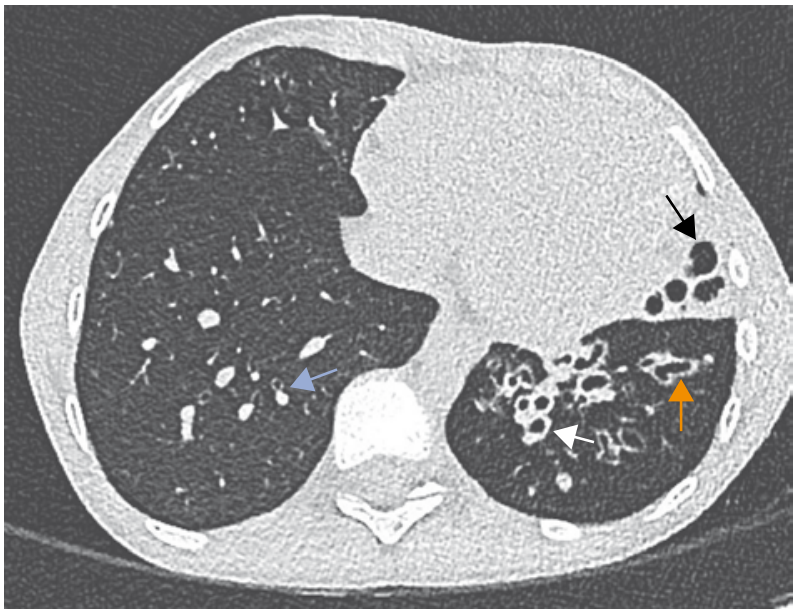

Figure 1. A single-slice cross-sectional view of a multidetector chest CT scan of a child with bronchiectasis, depicting saccular/cystic bronchiectasis (black arrow) within a collapsed lobe, varicose bronchiectasis (orange arrow), a signet ring (white arrow) and appearance of bronchodilatation (blue arrow) that does not meet the BAR criteria for bronchiectasis.

Epidemiology of bronchiectasis

The prevalence of bronchiectasis is difficult to estimate, as the diagnosis is dependent on having access to CT scans. CT scans performed under general anaesthesia are required for children unable to breath-hold and this service is usually limited to specialist centres. Thus, it is unsurprising that the prevalence is highly variable between and within countries, although it is known to be particularly high among indigenous populations of high-income countries (one in every 63–68 Aboriginal Australian/Alaskan native children). In adults, a 40% increase in bronchiectasis prevalence over the last 10 years was reported in the UK, but there are no equivalent paediatric data. It is highly likely, but remains unproven, that this large increase in reported prevalence is related to increased awareness and hence case ascertainment. However, it is now certain that bronchiectasis is no longer considered rare in mainstream settings in high-income countries.

Pathophysiology of bronchiectasis

Aetiologies

A myriad of heterogeneous risk and/or aetiological factors may lead to bronchiectasis in children, *i.e.* bronchiectasis is the "end consequence" of many conditions (table 1). The prevalence of these underlying aetiologies varies and is dependent on the region, country and depth of investigations undertaken (*e.g.* whether in-depth immune testing for a rare immunodeficiency was undertaken). Nevertheless, the aetiologies share a common thread of chronic cough and recurrent acute exacerbations with persistent lower airway infection/inflammation. Searching for an underlying aetiology (or aetiologies) is necessary as it alters treatment (*e.g.* use of systemic immunoglobulins) and is part of the initial evaluation of a child with, or suspected of, bronchiectasis (figure 2).

Pathobiology and pathophysiology

Readers are referred to the further reading list for an in-depth review of the pathophysiobiology of bronchiectasis as it is beyond this chapter's scope to describe

Table 1. A non-exhaustive list of the most common underlying aetiologies associated with development of bronchiectasis in children

Underlying aetiology	Examples	Suggestive clinical features	Key tests
Post-infectious	Post-TB, post-infectious BO	Clinical history, chest crepitations in BO	None for post-TB, chest CT features for BO
Immunodeficiency			
Primary	Multiple types affecting different cell lines	Recurrent severe and prolonged or atypical infections, family history, consanguinity, faltering growth	Immunoglobulin levels, response to vaccine and specific genetic tests, *e.g.* CD40 mutations
Secondary		Clinical history of immune suppressants, chemotherapy, oncology therapies or HIV	Immunoglobulin levels and tests for HIV
Airway lesions	Tracheobronchomegaly, tracheobronchomalacia, foreign body or other airway obstruction	Cough characteristics, associated risk factors, *e.g.* tracheo-oesophageal fistula, vascular rings/sling	Bronchoscopy
Syndromes		Specific to syndrome, *e.g.* facial features in trisomy 21 or velocardiofacial syndrome; yellow nail syndrome; polycystic kidney disease	Genetics
Aspiration±GOR		Dysphagia, neurological abnormality	Assessment of swallow, tests for GOR
PCD		Tachypnoea at birth, congenital cardiac disease, heterotaxy	Nasal nitric oxide, biopsy and ciliary motility, genetics
CF		Family history, growth faltering, diarrhoea	Sweat test and genotype
Concomitant lung disease	Asthma, prematurity, ILD/ connective tissue disease, non-post-infectious BO	Clinical history, *e.g.* preterm birth, post transplantation, medications, autoimmune diseases	Lung function, chest CT, lung biopsy
Idiopathic		Diagnosis of exclusion	Nil

BO: bronchiolitis obliterans.

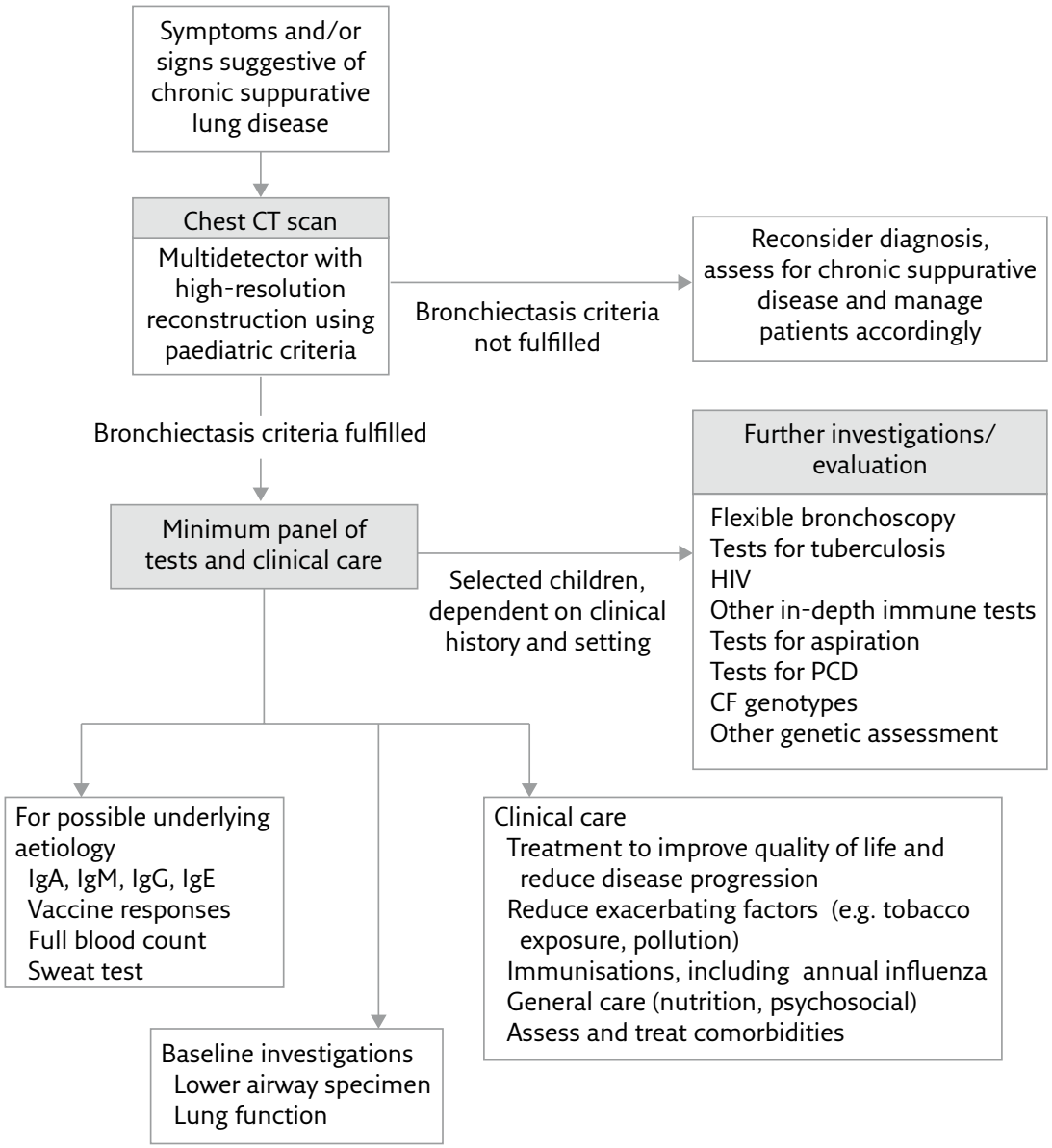

Figure 2. Simplified pathway for investigating a child suspected of having bronchiectasis. Clinician awareness of key pointers is required (see text). When any are present, the child should be evaluated for bronchiectasis. A minimum panel of tests is warranted to investigate for the presence of an underlying aetiology and for clinical care. Additional tests may be warranted, dependent on clinical features and setting (e.g. *HIV should be excluded in settings with a high prevalence).*

it in detail. Briefly, it involves a complex multilevel interaction between the host and various other factors including the environment, pathogens, clearance of pathogens, immunity and regulation of inflammation. Upon an environmental or bacterial insult on the background of genetic or epigenetic susceptibility or other host factors, a pathway involving impaired mucociliary clearance leads to (or is associated with) microbial colonisation/infection, causing chronic inflammation dysregulation and ongoing tissue damage. Without halting this process, the widely accepted "vicious cycle" of chronic infection and dysregulated airway inflammation leads to progressive destruction of bronchial walls, resulting in dilatation and airflow obstruction. Although classically described as a cycle, the various facets are not unidirectional but interlinked and multidirectional.

Histopathology specimens reveal bronchial wall inflammation (particularly in the small airways) with varying degrees of lymph follicle formation, destruction of elastic tissue

near the follicles, bronchial wall fibrosis, atelectasis and peribronchial pneumonic changes. These findings depend on the severity of bronchiectasis. The abnormal bronchial dilatation is caused by deficiency/loss of elastin and later destruction of muscle and cartilage. In some, particularly when bronchiectasis is severe, bronchial artery dilatation and neovascularisation occurs, which predisposes the patient to haemoptysis.

When considering lower airway infection, the type and specimen quality is important for interpretation. The recommended threshold for defining infection in children with bronchiectasis is $\geq 10^4$ cfu·mL^{-1} in BAL fluid. The lower airway microbiology of PBB and mild bronchiectasis are similar, often polymicrobial, dominated by *S. pneumoniae*, *H. influenzae* (mostly NTHi) and *M. catarrhalis*. *P. aeruginosa* and *Staphylococcus aureus* is also reported. *P. aeruginosa* is more likely to be found in those with more severe bronchiectasis, comorbidities, unrecognised CF or PCD. Atypical mycobacteria and aspergillosis are rare in children, unlike in adults. Microbiota studies using 16S rRNA gene pyrosequencing and phylogenetic analysis have shown that lower airway bacteria core and satellite microbiota of children with PBB and bronchiectasis are similar, but are different from children with CF and adults with CF or bronchiectasis. While viral infections trigger ~60% of exacerbations, adenovirus (species C) has been described in BAL fluid of children with bronchiectasis in stable state.

Studies have described high levels of pro-inflammatory neutrophilic inflammation and products, biofilms in the absence of *P. aeruginosa*, and impaired apoptosis and efferocytosis of lower airway cells. Also, *in vitro* studies have demonstrated altered systemic cell-mediated immune response to NTHi, specifically deficient interferon-γ response. These data support the interplay of infection and host immune defects in pathogenesis of bronchiectasis.

Clinical features of bronchiectasis

General

The prevalence of the individual symptoms and signs of bronchiectasis in children depends on severity and/or presence of an underlying disease. The dominant symptom is chronic wet cough but it may be intermittent post treatment. Clinical findings may or may not be present, *e.g.* recurrent wheeze or pneumonia, dyspnoea, exercise intolerance, fatigue, haemoptysis, chest pain, chest wall deformity, digital clubbing, growth failure or persistent chest crackles. Comorbidities such as airway hyperresponsiveness, GOR, impaired cardiac function, sleep dysfunction, and psychosocial or other QoL factors, may also be present but may not be used as direct markers of predicting bronchiectasis severity.

Failure of wet cough to resolve after 4 weeks of antibiotics predicts the presence of chest CT-defined bronchiectasis (adjusted odds ratio (OR_{adj}) 20.9, 95% CI 5.4–81.8). Recurrent PBB (>3 episodes per year) is also associated with future bronchiectasis within 2 years (OR_{adj} 11.5, 95% CI 2.3–56). Other pointers that should trigger evaluation for bronchiectasis include recurrent pneumonia/lower respiratory tract infections, persistent abnormal chest radiographs, clinical findings (haemoptysis, "severe asthma" or digital clubbing), positive sputum culture for atypical organisms (*e.g. P. aeruginosa*), and persistent respiratory symptoms after infection with certain organisms, *e.g. Bordetella pertussis*, adenovirus or *Mycobacterium tuberculosis*. Awareness of these pointers is important for case ascertainment and when present, they should trigger a pathway of action (figure 2).

Exacerbations

People with bronchiectasis often have recurrent acute flare-ups or exacerbations. However, defining exacerbations in children who are unable to expectorate sputum (thus unable to visualise sputum purulence and quantity) is not as straightforward as in adults. A standardised assessment of clinical features (major factors: increased cough or change in cough characteristics for ≥3 days; minor factors: chest pain, dyspnoea, haemoptysis, chest signs), with or without systemic markers, can give a valid prediction of exacerbations.

Prompt and effective treatment of acute exacerbations is important as they have major negative health impacts. Exacerbations are associated with increased distress, impaired QoL and lung function decline (–1.9% predicted FEV_1 per hospitalisation due to exacerbation).

Treatment of bronchiectasis

To guide appropriate treatment, determination of aetiology, definition of the presence and severity of bronchiectasis, and assessment of lower airway bacteriology should be performed (figure 2). Thereafter, treatment goals are to 1) optimise postnatal lung growth, 2) minimise exacerbations, 3) optimise QoL, and 4) prevent premature respiratory decline and complications. The first goal differs from adults as the human lung development continues throughout childhood, particularly in the first 7 years, with maximal postnatal lung growth occurring in the first 2 years of life.

There is a paucity of RCTs in children with bronchiectasis. Thus, current treatment recommendations are based largely on extrapolating results from adults with bronchiectasis, expert opinion and/or studies in CF. However, blind extrapolation of data from CF has risks, highlighted in the detrimental effects of using human deoxyribonuclease (rhDNase) in people with non-CF bronchiectasis. Despite the lack of high-quality RCTs in children with bronchiectasis, all should be actively treated, regularly reviewed and monitored to achieve the aforementioned goals. In addition to treating the underlying cause when possible (not further discussed here), treatment options can be classified as specific bronchiectasis treatments and generic lung healthcare, briefly summarised in the following sections.

Specific treatments

Antibiotics

Antibiotics are required to halt and/or disrupt the lower airway infection cycle. There is good evidence (*i.e.* RCTs) for using antibiotics in exacerbations and for maintenance (stable state). The latter is usually reserved for those with frequent (≥3 per year) or recurrent severe exacerbations. While different antibiotic types are available in oral (*e.g.* macrolides, co-trimoxazole) and inhaled (*e.g.* aminoglycosides, aztreonam) formulations, macrolides are the best studied. In children, once-weekly azithromycin (30 $mg \cdot kg^{-1} \cdot dose^{-1}$, maximum 600 mg) halves exacerbation frequency and improves growth, compared to placebo. Some centres, however, use 10 $mg \cdot kg^{-1} \cdot dose^{-1}$ three times a week.

For exacerbations, the antibiotic choice is based on the child's lower airways microbiology. When unknown, amoxicillin-clavulanate is the empirical antibiotic of choice (covering the common respiratory pathogens), unless *P. aeruginosa* has been recently isolated. The recommended treatment duration is 14 days. However, intravenous antibiotics are required when the symptoms continue despite oral antibiotics (intolerance to oral antibiotics or persistence of exacerbation symptoms).

Airway clearance techniques

Individualised therapy using ACTs (tailored for the child's age, cognitive ability and disease severity) is standard treatment. As there are many different ACT types (*e.g.* active cycle of breathing, autogenic drainage, chest percussion) and devices (*e.g.* for oscillatory positive expiratory pressure), ACT education and review by a physiotherapist with respiratory expertise is advocated. The optimal ACT frequency to maintain lung health and prevent exacerbations is unknown. In those with daily wet cough, daily ACTs are recommended. During exacerbations, ACTs should be intensified.

Muco-active agents

Muco-active agents are subcategorised into expectorants, mucoregulators, mucolytics and mucokinetics, and aim to mobilise airway secretions (reducing mucous plugging) and/or reduce mucous hypersecretion. The most commonly used muco-active agent is inhaled hypertonic saline (often with chest physiotherapy), although high-quality RCTs in children are lacking. Other agents include inhaled mannitol, inhaled or oral *N*-acetylcysteine and oral erdosteine and ambroxol, all of which also lack RCT evidence. rhDNase, beneficial in CF, is harmful in non-CF bronchiectasis (causing increased lung function decline and exacerbations, compared to placebo).

Asthma-based therapies

Unless asthma is concurrent, there is no role for routinely using asthma therapies (corticosteroids, short- and long-acting β_2-agonists or leukotriene antagonists). Side-effects of long-term inhaled corticosteroid therapy (*e.g.* increased risk of pneumonia and osteoporosis) have been reported in adults but there are no paediatric studies. Airway hyperresponsiveness may be found, especially in more advanced disease. When asthma is concurrent, it should be optimally managed as a "treatable trait".

Others

A variety of other currently available medications (*e.g.* non-steroidal anti-inflammatories and statins) and experimental drugs have been/are being studied but none are recommended routine therapies. Surgical removal of the affected bronchiectatic lung, now rare in high-income countries but still common in some low/middle-income countries, should only be undertaken in specialised centres. Lung transplant remains an option but is rare in children with bronchiectasis living in high-income countries.

A tailored bronchiectasis action management plan is recommended, although there are currently no published data to guide such plans. These plans assist families in self-management of exacerbations and guide primary care physicians in the optimal management of the child.

Generalised lung health and model of care

General care of children with bronchiectasis includes attention to nutrition (*e.g.* vitamin D deficiency and macronutrition), encouraging physical activity, avoiding environmental tobacco and pollutants, and immunisations. Pneumococcal polysaccharide vaccine-23 and annual influenza vaccination are generally recommended. Objective studies have shown that children with bronchiectasis are insufficiently active for health benefits. As exercise is considered important in the overall management of bronchiectasis (as shown in children with CF), exercise regimes should be promoted.

The psychosocial aspects of both the child and parents need to be considered when managing childhood bronchiectasis. In hospital clinics, they should be separated from those with CF to minimise cross-infection.

Ideally, children with bronchiectasis should be under a multidisciplinary team approach, with incorporation of allied health expertise (nursing, physiotherapy, nutritionist and social workers). Acknowledgement of increased challenges during the adolescent years, particularly in middle and late adolescence, may mitigate problems and improve adherence. Like other chronic diseases, appropriate transfer from paediatric to adult care should be planned ahead and skilfully done.

Monitoring of bronchiectasis

Monitoring includes regular multidisciplinary team review focusing on treatable traits, factors specific to bronchiectasis severity (*e.g.* exercise tolerance, symptoms of cough, sputum, dyspnoea and wheeze, frequency of exacerbations, QoL), complications and comorbidities (*e.g.* sleep, GOR) and overall general health (*e.g.* nutrition, exercise and psychosocial care). Sputum microbiology (for changes in bacteria, *e.g. P. aeruginosa* and nontuberculous mycobacteria) should also be undertaken in children who can expectorate. Spirometry in cooperative children is part of standard care, although it correlates poorly with radiological severity in children with mild bronchiectasis. ACTs should also be reviewed by a respiratory physiotherapist.

In adults, bronchiectasis severity scores (*e.g.* the Bronchiectasis Severity Index and the FACED score) may predict mortality and morbidity (*e.g.* QoL, hospitalisations and exacerbations). However, these scoring systems were developed in adults and are not likely to be applicable to children, as they include factors that are not possible to investigate in all children, *e.g.* sputum and lung function testing.

Prognosis of bronchiectasis

The outcome of bronchiectasis in children is very different to that in adults. Mild radiological bronchiectasis in children is reversible if treated early, thereby avoiding the later progressive decline in lung function. In contrast, adults with bronchiectasis often have progressive disease. Furthermore, adults with symptoms from childhood have worse disease (lower lung function, more exacerbations and worse radiology) and poorer prognosis compared to adult-onset bronchiectasis.

Poor prognostic indicators in adults include low lung function, presence of *P. aeruginosa* infection and reduced QoL scores. In children, under optimal management, lung function can initially increase and later stabilise (*i.e.* no decline). The sole factor found to influence lung function decline in children is hospitalised exacerbations. Although deaths are rare in children with bronchiectasis, childhood mortality from bronchiectasis has been reported in New Zealand and the UK in the last decade. Contrastingly, in the New Zealand data, there were no childhood deaths from CF in the same age group, raising issues about equity of resources and care.

New concepts in bronchiectasis

Classifying adults with bronchiectasis using latent class analysis suggests phenotypes exist (*e.g.* a group with frequent exacerbations). The concepts of endotypes (*e.g.* concomitant airway eosinophilia with neutrophilia), phenotypes and "treatable traits" have been proposed. These concepts have not yet been validated in children. Further exploration of such concepts will enhance understanding and lead to the improvement of short-term clinical outcomes and long-term prognosis in children with bronchiectasis.

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Lung involvement in the immunocompromised host

Rossa Brugha and Paul Aurora

Immunocompromise in children presents with recurrent infections or with opportunistic infections with atypical organisms. Immunodeficiency may be primary (inherited) or secondary to either infection (*e.g.* HIV) or medical treatments including cytotoxic chemotherapy or immunosuppression following haematopoietic stem-cell transplantation (HSCT) or solid-organ transplantation. As the lungs, along with the skin and gut, interact constantly with a diverse plethora of bacteria, viruses, fungi and protozoa, respiratory infection may be the first clue to a diagnosis of primary immunocompromise or a complication of secondary immunodeficiency.

Primary immunodeficiency is rare: common variable immunodeficiency (CVID) has an estimated prevalence of one in 25 000–30 000 people, and severe combined immunodeficiency (SCID) has an estimated annual incidence of one in 40 000–100 000 live births. Malignant disorders of the immune system such as leukaemia or lymphoma may present with respiratory symptoms including pleural effusion, large airway compromise (lymphoma with mass effect) or, rarely, acute eosinophilia presenting as lung disease (acute myeloid leukaemia). Teams caring for children with iatrogenic immunosuppression, whether from treatment for malignancy or following HSCT or solid-organ transplant, may request input from respiratory specialists in the diagnosis and management of pulmonary complications. Respiratory paediatricians need to be able to recognise unusual presentations that may represent immunocompromise and to initiate management of respiratory complications in children with impaired immunity.

Components of the immune system in the respiratory tract

Innate immunity

Potential pathogens are inhaled *via* the nose or mouth, where they must first avoid physical barriers including mucus and nose hairs, aggregates of lymphoid tissue in the

Key points

- Primary immunodeficiencies in children may present with respiratory symptoms.
- Respiratory infection is common in children on immunosuppressive therapy.
- Prolonged, recurrent or opportunistic infections should prompt investigations for immunodeficiency in children.

oro- and nasopharynx, and the cough reflex. In the lower respiratory tract, pathogens may be trapped by the mucus airway surface layer and expelled *via* mucociliary clearance. Defects in either system (*e.g.* an abnormal airway surface layer in CF, or abnormal ciliary clearance in PCD) may lead to repeated cycles of infection and inflammation in the lungs with subsequent airway wall destruction.

In addition to physical barriers, soluble extracellular proteins act to recognise pathogens and initiate adaptive immune responses. Mannose-binding lectin (MBL) is a protein found in the serum: it recognises carbohydrate structures on pathogens and initiates the complement cascade. MBL deficiency has been linked to an increased risk of invasive pneumococcal (*Streptococcus pneumoniae*) disease, although this is controversial and the relationship is not replicated consistently in association studies.

Adaptive immunity

Adaptive immune responses involve recognition of, response towards and memory of foreign antigen signatures from pathogens, with an enhanced response on subsequent exposures. Recognition of pathogens occurs when antigen-presenting cells in the lungs (predominantly macrophages, B-cells and dendritic cells) present fragments of phagocytosed pathogens as antigens on their surface, within the major histocompatibility complex (MHC). T-cells express the T-cell receptor, which binds to the MHC and, if the peptide fragment is recognised as foreign, the T-cell is activated. Activated T-cells direct immune responses by B-cells (to make antibodies), recruit neutrophils and macrophages to clear infecting pathogens and infected cells, and directly trigger apoptosis of virus-infected cells. If a step in this pathway (T-cell responses, neutrophil and macrophage function, B-cell activity or antibody production) has a reduced or absent function, then recurrent or opportunistic infections may occur.

Respiratory presentations of primary immunocompromise in children

Recurrent lower respiratory tract infection

It is normal for children in their first year of life to have between three and eight episodes of upper respiratory tract infection. Three or more lower respiratory tract infections per year (pneumonia, bronchiolitis or bronchitis) is an accepted threshold for further investigation. The duration of symptoms is also important: a wet cough every day for ≥4 weeks should be investigated further.

Opportunistic respiratory tract infection

Opportunistic infection occurs when a pathogen that does not usually cause infection in an immunocompetent host is able to establish an infection in an individual who is immunocompromised. A wide array of organisms have been identified in such cases, including cytomegalovirus (CMV), *Pneumocystis jirovecii*, nontuberculous mycobacteria (NTM), and *Aspergillus* and *Candida* spp. The presenting symptoms are variable, and include cough, breathlessness, wheeze, chest pain, pyrexia and hypoxia. There may be additional clues such as a rash (*e.g.* CMV), oral candidiasis, lymphadenopathy (*e.g.* NTM), brown flecks in the sputum (*e.g. Aspergillus*) or signs of restrictive lung disease (*e.g. Pneumocystis* and some viral pneumonias).

Initial screening investigations and further tests

If you suspect immunocompromise in a child, a basic screening approach is to test each component of the immune system (table 1). The first step is to take a history, in which the key points are the child's age (as severe immunocompromise may present when transplacental antibody levels begin to wane at ~4–6 months), any other

Table 1. Primary immunodeficiencies

Disorder	Immune system component	Presentation (signs and symptoms)	Investigations	Common pathogens
SCID	T-cells, B-cells, natural killer cells	Age ≤6 months, tachypnoea, failure to thrive, chronic diarrhoea, rashes	Low/absent lymphocyte count, abnormal T-cell PHA stimulation, diffuse infiltrates on chest imaging	*Pneumocystis jirovecii*, respiratory syncytial virus, rhinovirus
CVID	B-cells and antibody production	Childhood (5–10 years), repeated prolonged sinopulmonary infections	Low IgG with low IgA/IgM, reduced/ absent vaccine responses	*Streptococcus*, *Haemophilus*
Chronic granulomatous disease	Neutrophil and monocyte/ macrophage oxidative burst	Age <5 years, pneumonia, skin abscesses, cellulitis, impetigo, granulomas	Neutrophil oxidative burst test	*Staphylococcus*, *Serratia*, *Listeria*, *Aspergillus*, *Candida*
Hyper-IgE syndrome (Job syndrome)	STAT3-dependent cytokine signalling, Th17 differentiation	Eczema, cold abscesses, pneumonia, bronchiectasis, pneumatocele	Serum eosinophilia, IgE >2000 IU·mL^{-1}, STAT3 mutation	*Staphylococcus*, *Haemophilus*, *Streptococcus*, *Aspergillus*, *Pseudomonas*, *Scedosporium*

PHA: phytohaemagglutinin; STAT3: signal transducer and activator of transduction 3.

unusual infections (such as on the skin or in the gut, *e.g.* persistent diarrhoea due to *Cryptosporidium* spp.), weight loss or failure to thrive, and HIV status.

The initial blood investigations for immune defects test for:

- Absolute number and differential count of white blood cells (full blood count)
- B-cell function (immunoglobulin levels)
- T-cell function (antibody levels to antigens in vaccines, typically to a protein antigen such as tetanus and to a carbohydrate antigen such as pneumococcal vaccine)

If possible, consideration should also be given to measuring the number of T-cell functional classes (subsets), MBL levels and an HIV test. A sweat test should be requested for any child with repeated respiratory infections or an opportunistic infection to rule out CF, and ciliary brushings considered (with nasal nitric oxide levels if available) to rule out PCD. This initial screening panel can then direct further tests, and may be augmented on the basis of the history. For example, in a child with a suspected 22q chromosome deletion and recurrent respiratory infections, T-cell subsets must be included in the initial screening. A "second-line" screen for immunocompromise may include a neutrophil oxidative burst test, a T-cell phytohaemagglutinin stimulation test, a complement assay and analysis of IgG subsets.

Specific primary immune disorders and respiratory management

Severe combined immunodeficiency

SCID is an umbrella term for a group of inherited disorders that result in nonfunctioning lymphocytes (T-cells, B-cells and natural killer cells). It presents at ~3–6 months of age as maternal antibodies wane (this may be earlier in premature babies). Symptoms of persistent cough, failure to clear colds and a limited response to prolonged courses of antibiotics may be associated with rashes, and persistent diarrhoea with failure to thrive. Chest radiography may show bilateral interstitial infiltrates if there is established *P. jirovecii* infection (and ILD may be part of the differential diagnosis). Suspicion of SCID will be further raised by a low or absent lymphocyte count, and *P. jirovecii* may be detected by PCR of a nasopharyngeal aspirate. There may be a family history. Early contact with the immunology team is essential, and they may advise starting co-trimoxazole therapy before transferring for ongoing care. Live vaccines (bacillus Calmette–Guérin (BCG), and measles, mumps and rubella (MMR)) should not be given if there are concerns about primary immunodeficiency.

Common variable immunodeficiency

CVID comprises a group of disorders characterised by decreased production of immunoglobulin (predominantly IgG in combination with low IgA and/or IgM) with decreased or absent vaccine responses. It is a diagnosis of exclusion once other causes of hypogammaglobulinaemia have been excluded. Children usually present at primary school age (5–10 years) or in later teenage/early adulthood years with recurrent bacterial infections. In the respiratory tract, CVID manifests most commonly as otitis media, sinusitis and endobronchial infection, as the responsible organisms (typically *Streptococcus* and *Haemophilus* spp.) are not opsonised by antibodies. Chronic bronchitis and bronchiectasis may result. Patients are also prone to gastrointestinal infection and autoimmune diseases. Immunisations are recommended but may not be effective due to poor antibody production. Treatment of infections should be specific to the organisms identified, along with immunoglobulin replacement therapy to maintain effective IgG levels.

Chronic granulomatous disease

Chronic granulomatous disease is a disorder of neutrophil and monocyte/macrophage function (the phagocytic leukocytes) in which there is a defect in a subunit of the NADPH oxidase complex responsible for the generation of reactive oxygen species as part of the respiratory burst. These immune cells therefore struggle to clear catalase-positive bacteria, as well as fungi. This results in large aggregations of nonfunctioning neutrophils and monocytes being recruited to sites of infection, causing granulomas to form, typically in the skin, lungs and lymph nodes. Patients typically present in infancy or childhood. Part of the NADPH oxidase complex is encoded on the X chromosome, and approximately two-thirds of cases of chronic granulomatous disease are X-linked. Typical infecting organisms include *Staphylococcus aureus* and *Aspergillus*, *Serratia*, *Nocardia* and *Mycobacterium* spp. Children typically present before the age of 5 years. Diagnosis is made by the neutrophil oxidative burst test, where neutrophils from an affected patient will fail to produce reactive oxygen species in response to stimulation *in vitro*. Management involves prophylactic antibiotics (typically co-trimoxazole) and azole antifungals, with early and aggressive treatment of infections. HSCT is curative, with improving outcomes in recent decades, and gene therapy approaches have been reported in clinical trials.

Hyper-IgE syndrome (Job syndrome)

Hyper-IgE syndrome is characterised by recurrent eczema, skin rashes and abscesses, pulmonary infection, serum eosinophilia and raised levels of serum IgE (>2000 IU·mL^{-1}). The majority of cases (either *de novo* mutations or mutations inherited in an autosomal-dominant pattern) are due to a mutation in the gene encoding the transcription factor STAT3 (signal transducer and activator of transduction 3). STAT3 is involved in cytokine signalling, particularly T-helper type 17 (Th17) cell differentiation, and is expressed in multiple tissues. Children present with eczema-like rashes within the first few weeks of life, followed by recurrent boils caused by *S. aureus*. Sinus and pulmonary infections (due to *Staphylococcus* spp., as well as *Haemophilus* and *Streptococcus* spp.) are common and may result in bronchiectasis or pneumatoceles; these in turn may be infected by *Pseudomonas aeruginosa* and *Aspergillus* and *Scedosporium* spp. Other common findings in this condition include scoliosis, retained primary teeth, mucocutaneous candidiasis and a characteristic facies. Patients with hyper-IgE syndrome may not exhibit classic signs of infection (fever and rigors) as cytokine signalling is impaired. Treatment is therefore aimed towards early identification of infections with a low threshold for chest imaging, as well as prophylactic antibiotics (co-trimoxazole) and skin washes with chlorhexidine; use of the anti-IgE monoclonal antibody omalizumab has been described in case reports.

Approach to respiratory care in secondary immunocompromise

Children who are immunosuppressed due to HIV infection, treatment for malignant disease, HSCT or solid-organ transplantation are at increased risk both from common respiratory viruses and bacteria and from opportunistic infections. It may be challenging to differentiate opportunistic infection from a complication of the child's treatment (such as graft-*versus*-host disease, radiation pneumonitis or post-transplant lymphoproliferative disease), and a patient may be affected by multiple concurrent opportunistic infections. A full description of potential complications and post-operative management in children following lung transplantation can be found in the chapter "Lung transplantation and management after transplantation". Baseline assessments of respiratory function (spirometry, plethysmography and assessments of gas transfer, and PSG) may be useful in evaluating compromise and tracking respiratory indices over time.

Presentation of opportunistic infections

Herpesviridae: CMV, herpes simplex virus and varicella-zoster virus

If a patient is CMV seronegative pre-immunosuppression, they may acquire CMV *de novo*, from infected blood products or from transplanted solid organs. CMV-seropositive patients may experience re-activation of dormant CMV. Symptoms of CMV infection are nonspecific and include fever, myalgia, malaise and a macular rash. CMV pneumonitis presents with a persistent dry cough and breathlessness. Imaging typically shows diffuse bilateral infiltrates on a chest radiograph, with nodular shadowing on CT. CMV may be identified by PCR analysis of BAL fluid, peripheral blood monocytes or blood, or by transbronchial or open lung biopsy. Clinically significant CMV infection is challenging to diagnose, as CMV may be a commensal in a patient who was seropositive prior to their immunosuppression. It is therefore possible that CMV may be detected in samples, although the child's symptoms are due to an alternative undetected organism. In the acute phase, treatment is with intravenous ganciclovir, with foscarnet or cidofovir as a second-line alternative.

Herpes simplex virus (HSV) and varicella-zoster virus (VZV) cause skin and mucous membrane infections in immunocompetent individuals, and may cause disseminating disease (particularly to the lungs and viscera) in the immunosuppressed. Symptoms include chest pain, fever, cough and breathlessness. VZV will typically be accompanied by skin lesions, while disseminated HSV may be more insidious. In HSV pneumonitis, a chest radiograph may show bilateral, scattered, ill-defined nodules. Treatment for disseminated VZV is VZV-specific immunoglobulin and acyclovir, while disseminated HSV may respond to acyclovir.

Opportunistic bacterial infections

Gram-negative rods (*e.g. Klebsiella* and *Pseudomonas* spp.) and Gram-positive cocci (*e.g. Staphylococcus* and *Streptococcus* spp.) may cause early infection after solid-organ transplant or HSCT, and indwelling catheters, if present, should be considered as a possible source of infection. Later complications of immunosuppression include NTM and *Legionella* spp. infection.

Pneumocystis jirovecii

Pneumocystis jirovecii (formerly *Pneumocystis carinii*) causes *Pneumocystis* pneumonia (PCP). Symptoms include fever, cough, breathlessness and tachypnoea. Infected infants may show failure to thrive and there may be mild hypoxaemia. Older children may report restriction or pain on inspiration, with a characteristic "catch" if a deep inspiration is attempted. Chest radiography shows diffuse bilateral infiltrates, and *P. jirovecii* may be identified in BAL or by PCR of respiratory secretions. Co-trimoxazole is an effective medication for both treatment and prophylaxis.

Aspergillus and *Candida* spp.

Members of the genus *Aspergillus* are fungi found ubiquitously in soil, with small airborne spores that are commonly found in hospital environments. Species include *Aspergillus fumigatus*, *A. flavus* and *A. niger*. Infection may cause an acute invasive pulmonary disease, or a chronic aspergillosis with parenchymal abscesses, cavitations and diffuse interstitial pneumonia. CT may show nodules with a surrounding halo or crescent. Formal diagnosis may be made using BAL or tissue biopsy. *Candida* spp. commonly cause oro- and mucocutaneous infection in children with immunocompromise and may also penetrate the lungs, although the latter is unusual. Treatment of pneumonia caused by *Aspergillus* or *Candida* spp. is with antifungal agents such as amphotericin and caspofungin, as well as imidazoles.

Mycobacterial infection

Respiratory infection with *Mycobacterium tuberculosis* complex or with NTM is more common in children with immunodeficiency. The clinical and radiological features of these two infections are very similar, but the treatment approach is very different. Confirmation of diagnosis therefore usually requires microbiological analysis. It should be noted that pulmonary NTM disease is extremely rare in healthy children, and identification of NTM infection should raise suspicion of an underlying diagnosis of CF or immunodeficiency.

Diagnostic approach and differential diagnosis

The examples described in this chapter demonstrate that diagnosing opportunistic infection is challenging, with nonspecific signs, symptoms and imaging meaning that a number of infections may either overlap or coexist. Detailed imaging and invasive investigations such as bronchoscopy and possibly tissue biopsy samples may be required to make a diagnosis, along with detailed microbiological sampling of multiple sites for viral, bacterial and fungal entities. In addition to infection, an exacerbation

or relapse of the underlying primary diagnosis should be considered in a child who deteriorates while immunosuppressed, as well as:

- Medication side-effects (*e.g.* pulmonary fibrosis or leukodyscrasia)
- Radiation pneumonitis
- Pleural effusion
- Post-transplant lymphoproliferative disease
- Graft-*versus*-host disease
- Pulmonary hypertension
- Pulmonary thromboembolic disease
- Alveolar haemorrhage
- Aspiration/reflux–aspiration lung disease

Prognosis

This is dependent on the nature of the underlying condition, with phenotypic variation. Children with immunodeficiency/immunocompromise should be counselled that they have ongoing susceptibility to respiratory infection and in many cases a risk of progressive lung damage such as bronchiectasis (*e.g.* in hypogammaglobulinaemia) or cystic lung disease (*e.g.* in hyper-IgE syndrome). Lifelong monitoring and prompt treatment of early infection are required, and transition to adult respiratory services should be arranged using similar principles to those for children with CF.

Summary

Primary immunocompromise is rare in paediatric respiratory practice. It is important to be able to recognise these disorders and differentiate those children with abnormally frequent or abnormally prolonged infections from those who are experiencing repeated, short, mild viral infections within the normal population distribution for their age. In contrast, children with iatrogenic immunosuppression require specialist input from a number of teams, with the lungs as an at-risk organ for opportunistic infections, which respiratory specialists need to be able to identify and treat in concert with professionals in haematology, oncology and immunology.

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Microbiology and infectivity

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Respiratory tract infections constitute a major health problem, with significant cost and mortality worldwide. These infections are caused by viruses, bacteria, mycobacteria and fungi.

Viral infections

The majority of childhood lower respiratory tract illnesses are caused by viruses. Technological developments in molecular biology have shown that known respiratory viruses and multiple viral infections are more prevalent than previously thought across the childhood age range. The presence of more than one virus may result in more severe or prolonged infection, and viruses may also be co-pathogens with bacteria. The most common viruses that cause lower respiratory tract illnesses are shown in table 1.

The optimal method for virus detection depends on the clinical situation, the suspected agent and the test availability in a particular laboratory. Antigen detection assays and molecular methods are the preferred diagnostic approaches for the detection of respiratory viruses. Immunodiagnostic methods are easy to perform, and can be carried out within 15 min to a few hours. Antigens of the common respiratory viruses can be detected by direct immunofluorescence or using commercially available enzyme immunoassays; the sensitivities of these tests vary from 50% to 90%. Nucleic acid amplification tests (NAATs), mainly real-time PCR, can be applied to any virus for which part of the genome sequence is known. Multiplex PCR for detection

Key points

- Rapid antigen detection and molecular tests are the methods of choice for the identification of viral pathogens involved in respiratory tract infections.
- Blood culture is positive in <10% of paediatric patients with bacterial lower respiratory tract infections.
- Interferon-γ release assays have the potential to discriminate *Mycobacterium tuberculosis* complex infection from nontuberculous mycobacterial disease and *Mycobacterium bovis* bacillus Calmette–Guérin (BCG) vaccination.
- Detection of galactomannan in BAL samples is a reliable test for the diagnosis of invasive aspergillosis.

Table 1. Common viruses causing lower respiratory tract infections

Virus	Details of infection
Rhinovirus	Known as "common cold" viruses, these are the most prevalent cause of lower respiratory tract infection, usually causing mild disease. Although the severity of upper respiratory tract symptoms after rhinoviral infection does not differ between patients with asthma and normal subjects, both the duration and severity of lower respiratory tract symptoms are more pronounced in patients with asthma.
Respiratory syncytial virus (RSV)	RSV follows a well-characterised epidemiological pattern, with annual outbreaks occurring between October and May in temperate climates. At least half of the infant population becomes infected during their first RSV contact and almost all children have been infected by 2 years of age. RSV infection has been identified as a high-risk factor that predisposes children with prematurity, congenital heart disease, neurodevelopmental disorders and Down syndrome, as well as severely immunocompromised patients, to higher morbidity and mortality.
Influenza virus	Three types of influenza virus have been identified, designated A, B and C. They are responsible for epidemics of respiratory illness that occur almost every winter and are often associated with increased rates of hospitalisation.
Human parainfluenza virus (HPIV)	HPIV-1 and HPIV-2 are generally associated with laryngotracheobronchitis (croup), upper respiratory tract illness and pharyngitis, whereas HPIV-3 is a major cause of infant bronchiolitis and is associated with the development of pneumonia in susceptible subjects.
Adenovirus	Adenoviruses may cause conjunctivitis, pharyngitis (pharyngoconjunctival fever), bronchiolitis and pneumonia.
Coronavirus (CoV)	CoVs are a large family of RNA viruses. CoVs can rapidly mutate and recombine, leading to novel CoVs. The novel CoV severe acute respiratory syndrome coronavirus (SARS-CoV-1) emerged in 2002 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012. The 2019 novel CoV, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is currently causing a severe outbreak of disease (termed COVID-19). In humans, CoVs mostly cause respiratory and gastrointestinal symptoms. Clinical manifestations range from a common cold to more severe disease such as bronchitis, pneumonia, SARS, multiorgan failure and even death. SARS-CoV-1, MERS-CoV and SARS-CoV-2 seem to affect children less commonly and to cause fewer symptoms and less severe disease in this age group compared with that in adults and are associated with much lower case-fatality rates.
Human metapneumovirus (HMPV)	Symptoms of HMPV infection range from upper respiratory tract disease to severe bronchiolitis and pneumonia. HMPV is an important cause of RSV-like illness.
Human bocavirus (HBoV)	1–3% of lower respiratory tract infections in infants are caused by HBoV. A variety of signs and symptoms have been described, including rhinitis, laryngitis, cough, dyspnoea, wheezing, pneumonia, acute otitis media, fever, nausea, vomiting and diarrhoea. HBoV1 is an important cause of lower respiratory tract illness.

of a panel of respiratory pathogens may give both quantitative and semi-quantitative results, allowing the detection of up to about 20 different pathogens in parallel in a clinical sample.

The main value of testing for viruses in children who present with a respiratory tract infection is to differentiate between viral and bacterial infections to facilitate clinical decision making regarding further investigations, the need for antibiotic therapy and the use of oseltamivir in influenza, and also from the perspective of infection control. We suggest that for many healthy immunocompetent children presenting with typical viral respiratory tract symptoms, the diagnosis can be made clinically, and frontline clinicians should think critically before automatically requesting an expensive respiratory viral test, the results of which may not contribute to the child's treatment.

Bacterial infections

Specimens for bacteriological culture should be collected as soon as possible after the onset of disease and before the initiation of antimicrobial therapy.

Upper respiratory tract infections

Pharyngitis includes tonsillitis, tonsillopharyngitis and nasopharyngitis. *Streptococcus pyogenes* causes 15–30% of acute pharyngitis in children. Identification can be by culture or from a rapid antigen detection test from a throat swab. Retropharyngeal, parapharyngeal and peritonsillar abscesses have a similar microbiology; most are polymicrobial infections and include anaerobes.

In acute otitis media, there is acute inflammation; the aetiology is 5% viral, 75% bacterial, and 20% mixed bacterial and viral. The most common causative organism is *Streptococcus pneumoniae* (pneumococcus).

The common causes of sinusitis are *S. pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. These organisms, along with *Staphylococcus aureus* and *S. pyogenes*, account for >90% of sinusitis in children. Other causative organisms include nontypeable *H. influenzae*, *Haemophilus parainfluenzae*, *S. aureus* and *S. pneumoniae*.

S. aureus is the most common bacterium causing tracheitis. A significant proportion of infections are polymicrobial.

Fresh pus, fluid or tissue from the sinuses and pharyngeal swabs from the tonsils and/or the posterior pharynx are the main upper respiratory tract specimens taken for microbiology culture or PCR (*e.g.* for *Bordetella pertussis*, causing whooping cough, or *Mycoplasma pneumoniae*, an atypical bacterium causing mild respiratory infection, which are difficult to culture). Following detection of the pathogen in culture, antibiotic susceptibility testing is usually performed.

Lower respiratory tract infections

Lower respiratory tract infections (pneumonia, bronchitis and bronchiolitis) are the third most important cause of mortality worldwide and are responsible for millions of deaths annually. The aetiology of pneumonia varies based on patient age, vaccination status, immunological status and the clinical setting. Determining the aetiology of pneumonia is difficult, and the choice of antimicrobial therapy is often empirical. *S. pneumoniae* is the most common bacterial aetiology of community-acquired pneumonia in children. *H. influenzae* type b (Hib) was an important cause but is now rare since the introduction of the Hib vaccine. *S. aureus* pneumonia is also infrequent but may progress rapidly. In hospital-acquired pneumonia, pathogens such as *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Serratia* spp. occur most

frequently. In addition, there are many bacteria that may infect the lower respiratory tract and cause secondary bacteraemia.

Candidate lower respiratory tract specimens for processing include sputum, BAL and pleural fluid (*via* thoracocentesis). Gram staining is an easy, cheap and fast method that may provide helpful information within 1 h (*e.g.* from BAL samples). Culture for identification of the responsible organism and susceptibility testing are useful in cases of resistance to initial antibiotic treatment and in immunocompromised or CF patients.

Antigen detection in blood and urine has a limited role in the diagnosis of bacterial pneumonia. Urine specimens may be used for the detection of antigens from *S. pneumoniae* and *Legionella* spp. Urine detection of the polysaccharide antigen C, which is present in all pneumococcal serotypes, has high sensitivity among children with documented invasive pneumococcal infection; however, the ability of this method to discriminate between true pneumococcal disease and rhinopharyngeal carriage is questionable, and it is not recommended in the recent guidelines for diagnosis of community-acquired pneumonia.

Acute and convalescent serological testing is used for the diagnosis of pathogens of atypical pneumonia such as respiratory viruses and *Mycoplasma* and *Chlamydia* spp. A significant rise in serum titre (≥4-fold) is of diagnostic value. An ELISA for IgM detection may diagnose infection using only one sample if this is collected after day 10 of illness.

Nucleic acid persists in specimens after the initiation of treatment and may be detected in smaller and noninvasive specimens. PCR using blood or pleural fluid specimens is used mainly for the detection of *S. pneumoniae* and *H. influenzae*, with the sensitivity and specificity of the method depending on the specimen.

The diagnosis of empyema is strongly supported by the presence of thick pus with bacteria demonstrable by Gram staining, a pH <7.3 or a glucose concentration <60 mg·dL^{-1}. The average white blood cell count in empyema fluid is 19 000 cells·mm^{-3}. These findings may be variably present and must be interpreted in their clinical context.

Despite tremendous advances in diagnostic laboratory technology, identifying the pathogen(s) causing pneumonia remains challenging because clinicians and researchers test specimens distant from the site of infection. These tests may lack sensitivity (*e.g.* blood culture, which is only positive in a small proportion of children with pneumonia) and/or specificity (*e.g.* detection of pathogens in upper respiratory tract specimens, which may indicate asymptomatic carriage or upper respiratory tract infection). While highly sensitive nucleic acid detection methods and testing of multiple specimens improve sensitivity, multiple pathogens are often detected, and this adds complexity to the interpretation and/or identification of the aetiological agent.

Mycobacterial infections

TB is the most prevalent chronic infection in the world, with one-third of the global population infected. Most infections are asymptomatic (latent TB). Children ≤5 years of age have a high risk for progression to active TB disease. In adults and older children, re-activation of latent TB causes active pulmonary TB disease in ~10% of individuals. To diagnose TB disease, appropriate specimens are sputum, induced sputum, gastric aspirate, BAL fluid, transbronchial biopsy material, urine, blood and cerebrospinal

fluid. Gastric aspirates are frequently obtained, as children cannot easily produce sputum. *Mycobacterium tuberculosis* complex, comprising different mycobacterial species (mainly *M. tuberculosis*), may be recovered from gastric aspirates in almost 40% of children with radiographic evidence of significant pulmonary TB; the culture yield for *M. tuberculosis* is 10–20% from BAL samples and 20–30% from (induced) sputum.

Tuberculin skin test

The tuberculin skin test (TST) remains the most widely employed test for the diagnosis of active and latent TB in children. The tuberculin reaction should be read 48–72 h following injection of tuberculin into the skin. A number of factors have been associated with false-positive tuberculin reactions and decreased TST specificity including reactivity in children vaccinated with the bacillus Calmette–Guérin (BCG) vaccine, an attenuated strain of *Mycobacterium bovis*. The TST should be interpreted in the same way for patients who have or have not received a BCG vaccination; however, this will lead to some children with false-positive TST results being treated.

Interferon-γ release assays

The identification of genes in the *M. tuberculosis* genome that are absent from the *M. bovis* BCG vaccine and most nontuberculous mycobacteria has allowed the development of more specific and sensitive tests for detection of *M. tuberculosis* infection, including latent infection. Interferon (IFN)-γ release assays (IGRAs) are designed to measure the host immune response to *M. tuberculosis* complex rather than the presence of the organism itself. In persons with *M. tuberculosis* infection, sensitised memory/effector T-cells will produce IFN-γ in response to *M. tuberculosis* antigens, which is the biological basis for IGRAs. Available data suggest that the TST and IGRAs have similar accuracy for the detection of *M. tuberculosis* infection or the diagnosis of active TB in children. Compared with the TST, IGRAs are more specific (>90%) and are not affected by BCG vaccination, as the target antigens are not present in the *M. bovis* BCG vaccine strains. Although the direct cost of IGRAs is greater than that of the TST, IGRAs may be cost-effective in cases where there is difficulty in interpreting a TST or where the clinical index of suspicion is high but the TST is negative.

Tests such as IGRAs and the TST for the detection of *M. tuberculosis* infection are most helpful as adjunctive tests to confirm disease in a patient with a high probability of active disease. The likelihood that a positive TST represents true infection (positive predictive value) increases as the prevalence of infection with *M. tuberculosis* increases in that population. The same is true for IGRAs. Interpretation of the TST reaction is based on risk of infection. In general, in children <5 years of age, a TST should be the preferred method, while in children ≥5 years an IGRA should be used.

Staining and microscopic examination of sputum or BAL fluid

Acid-fast staining using the Ziehl–Neelsen technique and microscopic examination is the easiest, quickest and least expensive diagnostic procedure but is of limited sensitivity (the lower limit of detection of ~10^4 bacteria·mL^{-1} corresponds to a sensitivity of 60%), particularly in children due to the higher frequency of paucibacillary TB.

Culture of mycobacteria for identification and susceptibility testing

Culture is the most important laboratory test for the diagnosis and management of TB. Mycobacterial culture from gastric aspirates is a useful method of diagnosis in

children with suspected pulmonary TB. The role of bronchoscopy in evaluating children with pulmonary TB is controversial. Bronchoscopy can be useful to define anatomy or bronchial obstruction, or to clarify the diagnosis, but cannot be recommended solely to collect culture specimens in children. In high-risk groups, such as patients with immunodeficiency where a positive diagnosis is needed and TSTs are often falsely negative, bronchoscopy can be useful.

Detection of mycobacterial nucleic acid

Direct detection of *M. tuberculosis* DNA in clinical samples has been performed using NAATs, most often PCR. When compared with the clinical diagnosis of pulmonary TB in children, the sensitivity of PCR for sputum or gastric aspirates has varied from 25% to 83% and the specificity from 80% to 100%. The major use of PCR in children may be when the diagnosis of TB is not readily established on clinical and epidemiological grounds, and perhaps in children with HIV infection for whom a greater variety of causes of pulmonary disease must be considered.

NAATs should not be used for treatment monitoring as they will continue to give positive results for long periods after therapy because they are unable to distinguish live from dead bacilli. Further research is needed before NAATs can be recommended for diagnosis. NAATs are also able to detect drug resistance. The World Health Organization (WHO) recommends the Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) as the initial diagnostic test in children and adolescents suspected of having multidrug-resistant TB or HIV-associated TB.

Summary

The gold standard for diagnosis of childhood TB is the triad of:

- An abnormal chest radiograph and/or clinical findings consistent with TB
- A positive TST or IGRA result
- A history of contact with an infectious TB case within the past year

In all children presumed to have intrathoracic TB, bacteriological confirmation should be sought through examination of appropriate biological samples by smear microscopy, rapid molecular tests, species identification and drug-susceptibility testing with culture-based techniques in a quality-assured laboratory. In the event of negative bacteriological results, a diagnosis of TB should be based on the presence of abnormalities consistent with TB on chest radiography or other imaging, a history of exposure to an infectious case, evidence of TB infection (positive TST and/or positive IGRA) and/or clinical findings suggestive of TB. For children presumed to have extrapulmonary TB, appropriate specimens from the suspected sites of involvement should be obtained for microscopy and rapid molecular tests recommended, together with species identification and drug-susceptibility testing with culture-based techniques, plus histopathological examination.

Fungal infections

Filamentous fungi of the genus *Aspergillus* may cause transient asymptomatic colonisation, pulmonary hypersensitivity reactions and life-threatening tissue-invasive infections predominantly of the lung with or without dissemination in patients with congenital or acquired deficiencies in host defences. Most cases of human disease are caused by *Aspergillus fumigatus*, followed by *Aspergillus flavus* and, less commonly, *Aspergillus niger* and *Aspergillus terreus*. Hypersensitivity reactions caused by *Aspergillus* spp. result mainly in allergic bronchopulmonary aspergillosis.

Bronchopulmonary colonisation occurs in patients with asthma, bronchiectasis, CF and PCD. In severely immunocompromised patients, invasive aspergillosis is the most frequent entity, while a variety of fungi can cause invasive sinopulmonary disease, including Zygomycetes, *Fusarium* spp. and *Scedosporium boydii*.

Lung or airways infection by endemic fungi or *Aspergillus* spp. can be diagnosed by respiratory tract culture or serum IgG testing. Sputum, induced sputum and bronchial specimens are all suitable for detecting fungi; microscopy, fungal culture, detection of galactomannan antigen, and PCR for detection of *Aspergillus* spp. and Zygomycetes are useful tests. Chest CT and bronchoscopy with BAL are very helpful in the diagnosis of pulmonary invasive aspergillosis.

Microscopic examination of sputum or BAL fluid, and culture

Microscopy and culture of samples from the clinically affected site remain the gold standard, but technical problems in obtaining an appropriate specimen, the time required for culture and negative results all limit an efficient and rapid diagnosis. Although *Aspergillus* spp. can colonise the respiratory tract, isolation from sputum or BAL fluid in an immunocompromised patient with pneumonia is highly suggestive of invasive disease.

Given this background, detection of fungal cell wall antigens and DNA in blood and other tissues may enhance the diagnosis of invasive aspergillosis.

Galactomannan assay of serum and BAL fluid

Detection of galactomannan, a polysaccharide component of the *Aspergillus* cell wall, is a diagnostic test for invasive aspergillosis, but most data refer to results in adults. The presence of galactomannan in BAL fluid is an alternative serological diagnostic marker, especially for invasive pulmonary aspergillosis, which constitutes the most common presentation of invasive aspergillosis. False-positive tests occur more commonly in children than in adults, and a negative test does not exclude the diagnosis. The reported sensitivity of galactomannan detection in BAL fluid is in general higher than that in serum due to the increased fungal burden in the bronchi of patients with pulmonary invasive aspergillosis.

Detection of fungal nucleic acid

PCR amplification coupled with DNA sequencing can provide valuable diagnostic information for patients whose specimens have yielded negative results from culture assays. The tests provide valuable and rapid information and have the potential to reduce morbidity and mortality.

Summary

The galactomannan test can be used in children with caution. Molecular methods such as PCR present the same problems and difficulties as in adults. Chest CT, as well as bronchoscopy with BAL, are strongly recommended in patients with the suspicion of pulmonary invasive aspergillosis. Serum and BAL fluid galactomannan assessments are recommended as markers for the diagnosis of invasive aspergillosis. PCR should be considered in conjunction with other diagnostic tests. Pathogen identification to the species complex level is strongly recommended for all clinically relevant *Aspergillus* isolates, and antifungal susceptibility testing should be performed in patients with invasive disease in regions with resistance found in contemporary surveillance programmes.

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Immunisation against respiratory pathogens

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Acute lower respiratory tract infections are still the leading cause of global child mortality. Acute lower respiratory tract infections caused by respiratory syncytial virus (RSV) (an enveloped single-stranded RNA paramyxovirus), *Streptococcus pneumoniae* (a Gram-positive bacterium), influenza viruses and *Bordetella pertussis* (a Gram-negative bacterium), and their prevention by vaccination, will be addressed in this chapter.

Key points

- There is broad agreement that prematurely born children with BPD in infancy and children with haemodynamically relevant heart disease during the first year of life may benefit from passive immunisation with palivizumab against respiratory syncytial virus. However, we recommend following the most recent versions of the national guidelines, as they may differ between countries.
- Active immunisation against *Streptococcus pneumoniae* serotypes with polysaccharide–protein conjugate vaccines is recommended during the first 2 years of life, to avoid a significant number of serious pneumococcal diseases.
- Influenza causes seasonal epidemics, but while children are at high risk of infection and hospitalisation, mortality is higher in the elderly. Childhood influenza vaccinations can reduce the disease burden in the paediatric population and prevent the spread of infection in the community. Although currently available influenza vaccines are far from being optimal, they are the best available option.
- Pertussis still represents a relevant health burden, although introduction of vaccination programmes has reduced incidence significantly. A re-emergence of the disease and a shift of infections into older age groups are reported worldwide. Childhood vaccination, repeated booster vaccination and vaccination of pregnant women contribute to herd immunity and to the protection of unvaccinated neonates and infants who are at high risk for severe and even fatal disease courses.

RSV infection

Epidemiology and risk factors

RSV infects 99% of all children by the age of 2 years, with an estimate of 66 000–199 000 deaths being associated with RSV worldwide, 99% of these occurring in developing countries. Generally accepted independent risk factors for severe RSV infection requiring hospitalisation are 1) prematurity, and 2) age <6 months at the start of the RSV season (ranging from October/November to March/April in the northern hemisphere). Other risk factors are: male sex, haemodynamically significant congenital heart defects, BPD, Down syndrome, presence of older siblings/residential crowding and exposure to environmental tobacco smoke. Additional risk factors for severe RSV infection are malformations, neuromuscular disease, liver disease, chromosomal abnormalities, immunodeficiencies (congenital and acquired) and inborn errors of metabolism. A comprehensive review of risk factors predisposing to RSV infection is beyond the scope of this chapter.

Immunisation

The development of RSV vaccines to actively immunise the host has not yet led to satisfying results. In summary, either the immune responses were weak or short lasting, repetitive immunisation was required, or live attenuated vaccines even led to vaccine-primed disease enhancement, which is unacceptable in children at risk. However, the natural course of RSV infection can be modified by passive immunisation with neutralising antibodies by monthly intramuscular administrations of palivizumab, a humanised monoclonal IgG1 antibody directed against the F-protein of RSV. Palivizumab was originally approved for the prophylactic treatment of infants born prematurely (before the 35th week of gestation) and for the prophylactic treatment of children up to 2 years of age treated for BPD <6 months before the anticipated RSV season. This recommendation was based on a double-blind, placebo-controlled, multicentre, multinational trial mainly conducted in northern America. Approval was later extended to children <2 years of age with pulmonary hypertension, relevant left–right or right–left shunting, and pulmonary venous congestion.

Given the high costs of passive immunisation with palivizumab, and the fact that palivizumab never proved to lower RSV-associated mortality but only to protect a subpopulation of patients from rehospitalisation, passive immunisation against RSV remains a highly debated public health issue, as (from an economic point of view) the costs of passive vaccination of large populations should be lower than the costs of rehospitalisation of patients with RSV infection. The number needed to treat to avoid rehospitalisation depends on the baseline rehospitalisation rate without RSV prophylaxis, a number that depends strongly on the proportion of children developing BPD. If the basal proportion of prematurely born children with BPD is lower, the rehospitalisation rate due to RSV will be lower than published by the IMpact trial in 1998 (for patients in the USA, UK and Canada) and the number needed to treat will be higher than originally proposed in 1999 for a cohort comprising almost 50% prematurely born children with BPD.

Notably, national guidelines on who should receive palivizumab differ substantially. This can be exemplified by comparing the Swiss and Austrian recommendations. Although it is rather unlikely that the Swiss and Austrian populations differ significantly in 1) ethnic or genetic background, 2) risk factors for severe RSV infections, or 3) rehospitalisation rates due to RSV infection, the Swiss recommendations are more restrictive than the Austrian guidelines. In Switzerland, palivizumab is recommended only for infants

aged <12 months with severe BPD or with haemodynamically significant heart disease and additional risk factors. In contrast, the Austrian guidelines recommend the use of palivizumab for all children 1) born prematurely under 28 weeks of gestation below the age of 12 months, 2) born prematurely at 28–32 weeks of gestation and with certain risk factors under the age of 6 months, or 3) born prematurely at 32–36 weeks of gestation below the age of 3 months until the beginning of the RSV season based on a risk score.

Given the lack of evidence for the effectiveness of passive immunisation against RSV for many conditions, recent recommendations of the American Academy of Pediatrics have become more restrictive. In general, children born before 29 weeks of gestational age may receive palivizumab under the age of 12 months. A general recommendation for children no longer exists, despite individual indications. For children with BPD, there is an indication for palivizumab when born under the gestational age of 32 weeks with oxygen supplementation for >28 days during the first year of life. In the second year of life, palivizumab may be given to children born under 32 weeks of gestational age during continuous oxygen supplementation. Also, children with significant congenital heart defects may benefit from palivizumab during the first year of life.

A recently published German guideline clearly recommends palivizumab for prematurely born children at the age of ≤24 months at the start of the RSV season, who were supplemented with oxygen due to BPD ≥3 months before the RSV season. Children born at or before 28 weeks plus 6 days gestational age are at medium risk during the first 6 months and may receive palivizumab. Children born between 29 and 35 weeks gestational age are at medium risk during the first 6 months and may receive palivizumab if certain risk factors are present, although there are insufficient data for a clear recommendation for or against the immunisation.

Summary

In summary, over 20 years after approval of passive immunisation against RSV, recommendations are still mainly based on a single multinational, randomised, placebo-controlled trial for prematurely born children and on a single multinational, randomised, placebo-controlled trial for children with congenital heart disease. According to medical as well as economic criteria, there is broad agreement that prematurely born children with BPD in infancy and children with haemodynamically relevant heart disease during the first year of life may benefit from passive immunisation against RSV. However, many guidelines recommend the use of palivizumab for children born before 28 weeks of gestation regardless of additional risk factors, which is an approach that is still under debate. There are no sufficient data about the long-term outcome of severe RSV disease, a highly important aspect from a clinical point of view.

RSV infection represents an at least partly unresolved health issue. We recommend following the most recent versions of the national guidelines, as they may differ between countries.

Pneumococcal pneumonia

Epidemiology and risk factors

While viral pneumonia is very common, especially in young children, *S. pneumoniae* leads to substantial morbidity and mortality in children, with an estimated 10 million deaths per year worldwide, particularly in developing countries. The most common form of the disease is bacteraemic pneumococcal pneumonia, which shows peaks

of incidence below 2 years of age and above 65 years of age. In acute otitis media, *S. pneumoniae* remains the most frequent bacterial pathogen. While in developed countries *S. pneumoniae* in adults is a common cause of community-acquired pneumonia, in children in developed countries *S. pneumoniae* is a leading cause of invasive pneumococcal diseases (IPDs), notably meningitis and sepsis. The annual overall European incidence of IPDs in children aged <2 years is estimated to be 44 cases per 100 000 population. Children born prematurely, and those with sickle cell disease, cochlear implants and cerebrospinal fistulae, HIV infection, secondary loss of the spleen, or primary immunodeficiencies due to either a defect in opsonisation, phagocytosis of opsonised bacteria or in Toll-like receptor signalling, are at increased risk of pneumococcal diseases. There are 40 serogroups and 91 serotypes of *S. pneumoniae*, and 20 of these account for >70% of IPDs occurring in all age groups. The only natural reservoir of *S. pneumoniae* is the human nasopharynx, and colonisation of the nasopharynx is a prerequisite for both individual disease and infections of others. Generally speaking, active vaccination is the most promising strategy to prevent pneumococcal diseases worldwide. Given that pneumococcal resistance to antimicrobial agents is a growing problem in all age groups, vaccination strategies as the most effective form of prevention seem even more critical.

Immunisation

Current vaccines use bacterial capsular polysaccharides. These induce serotype-specific antibodies that activate and fix complement, and promote bacterial opsonisation and phagocytosis. The 23-valent pneumococcal polysaccharide vaccine (PPV23) is based on purified polysaccharide and was introduced in 1983. The heptavalent polysaccharide–protein conjugate vaccine (PCV7), introduced in 2000, is based on capsular polysaccharides covalently conjugated to a protein carrier. PCV7 and later PCV10 have been replaced by PCV13.

PPV23 elicits antibody responses in 60–80% of children aged >2 years after a single intramuscular injection. PPV23 is not sufficiently immunogenic in children <2 years of age: it does not prevent mucosal colonisation and does not elicit immune memory. The clinical effectiveness of PPV23 in children between 6 and 24 months of age for the prevention of pneumococcal diseases is limited. In high-risk patients (*e.g.* asplenic patients or before the start of an immunosuppressive therapy), PPV23 administered (at least) 8 weeks after a PCV may prove to exert additional effects.

PCVs, in contrast, are sufficiently immunogenic in children <2 years of age after three or four intramuscular injections. PCVs elicit immune memory and prevent nasopharyngeal colonisation, thus promoting herd immunity. This has probably led to an even more substantial decrease in pneumococcal diseases in the elderly than in those vaccinated. Since the introduction of PCVs in 2000, vaccine efficacy has been shown to be 77–97% for the avoidance of IPDs and 19–37% for the avoidance of pneumococcal pneumonia. Also, PCV7 vaccination has demonstrated modest beneficial effects in healthy infants with a low baseline risk for acute otitis media. Furthermore, PCVs have proved beneficial in HIV-infected children for the prevention of both IPDs and pneumococcal pneumonia. Active vaccination against *S. pneumoniae* is beneficial not only from the individual, medical point of view but also from the socioeconomic point of view. The saved costs from reduced morbidity and mortality outweigh the costs of vaccination, regardless of the epidemiological background and the price of the vaccine. The obvious current success of pneumococcal vaccines has been shadowed by concerns about serotype replacement. With regard to PCV7, studies have confirmed that serotypes not contained in PCV7 not only repopulated the

niche in the human nasopharynx but may also have caused pneumococcal diseases (*e.g.* serotype 19A). The challenge of serotype replacement has partly been met by the introduction of PCV10 and later PCV13 vaccines comprising more serotypes. However, the approach to overcoming serotype replacement by introducing more and more serotypes in one vaccine is technically limited. Thus, it may become necessary to change the strategy by vaccinating against stable cell surface virulence protein(s), such as pneumolysin and pneumococcal surface protein A, which are shared by many pneumococcal serotypes.

Summary

We strongly recommend active immunisation against *S. pneumoniae* serotypes with PCVs during the first 2 years of life, as active immunisation will avoid a significant number of serious pneumococcal diseases.

Influenza

Epidemiology and risk factors

Influenza is caused by a group of RNA viruses divided into three genera (influenza A, B and C), with influenza A and B being the more relevant. Even within these genera, influenza viruses are diverse and undergo dynamic changes of their RNA (genetic shift and genetic drift), along with changes of their membrane proteins like haemagglutinin (H1–H18) and neuraminidase (N1–N11). These differences have effects on the pathogenic and immunological properties of the viruses.

Each year, seasonal influenza affects 5–20% of the general population during the winter season. Complications comprise pneumonia (including bacterial superinfection), myocarditis, febrile seizures, encephalitis, sinusitis and otitis media.

Out of 1 billion cases worldwide each year, 3–5 million are estimated to be severe, leading to 290 000–650 000 influenza-related deaths annually. Children are at high risk of influenza infection and play an important role in spreading the virus within families and the community. Children aged <5 years and especially <2 years are at high risk of serious disease, hospitalisation, complications and even death.

Immunisation

Currently available influenza vaccines do not provide long-lasting universal immunity against a high number of different strains of the virus. Consequently, production of vaccines against influenza has to consider the antigenic variability of seasonal influenza viruses. Each year, the World Health Organization (WHO) makes recommendations on the composition of the influenza vaccines based on the expected prevalence of circulating viruses in the following season indicated by surveillance data obtained by designated influenza centres around the world.

Currently available influenza vaccines contain two lineages of influenza A virus (H1N1 and H3N2) and either one lineage (making a trivalent vaccine) or two lineages (making a tetravalent vaccine) of influenza B virus. While most of the available influenza vaccines are inactivated vaccines for intramuscular administration, a tetravalent live attenuated influenza vaccine for intranasal administration has also been distributed in recent years.

As for many other vaccines, recommendations vary widely, from vaccinations only of high-risk persons to universal yearly vaccination of all persons aged >6 months. The WHO recommends seasonal influenza vaccination of children aged 6 months to

5 years, elderly individuals (aged >65 years), individuals with specific chronic medical conditions, and healthcare workers. With highest priority, the WHO additionally recommends vaccination of pregnant women. Children aged <9 years who are vaccinated against influenza for the first time should receive a second dose of the seasonal influenza vaccine ≥4 weeks after the first dose.

Many studies analysing efficacy (comparing vaccinated and unvaccinated people) or effectiveness (evaluating community effects in vaccinated and unvaccinated people) of influenza vaccination have showed benefits, with heterogeneous significance. Several factors contribute to the diversity of results, as vaccine efficacy/effectiveness varies 1) by season, due to the degree of mismatch between circulating strains and vaccine strains, 2) for different strains and consequently by season, depending on the dominant strains, 3) by age of the vaccinated cohort, and 4) by the vaccine type used (inactivated influenza vaccine *versus* live attenuated influenza vaccine), also depending on the dominating strains. Additionally, interpretation of the results varies due to different end-points, such as occurrence of proven influenza, influenza-like illness, hospitalisation and pneumonia. Besides individual efficacy, routine influenza vaccination of children has been shown to be able to induce indirect protection.

Many efforts are being made to improve the performance of influenza vaccines. Different adjuvants to gain long-lasting immunity and new production techniques (recombinant DNA technologies and reverse genetics technologies) to gain immunity against a high number of different antigenic variants are under development.

Summary

Influenza causes seasonal epidemics with high numbers of infected persons of all ages each year. While children are at high risk of infection and hospitalisation, mortality is higher in the elderly. The introduction of childhood influenza vaccination can reduce the disease burden in the paediatric population and mitigates the crucial role of children in spreading the infection in the community. Although currently available influenza vaccines are far from being optimal, they are the best available option to prevent this disease and to alleviate its impact on individuals and public health.

Pertussis

Epidemiology and risk factors

Pertussis (also known as "whooping cough") is a respiratory infection caused by *B. pertussis*, causing endemic outbreaks without seasonality in developed as well developing countries worldwide. Cough caused by other species (*Bordetella parapertussis* and *Bordetella holmesii*) may resemble symptoms of pertussis. Typical symptoms of pertussis comprise paroxysmal rapid coughing leading to expulsion of air from the lungs and consequently to enforced inhalation with a loud "whooping" sound.

Although vaccination programmes decreased the incidence of pertussis decades ago, re-emergence of pertussis has been recognised worldwide during the last 20 years, with global estimates of 10–50 million cases and 200 000 deaths each year.

The natural course of the disease is characterised by three typical stages (catarrhal, paroxysmal and convalescent stages) but atypical presentations in neonates and infants or adults are not infrequent. While adults often show milder disease courses, which may delay diagnosis and therefore represent an epidemiological risk of transmission, neonates and infants are at high risk of developing severe disease with

hyperleukocytosis and respiratory failure. The rate of fatal outcomes is high in this age group and is considered to account for 80% of pertussis-related deaths. Viral co-infections are common in patients of this age group.

In Europe, the notification rates vary between six and 10 per 100 000 inhabitants. Distribution between European countries is unequal, with a few countries like Germany, Denmark, Norway and Sweden contributing high proportions of cases. In these countries, adults account for the majority of reported cases. It is noteworthy that these data are subject to significant changes over the years, due to the outbreak-based characteristics of the disease.

Several factors are discussed as potential explanations for the worldwide re-emergence of pertussis infections after immunisation programmes had led to a significant decline before: 1) evolution of circulating *B. pertussis* strains, 2) under-immunisation and loss of immunity among adults and consequently increasing transmission, 3) better diagnostics (PCR and multiplex PCR) with enhanced availability, 4) changes in awareness and notification, and 5) the switch from whole-cell to acellular pertussis vaccines.

Immunisation

A whole-cell pertussis vaccine became available for routine childhood vaccination in the 1940s in the USA, where it was administered in a combination with vaccine components against diphtheria and tetanus toxoid (in a combination vaccine known as "DTP"). Observational studies and clinical trials showed an efficacy of these vaccines of 70–90% to prevent serious pertussis disease. In the USA, the annual rate of pertussis cases per year dropped from >200 000 in the 1930s to approximately 1000 in the 1970s. Actual adverse events (like local and systemic reactions) as well as assumed adverse events (like neurological diseases and sudden infant death syndrome) led to the development of less reactogenic acellular pertussis vaccines (known as "aP") with varying numbers and quantities of antigens, different purification and toxin inactivation methods, and different adjuvants. From the 1980s, these acellular pertussis vaccine components were included in combination vaccines (thus known as "DTaP") and replaced whole-cell components in many countries all over the world. Extensive studies before and after approval revealed a comparable or even better efficacy and effectiveness as well as lower reactogenicity of these DTaP vaccines compared to whole-cell DTP vaccines. In contrast, data suggest that current acellular pertussis vaccines are inferior in preventing nasopharyngeal carriage and transmission of *B. pertussis*, therefore being of limited value for the establishment of herd immunity.

Currently, there are varying recommendations for pertussis vaccines in routine immunisation programmes. In European countries and the USA, these recommendations comprise three or four doses during the first 18 months of life, followed by a booster dose between 4 and 7 years of age. In most countries, childhood pertussis vaccination is funded by the national healthcare systems. Repeated booster vaccinations for adults every 10 years (every 5 years for the elderly) are recommended in several countries but are funded in only some of them. Considering the high risk for severe disease in neonates and infants and the fact that primarily mothers (and other household contacts like older siblings) represent the main source of infection of these children too young to be vaccinated, recommendations for additional vaccinations of pregnant women during the second half or third trimester of pregnancy (regardless of the interval since the last pertussis vaccination) were recently introduced in national vaccination recommendations in many countries. In addition to the protection of the

closest contacts, high maternal antibody titres are transmitted placentally and confer passive humoral immunity, protecting the offspring until active vaccination. Although existing maternal antibodies at the time of first vaccination lead to diminished antibody responses, these differences are compensated after booster vaccination. Safety and effectiveness of pertussis vaccination during pregnancy has been documented in several studies, including thousands of mother–child pairs.

Importantly, neither pertussis immunisation nor natural infection confer life-long immunity. Therefore, persons who have experienced natural pertussis infection should be vaccinated/boostered like persons after primary immunisation.

Summary

Pertussis still represents a relevant health burden, although introduction of vaccination programmes has reduced incidence significantly. A re-emergence of the disease and a shift of infections into older age groups are reported worldwide. Several factors are discussed to be responsible for these observations. Routine childhood vaccination is implemented and funded in many countries. Repeated booster vaccination and vaccination of pregnant women contribute to herd immunity and to the protection of unvaccinated neonates and infants who are at high risk for severe and even fatal disease courses.

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Epidemiology and phenotypes of asthma and wheezing disorders

Franca Rusconi, Cristina Ardura-Garcia and Claudia E. Kuehni

Studies of the epidemiology of asthma have flourished in the last 30 years, reflecting the fact that the disease is common in developed and developing countries, the aetiology is still largely unknown and the costs are high. This chapter explains how asthma is assessed in epidemiological surveys, describes time trends and prevalence differences by age and sex, explains the concept of asthma phenotypes, and summarises the current knowledge on the natural history and long-term outcome.

Assessment of asthma in epidemiological studies and time trends

Paediatric asthma guidelines emphasise that asthma remains a complex clinical diagnosis that cannot be made by a single measurement or test. Physicians diagnose asthma on the basis of medical history, physical examination, and assessment of airway inflammation, bronchial hyperresponsiveness and reversibility of airway obstruction. In epidemiological studies, the most common approach uses questionnaires to ascertain whether subjects have had symptoms of asthma or have ever received a diagnosis and specific treatment for asthma from a physician.

The prevalence of asthma diagnosis and symptoms is dependent on the awareness of the disease in the populations studied and on diagnostic labels. The same child might be diagnosed with "asthma" by one doctor and with "wheezy bronchitis" by another. Thus, the preferred approach to assessing asthma prevalence in epidemiological studies is based on specific symptoms, particularly current wheeze (wheeze during

Key points

- Asthma and wheezing disorders are heterogeneous conditions in terms of risk factors, age of onset, clinical phenotype, severity, response to treatment and long-term course.
- Despite a large body of research, the factors explaining time trends and international disparities in asthma prevalence remain largely unknown.
- Both the severity of asthma and lung function show a strong trend from early childhood to adulthood.
- It is important to study phenotypes, endotypes and the clinical course of wheezing illness early in life when it might still be possible to modify the natural history of the disease.

the past 12 months). Ideally, this information is corroborated by physiological measurements, but this is often not affordable in large studies.

The International Study of Asthma and Allergies in Childhood (ISAAC; http://isaac.auckland.ac.nz) is a major initiative involving nearly 2 million children aged 6–7 and 13–14 years from more than 100 countries. It was designed to compare the prevalence of asthma, rhinitis and eczema among countries (phase I, 1994–1995) and their trends over time (phase III, 5–10 years later) using standardised questionnaires. Key findings included the high prevalence of asthma symptoms and asthma diagnosis in English-speaking countries and in Latin America (>20% in most centres), intermediate prevalence in Western Europe (7–18%) and low prevalence (<5%) in Eastern Europe, with a clear north-west to south-east gradient. The lowest prevalence is reported from Africa and Asia, with the exception of affluent countries such as Singapore and Japan. In most high-prevalence regions, particularly English-speaking countries, the prevalence of current wheeze changed little between phase I and III, and even declined in some cases, while most countries with low and intermediate prevalence reported increases. Other recent reports of time trends in Western countries, outside of ISAAC, also suggest that the prevalence of wheeze might have reached a peak. Virtually all countries reported increases in the lifetime prevalence of an asthma diagnosis, irrespective of the prevalence of the symptom of wheeze. This might indicate better recognition and diagnosis of the disease, and more frequent use of the diagnostic label, which is considered less stigmatising today than it has been in the past.

The ISAAC programme formally ended in 2012 and was replaced by the Global Asthma Network (GAN; www.globalasthmanetwork.org), which aims to improve asthma care globally, with a focus on low- and middle-income countries. Although asthma prevalence is on the whole lower in low- and middle-income countries, some have an asthma prevalence similar to that of Western countries. Severe asthma is more common, and inadequate treatment results in a high asthma burden. The Asthma Insights and Reality studies undertaken worldwide suggest a poor perception of asthma control and a low proportion of regular controller use: in Asia Pacific and Latin America, for instance, only 19% and 12%, respectively, of those with severe persistent asthma regularly use a controller medication. This could be influenced by the fact that rigid observation of World Health Organization (WHO) guidelines for treatment of pneumonia might lead, as a side-effect, to underdiagnosis and undertreatment of obstructive airway disorders. Combined guidelines for lower respiratory disease, rather than for pneumonia in isolation, might improve the situation.

The regional and temporal variations in asthma prevalence are mainly attributable to environmental and cultural factors because of wide variations in both asthma symptoms and diagnosis within genetically similar populations. However, the asthma risk factors studied so far (*e.g.* infant feeding, diet, maternal smoking, allergens and air pollution) explain only a small part of the regional variability and time trends. Studies in migrants have generally found a steep increase in prevalence among groups migrating from low- to high-prevalence areas, particularly among those who were born in the host country or migrated during the first years of life. This again suggests that sociocultural and environmental factors, including the interaction with the healthcare system, are important. Asthma risk factors are described in detail in the chapter "Genetic and environmental factors in asthma and wheezing disorders".

Prevalence by age and sex

Both cross-sectional and cohort studies suggest that the prevalence of wheeze is highest in infants and toddlers, and then decreases slightly to remain relatively stable

throughout school age. While viruses, in particular rhinoviruses, can trigger asthma at all ages, the perceived proportion of children with only virus-induced wheeze decreases with age, because other triggers become more important. In older children, wheeze triggered by exercise or aeroallergens and wheeze accompanied by shortness of breath become more frequent, while wheeze triggered by food or laughter and sleep disturbance because of asthma symptoms decrease in prevalence.

In most studies, young boys are reported to have more wheeze, asthma and allergic inflammation than girls. In adolescence, the pattern changes, and new-onset wheeze becomes more frequent in females. Explanations for this include age-related differences in the growth of the airways and lung parenchyma (so-called dysanaptic growth), sex-specific differences in environmental exposures and physical exercise, increased vulnerability towards infectious disease in young boys, hormonal changes occurring during puberty, changes in symptom reporting, and sex-related underdiagnosis and undertreatment in female adolescents.

Wheezing and asthma phenotypes

Wheezing disorders might comprise several distinct phenotypes, possibly representing different disease entities. If this is true, early distinction of phenotypes would allow more focused research into their aetiology and pathophysiology, prescription of treatments and preventative measures targeted to the phenotypes, and improvement in the prediction of long-term outcome. Classically, phenotypes have been distinguished based either on time course or on the main trigger factors.

A distinction of wheezing phenotypes based on time course was first propagated by the Tucson Children's Respiratory Study, based on assessments at 3 and 6 years of age. The study proposed four mutually exclusive wheezing phenotypes:

- Transient early wheezing: wheezing only during the first 3 years of life, triggered mainly by infections
- Persistent wheezing: wheezing beginning in early life and persisting up to school age
- Late-onset wheezing: onset at >3 years of age
- No wheezing

Subsequent cohort studies partly replicated these findings and suggested more temporal patterns, reflecting the highly variable time course of wheezing disorders. Classifications by time course, however, have the disadvantage that they can only be used retrospectively once a child has reached a certain age. Thus, they cannot be used to decide how to treat a child or to inform parents about the likely prognosis.

Phenotypes have also been described on the basis of trigger factors for wheezing. This led to the definitions of:

- Episodic viral wheeze: wheeze occurring episodically only during viral infections
- Multiple-trigger wheeze: wheeze also occurring in response to other factors such as crying, laughter, exercise or allergens, and often associated with atopy

While the distinction between these two groups has been challenged, there is some evidence that a large proportion of children keep their phenotype over time. Recently, multidimensional approaches have been used, whereby phenotypes are defined based on a wider range of concurrently assessed features using statistical clustering methods such as latent class analysis. Features used to define phenotypes include wheezing/asthma-related symptoms, lung function parameters, bronchial responsiveness, atopy and exhaled nitric oxide. This approach allows the identification of distinct groups

that are relatively homogeneous with respect to these features. Using such methods, a large number of intermediate or "new" wheezing phenotypes have recently been described, including trajectories of wheezing phenotypes or lung function over time and different phenotypes of atopy. The applied methods have been complemented by machine learning, neural networks and artificial intelligence. These methods have usually focused on mechanisms such as cytokine responses to rhinovirus, and have clustered the results into "endotypes" (according to specific underlying biological mechanisms) instead of "phenotypes". However, methodologically inherent to all clustering and machine-learning techniques is that these analyses will always distinguish different groups, and the larger the study population, the more groups can be distinguished; thus, results need to be interpreted carefully with respect to clinical or scientific usefulness.

Characterisation of asthma phenotypes or endotypes and trajectories associated with favourable/unfavourable prognosis could potentially allow more focused research into causal mechanisms, and ultimately targeted treatments and personalised preventative measures to decrease asthma morbidity. However, there are many areas of uncertainties, including:

- The influence of sample size, frequency and timing of data collection used for the analyses
- Whether resulting phenotypes and endotypes represent distinctive pathophysiological pathways, a key point for identifying causal factors
- Whether results are generalisable to other populations with different genetic and environmental backgrounds
- Whether the newly defined groups are clinically useful

Natural history and long-term prognosis

Childhood asthma is characterised by a highly variable time course, differing by age of onset, duration of symptomatic periods, and remissions and relapses. This complicates the study of the natural history of asthma. Nevertheless, long-term prospective studies have highlighted important aspects of the disease.

In one of the oldest cohort studies, the Melbourne Asthma Study (Australia), a population-based sample of 7-year-old children with a history of wheeze and an asymptomatic control group were followed over several decades (Phelan *et al.*, 2002). The study found consistent associations between the severity of symptoms in childhood and persistence of asthma up to the age of 50 years: children with frequent wheezing episodes in childhood had more severe asthma and a lower FEV_1/FVC ratio throughout adolescence and adulthood. Eczema, hay fever or allergic sensitisation in childhood also tended to result in more severe asthma later in life. In addition, in a study of the Dunedin birth cohort (New Zealand), children with persistent wheeze throughout follow-up were more likely to be sensitised to common allergens and had lower FEV_1/FVC ratios at 38 years of age than nonwheezers (Sears *et al.*, 2003). In both the Melbourne and Dunedin studies, the lung function deficit was already established by school age, suggesting an early loss of lung function in some asthmatic children.

The Tasmanian Longitudinal Health Study has recently published data from six decades of follow-up (Bui *et al.*, 2018). They identified six different lung function trajectories, of which some tracked throughout life (*i.e.* participants remained on their percentile of the population average), while two did not. Three trajectories were associated with an increased COPD risk, of which two originated in childhood and together explained 40% of COPD cases. Risk factors for these trajectories were early asthma, lower

respiratory tract infections in childhood (bronchitis, pneumonia), atopic disease in childhood and maternal smoking. The other lung function trajectory, which explained 35% of COPD cases in the sixth decade, was associated with active smoking and adult asthma. This study demonstrated how early life, childhood health and preventative measures (*e.g.* immunisations, protection from environmental tobacco smoke) influence the entire life course. However, it also showed that a substantial number of children with poor lung function had accelerated lung growth, with resulting normal lung function in adulthood.

A limitation of older cohort studies is that respiratory symptoms and lung function were first assessed at school age, with missing information on the first years of life. More recent cohort studies have followed children prospectively from fetal life up to adolescence, and assessed lung function in infancy, before the onset of disease. They found that lung function deficits might be congenital in some children, while in others the deficits might be a consequence of severe asthma. Some studies found that low lung function in infancy tracks into adulthood and is associated with irreversible airway obstruction, the hallmark of COPD, while others reported evidence for catch-up growth.

Many groups have attempted to develop prediction models, which would allow us to foretell the future course for affected children. They have tried to answer several questions, such as which preschool children with asthma-like symptoms are at risk of developing asthma at school age, or which school-aged children with asthma will develop persistent wheeze rather than intermittent mild asthma in the future. Studies were based on different populations, such as children who had had healthcare visits for wheeze or children with parent-reported symptoms only, those at high risk of asthma and children in the general population. Some prediction models included noninvasive, easy-to-obtain predictors only, such as family history, comorbidities and precursors of asthma, and severity of early symptoms. Other models included additional clinical tests, such as specific IgE or exhaled nitric oxide. Some models could better predict asthma development and other models could better rule out asthma development, but no model stood out in both aspects, and predictive performance in general remained disappointingly low, suggesting that the set of predictors used in these studies was inadequate, or that the asthma course is inherently nonpredictable.

New data sources in asthma epidemiology

Traditionally, asthma epidemiology has relied mainly on data from cross-sectional surveys or prospective population-based or clinical cohort studies. While cohort studies allow us to collect detailed information on many variables, they have limitations. For instance, they often rely on self-reported data on both exposures and outcomes. Self-reported environmental exposure data, however, might be biased, because parents of sick children might report harmful exposures such as road traffic more accurately than parents of healthy children, while they might underreport exposures for which they feel guilty, such as parental smoking. In addition, cohort studies are often not representative of the general population, because only a proportion of eligible children can be included, and an even smaller proportion remains in the study long term, because many get lost to follow-up.

Recent studies have attempted to avoid these biases by using data that are officially collected for the entire population. Examples include studies from the Nordic countries that use a unique person identifier to link datasets on prenatal care, birth records, hospitalisation records and drug dispensation for the entire population, often many hundreds of thousands or even millions of people. For instance, a study from Sweden

examined prospectively obtained data from three generations to show an effect of both grandmaternal and maternal smoking on child health (Bråbäck *et al.*, 2018). Other datasets that are increasingly used in epidemiology include the detailed health data collected by hospital information systems or health maintenance organisations. Mostly, they use structured data, for instance on coded hospital diagnoses and prescribed treatments. This has allowed, for instance, the linking of hospital admissions or emergency department visits to modelled environmental exposure data on millions of patients, or comparison of asthma exacerbation rates and asthma treatment steps across patients of all age groups in the entire UK population. Advanced text-mining methods using natural language-processing algorithms take the use of information from electronic health records even further by extracting structured information from free text. Preliminary studies have shown that this can be as precise as or even better than manual extraction of data from medical records, which opens the way for large-scale studies in clinical epidemiology in the future.

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Genetic and environmental factors in asthma and wheezing disorders

Erika von Mutius

Asthma is a complex disease attributable to a subject's genetic responsiveness to distinct environmental stressors and protectors. Asthma is not one disease but most likely a syndrome of clinically similar but pathogenically distinct and/or overlapping illnesses, which have not been well understood. Therefore, we use the term asthma in this chapter to include potential subtypes of the disease.

Genetic factors

Asthma heritability (*i.e.* the variance caused by genetic factors) has been estimated to be between 35% and 95%. Asthma heritability can be explained by genetic or epigenetic effects.

Epigenetics comprises functionally relevant changes to the genome that are not due to alterations in the DNA sequence but that influence gene expression. Examples of epigenetic modifications include DNA methylation and histone modification, as well as the production of different RNA forms. Epigenetic changes have been implicated in asthma pathology and have also been shown to be affected by environmental changes. A more detailed review of epigenetics in asthma is, however, beyond the scope of this chapter.

Key points

- Childhood asthma and wheezing disorders are complex diseases in which both genes and the environment play a role.
- Genetic studies have identified numerous risk loci for childhood asthma, in particular the 17q21 locus containing the *GSDMB* and *ORMDL3* genes, a result that has been replicated numerous times; this locus has the strongest effect on childhood-onset asthma to date.
- Epidemiological observations have identified both protective environments and risk factors associated with childhood asthma and wheezing disorders. The most robust and consistent finding relating to risk is environmental tobacco smoke exposure, particularly maternal smoking during pregnancy.
- Gene–environment interactions have been studied for the 17q21 asthma risk alleles, among others, and may be seen as a switch conferring either asthma risk or protection, depending on environmental exposures.

Understanding the genetic disease background is important, as it will help to decipher and better understand the different asthma phenotypes and also to delineate asthma and wheezing illnesses from associated comorbidities such as allergic rhinitis and atopic eczema, as well as from asthma-associated features such as allergic sensitisation, reduced lung function and airway hyperresponsiveness. There is evidence for genetic pleiotropy (*i.e.* genetic factors common to distinct clinical asthma entities) but interestingly also for a role of autoimmune diseases. However, distinct genetic factors have also been shown for asthma and related comorbidities and features. For example, loci found to be associated with lung function were not identified for asthma, implying distinct causal pathways.

Historically, different methods have been used to assess genetic associations with asthma-related traits. The first studies were genome-wide, family-based linkage studies with subsequent positional cloning. By generating hypotheses to be tested in subsequent analyses, these studies led to the discovery of various genetic loci and genes related to asthma, such as *ADAM33* (encoding a disintegrin and metalloproteinase domain-containing protein 33, with a potential role in airway remodelling), *SPINK5* (serine peptidase inhibitor Kazal-type 5, with a role in the integrity of airway epithelium) and *STAT3* (signal transducer and activator of transcription 3, affecting IgE levels). Many genetic variants in asthma have been discovered by candidate-gene approaches, such as *CD14* (cluster of differentiation 14, involved in innate immunity) and *TGFB1* (transforming growth factor β_1), *ADRB2* (β_2-adrenergic receptor) and *NOS1–3* (nitric oxide synthases 1–3) (with roles in lung function, lung growth and development, and allergic airway inflammation). Candidate-gene approaches have, however, been heavily criticised because of methodological problems (*e.g.* low numbers of involved subjects) and lack of reproducibility.

Since the emergence of high-throughput techniques, asthma-related genetic loci have been investigated in very large populations using genome-wide association studies (GWAS) including several hundred thousand single-nucleotide polymorphisms across the whole human genome. GWAS have identified about 20 asthma risk loci that meet stringent thresholds of statistical significance (typically $p<10^{-8}$) and that have been replicated across several studies. These loci include genes involved in immune and allergy (T-helper type 2) pathways (*e.g.* human leukocyte antigen, interleukin (IL)-13, IL-33, thymic stromal lymphopoietin and IL-1 receptor-like 1, which encodes ST2, the receptor for IL-33), transcription factors in many of the known immune pathways associated with asthma (*e.g.* RAR-related orphan receptor A, SMAD family member 3 and GATA binding protein 3), and novel loci (*e.g.* cadherin-related family member 3 and the 17q21 locus containing the ORM1-like 3 (*ORMDL3*) and gasdermin B (*GSDMB*) genes, among others). While the statistical associations are strong, the effect estimates are weak, and contributions of individual variants to asthma risk are quite small. They do not explain asthma heritability. This "missing heritability" may relate to the nature of GWAS in which thousands of patients with asthma are included, which often precludes better phenotyping beyond the "doctor's diagnosis of asthma". Another limitation of GWAS is that they ignore environmental factors, although these are strong determinants of asthma and wheezing illnesses.

Currently, we are far from being able to predict asthma and wheezing illnesses based on a subject's genetic architecture. Thus, the utility of genetic testing in the clinical context is extremely limited.

Environmental factors

Environmental exposures play a very significant role in asthma development. This is exemplified in several studies showing that the prevalence of asthma in genetically

very similar populations but who live in distinct environmental conditions can vary drastically. A recent example is a study among Amish and Hutterite populations in the USA (Stein *et al.*, 2016). Despite having otherwise similar lifestyles and ancestry, Amish school-aged children raised on traditional dairy farms had a 4-fold lower risk of asthma compared with Hutterite children raised on modern, mechanised farms in which the children were not exposed to farm animals early in life (5.2% *versus* 21.3%, respectively). Both populations were very comparable in their genetic make-up, which was distinct from other populations of European ancestry. Moreover, in the same study, the protective effect of the environmental exposure was transferred into an animal model of experimental allergic asthma. Mice administered dust extracts from Amish homes were strongly protected from developing airway hyperresponsiveness and eosinophilia, both hallmarks of asthma, again suggesting that environmental exposures are of tremendous importance.

The most robust and consistent finding conferring asthma risk is environmental tobacco smoke exposure, particularly maternal smoking during pregnancy. In numerous studies, these exposures have been shown to be associated with an increased risk of wheezing and childhood asthma. Passive smoke exposure through other family members also increases the risk of wheeze and childhood asthma in many studies. Interestingly, the ban on tobacco smoke established in Scotland in 2001 significantly decreased the rates of hospitalisation for asthma by ~15%. Moreover, active smoking in children and adolescents has been related to increased risk for new-onset or progression of asthma in this age group.

With respect to outdoor air pollution, studies relating to the density of car traffic, in particular truck traffic on roads in close proximity to the child's residence, have been the most conclusive. Here, particles with aerodynamic diameters between 2.5 µm (which are able to enter the alveoli) and 10 µm (which are too large to enter the alveoli) and ozone and nitrogen dioxide were demonstrated to affect lung growth and to be associated with reduced lung function and airway inflammation in children, even prenatally. This underlines the importance of adverse effects during the most vulnerable phases of lung development early in life and is not limited to outdoor air pollution. Indoor parameters, in addition to environmental tobacco smoke, may also play a role. Moisture damage and mould indoors have repeatedly and consistently been shown to increase the risk of childhood asthma and wheezing disorders.

Importantly, viral infections, particularly rhinovirus and respiratory syncytial virus, are highly prevalent exposures early in life through contact with siblings, day care and other sources. Viral infections interact with facultative pathogenic bacteria of the respiratory tract such as *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae* and can perturb the compositional structure of the upper and lower respiratory tract microbiome. Whether viral infections and certain microbiome compositions are causal factors resulting in the onset of disease or mere bystanders of ongoing inflammatory processes in the host has not been elucidated. An interaction of both viral and bacterial exposures with specific niches provided by inflamed airways resulting in increased damage by the microbes is equally conceivable.

The role of allergen exposure is equally debated. There is evidence that indoor allergen exposure is a determinant for the development of allergic sensitisation towards that particular allergen. In contrast, allergen exposure has not convincingly been associated with the development of childhood asthma and wheezing disorders. Avoidance of house dust mite exposure has not achieved a reduction in asthma risk. However, children who are already sensitised and allergic to indoor allergens such as

house dust mites or cat or dog dander should clear the indoor environments from these allergens as they may trigger their symptoms.

Other lifestyle factors have been shown to play a role. These include the maternal diet in pregnancy as well as the diet in early and later childhood, in particular breastfeeding, a Mediterranean diet and vitamin intake. BMI and obesity also play a role, and have been reported to induce inflammation and increased insulin resistance and further metabolic alterations, which may lead to asthma. Furthermore, there is evidence that, particularly in adolescent females, an increase in body weight, which may in turn be related to early menarche, is a determinant for new-onset asthma. The role of physical activity remains unclear. Reduced physical activity may be a consequence of asthma and wheeze rather than a causal factor for the new onset of disease.

In the context of protective environments, studies have consistently shown that growing up on a traditional farm reduces the risk for asthma and hay fever. These studies have consistently been reproduced in many countries worldwide. The important exposures relate to contact with dairy farm animals, their fodder and unprocessed cow's milk, and have been identified in a number of studies. The protective farm effect on asthma is, at least in part, attributable to environmental bacteria and fungi, which are highly prevalent in these environments. Experimental studies using microbes cultured from farming environments confirm the preventative effect of exposure for the development of allergic asthma in mice.

The role of gene–environment interactions

Given the high prevalence of asthma, it is of major public health relevance to elucidate the effects of genes and the environment. By fixing one parameter in the equation, it is possible to disentangle their individual impacts. As highlighted earlier, genetic factors can be identified by studying populations sharing similar environments, whereas by studying populations sharing the same genetic background but living under different environmental conditions, relevant environmental impacts can be determined. However, asthma and wheezing disorders probably result from a joint effect of genes and the environment and their interaction, *i.e.* the dependence of effects by one factor on the presence or absence of another factor. Technological progress has also advanced the field of gene–environment interactions in asthma, as analyses of gene–environment interactions on a genome-wide level (*i.e.* gene–environment-wide interaction studies) have also been performed. This poses a challenge to even highly advanced computational systems and has not resulted in major breakthroughs in our understanding of gene–environment interactions so far. There is probably even more complexity in gene–environment interaction analysis than in genomic studies alone. The time point when exposures have the greatest effect on the outcome under study has to be taken into account (the window of opportunity). Thus, for gene–environment interaction studies, there is a clear need for similar stringent quality control and replication and the same necessities in study design and careful phenotyping as discussed earlier.

There are examples of gene–environment interactions in the field of asthma and wheezing disorders at different levels of analytical approaches. The first level is that of a known candidate gene and a well-defined environmental exposure with suspected gene–environment interactions, such as in the interaction of endotoxin (a component of the cell wall of Gram-negative bacteria) with the gene for its receptor, *CD14*, for the risk of asthma and/or atopy. Another example is pollutant exposure and the genetic make-up of genes encoding detoxifying enzymes such as glutathione *S*-transferases. In the absence of exposure, no genetic effect is found. Conversely, in the absence of

the genetic shortcoming, no effect of the environmental exposure is seen. However, when both factors interact, then exposure in a genetically susceptible individual results in significant harmful effects.

Another approach is to study potential gene–environment interactions without prior knowledge of underlying mechanisms as, for example, with the 17q21 gene locus in relation to children's environmental exposures, in particular with respect to rhinovirus-induced wheezing illnesses. In two birth cohorts, COAST (Childhood Origins of Asthma) and COPSAC (Copenhagen Prospective Study on Asthma in Childhood), the risk of subsequent asthma among children with recurrent wheeze was strongly increased for carriers of the 17q21 risk alleles (Calışkan *et al.*, 2013). This observation was confirmed in the PASTURE (Protection Against Allergy: Study in Rural Environments) cohort without taking the nature of the viral infection into account (Loss *et al.*, 2015). Interestingly, this locus also interacted with environmental tobacco smoke exposure, thereby possibly increasing the risk of subsequent asthma. Conversely, the 17q21 risk allele carriers are those subjects benefiting most from protective farm animal exposures. Thus, the 17q21 genetic make-up may be seen as a "switch" of responsiveness or lack of responsiveness to environmental exposure, the genetically determined responsiveness to the environment being associated with risk or protection from asthma development.

Summary

Asthma is a complex syndrome where environmental and genetic factors interact in different pathophysiological backgrounds. Deciphering the individual contributions is difficult, as their significance depends on the variance of the cofactors. Only when the exposure is taken into account can the significance of the genetic susceptibility be estimated. Conversely, only when the genetic susceptibility to a certain exposure is known can the effect size of the environmental influence be better understood. A third dimension in childhood asthma is the developmental aspect of growing and maturing immune, airway, lung and neurological systems where certain ages of the child may confer stronger susceptibility to environmental exposures, depending on their genetic make-up. Epidemiological studies may lack sufficient depth of assessment of the environmental, genetic and biological processes to elucidate these complex interactions, given that large studies are usually at the expense of precision owing to the associated costs. Thus, experimental work needs to complement the population-based studies that will have generated the hypotheses to be tested. This iterative process will in the future identify important processes and mechanisms in the pathogenesis of asthma and help identify and better understand the diverse underlying asthma phenotypes.

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Preschool wheezing

Giorgio Piacentini and Laura Tenero

Wheezing and dyspnoea in preschool children are among the most common presenting signs and symptoms in paediatric practice. Approximately one in three children will have at least one episode of wheeze before their third birthday. There is much clinical heterogeneity in phenotypes of children with preschool wheeze, which appears to be similar between populations. Due to this heterogeneity, and despite its common occurrence, relatively little evidence is available on the pathophysiology and treatment of wheezing in preschool children. Therefore, considerable controversy exists in the literature about the classification and the treatment of preschool wheezing disorders. To end this controversy, the underlying pathophysiology and aetiology of preschool wheezing disorders need to be properly understood.

Classification of preschool wheeze

Epidemiological classification

Much of the knowledge on recurrent wheeze and dyspnoea in preschool children comes from a series of well-designed, large-scale birth cohort studies. The most well-known of these was conducted in Tucson, AZ, USA. The main results of this

Key points

- Despite the favourable natural history in the majority of children with wheeze during preschool years, symptoms in this age range can be severe or frequent, justifying maintenance treatment.
- Limited information is available on the pathophysiology of recurrent wheeze in preschool children, which is likely to be complex and multifactorial. As a result, one-dimensional classification systems (*e.g.* episodic viral *versus* multiple-trigger wheeze) are of limited value in diagnosis and management.
- Inhaled corticosteroids are recommended as first-choice maintenance therapy in children with frequent or severe symptoms, irrespective of phenotype.
- If symptoms persist despite maintenance treatment, ongoing exposure to relevant inhalant allergens and tobacco smoke, poor adherence or inhalation technique, alternative diagnoses and relevant comorbidity should be excluded before stepping up therapy.

landmark study, the Tucson Children's Respiratory Study, for children enrolled at birth between 1980 and 1984, are as follows:

- 826 infants were followed from birth
- During the first 3 years of life, 30% of children had had at least one episode of wheeze and half of these children had wheezed more than once
- 60% of wheezy preschool children ceased to wheeze before the age of 6 years (transient wheeze associated with maternal smoking and with wheeze occurring only during viral colds)
- 40% continued to wheeze after their sixth birthday (persistent wheeze associated with eczema, maternal asthma and elevated cord blood IgE)

In contrast with asthma in school-aged children, which is more likely to persist throughout childhood, many wheezy preschool children outgrow their symptoms by school age. This prompted efforts to identify factors that could predict persistence of preschool wheeze into school age, and to classify preschool wheezing disorders into different phenotypes with different treatment response or outcome.

From the birth cohort in the Tucson Children's Respiratory Study, Castro-Rodríguez developed the asthma predictive index (API) in 2000, which is based on a loose and a stringent index (age at onset of wheezing, frequency of wheezing, parental history of asthma, wheezing without colds, eczema, allergic rhinitis, and eosinophilia) to predict outcome at 6 years of age. A negative API (few risk factors for ongoing asthma symptoms by school age) is frequently associated with transient wheezing, whereas a positive API is considered related to persistent asthma.

Other predictive markers have been derived from other cohorts (the Avon Longitudinal Study of Parents and Children (ALSPAC) and the Dutch Prevention and Incidence of Asthma and Mite Allergy (PIAMA)), with the aim of predicting asthma at 6–10 years, although they have some limitations regarding the therapeutic approach to wheeze in preschool children.

Pathophysiological classification

Despite differences between studies, atopy during early childhood has consistently been identified as the most important risk factor for wheeze persisting beyond the sixth birthday, in a dose–effect relationship: the more allergens the child is sensitised to, and the stronger the degree of sensitisation, the greater the likelihood the child's wheeze is going to be persistent. Although asthma risk indices constructed of different risk factors are significantly associated with persistent wheeze in groups of children in birth cohort studies, they have not been validated prospectively, and the predictive value of these indices is too poor to allow meaningful prediction of outcome of preschool wheeze in individual cases.

In 2013, Lazic and colleagues generated a five-class model based on skin-prick tests and specific IgE to common allergens, for two birth cohorts. In the "multiple early" sensitisation class they found a strong correlation of wheeze with asthma, lower lung function, airway reactivity and hospital attendance. The associations were significantly stronger than those related to the presence of only atopic sensitisation.

Phenotypic classification

The finding in the Tucson study that wheeze occurring only during viral colds was associated with transient wheeze suggested that exclusive viral-induced wheeze in early childhood might be an innocuous disease, which is likely to disappear when children get older. However, this hypothesis is not supported by follow-up studies,

Table 1. Different classification systems for preschool wheeze

Atopic *versus* non-atopic wheeze	
Atopic wheeze (or allergic asthma)	≥3 episodes of wheeze and dyspnoea, and demonstrated sensitisation to inhalant or food allergens
Non-atopic (or viral) wheeze	≥3 episodes of wheeze and dyspnoea, only occurring during upper respiratory tract infections, and no evidence of allergic sensitisation to inhalant or food allergens
EVW *versus* MTW	
EVW	Wheezing during discrete time-periods, often in association with clinical evidence of a viral cold, with absence of wheeze between episodes
MTW	Wheezing during discrete episodes, but also between episodes
Mild and infrequent wheeze *versus* severe or frequent wheeze	
Mild and infrequent wheeze	Wheeze with little impact on daily life of affected children, and with a low frequency of episodes (<1 episode per month)
Severe or frequent wheeze	Wheeze with considerable impact on daily life of affected children (requiring hospital admission or emergency room visit), or with a high frequency of episodes (≥2 per month)

EVW: episodic viral wheeze; MTW: multiple-trigger wheeze. Data from Brand *et al*. (2008), Pedersen *et al*. (2011), and Schultz *et al*. (2011).

which showed that the majority of children with episodic viral wheeze (EVW) seen in secondary care continue to wheeze beyond the age of 6 years.

In 2008, a European Respiratory Society (ERS) task force report proposed distinguishing two wheezing phenotypes in preschool children: 1) EVW, defined as wheeze during discrete episodes associated with viral upper respiratory tract infections and no symptoms between episodes; and 2) multiple-trigger wheeze (MTW), defined as wheeze both during discrete episodes and between episodes, with numerous triggering factors including viral colds, mist, exercise, *etc.* (table 1). Based on the evidence available at that time, this distinction was considered to be both clinically plausible (most experts in the ERS task force felt they could distinguish these phenotypes reliably based on the patient's history) and meaningful, because the few published studies appeared to support the view that inhaled corticosteroids (ICS) were the treatment of choice for MTW, and that EVW might respond more favourably to maintenance treatment with montelukast. The ERS task force acknowledged that these recommendations were likely to change with new evidence becoming available.

Limitations of the EVW–MTW phenotype distinction

Although the 2008 ERS task force classification system has been widely adopted, it has been criticised as being too simple to capture the multidimensional nature of preschool wheezing, and it has been suggested that EVW and MTW do not represent different phenotypes, but rather different degrees of severity of the same disease. Characteristics of wheeze that could be used for classification are shown in table 2.

Table 2. Different characteristics of preschool wheeze episodes

Frequency	Frequent *versus* infrequent
Severity	Mild to severe
Pattern	EVW or MTW
Outcome	Transient *versus* persistent

The EVW–MTW classification system is hampered by the fact that viral colds are the main cause of exacerbations, both in EVW and in MTW. New evidence from recent studies has become available on the classification and management of preschool wheezers, and updated recommendations were proposed in 2014 by an international consensus group. First, prospective studies have shown that these phenotypes are not stable over time: when repeatedly taking a history from parents about their preschool child's wheeze symptoms, the symptom pattern changes over time from EVW to MTW and *vice versa*. Secondly, the distinction between EVW and MTW does not take the severity and frequency of episodes of wheeze into account, while in clinical practice these factors are more important in determining the initiation and choice of maintenance therapy than the temporal pattern of symptoms. Thirdly, although statistically significant differences in physiology and pathology between the two phenotypes have been demonstrated, the two phenotypes also show considerable clinical overlap and it is only the final pathway that is different for several risk factors, which makes it difficult to categorise patients into the two phenotypes. Furthermore, the EVW and MTW classification is an ineffective predictor of long-term outcomes, unlike the frequency and severity of the symptoms.

With respect to ICS treatment, a systematic review showed that ICS are effective in reducing preschool wheeze, irrespective of the reported symptom pattern (EVW or MTW). A recent large trial in the USA showed that daily nebulised low-dose budesonide was no more effective in reducing the number and severity of wheezing episodes in preschool children than intermittent use only during symptomatic episodes. While episodic nebulised budesonide was no more effective than episodic use of montelukast in preschool children with viral-induced wheeze, daily use of nebulised budesonide was more effective than daily montelukast in children aged 2–8 years with mild persistent wheezing.

Although the EVW–MTW classification is imperfect in relation to phenotypic instability and absence of clear pathophysiological and therapeutic response, it remains the most useful available classification. However, the wheeze patterns in young children vary over time and with treatment so the distinction between EVW and MTW is difficult in many patients. Based on the available evidence, several classification systems of preschool wheeze have been proposed (table 1). None of these systems is universally accepted, which is not surprising given the limited evidence on which they are based. There is no consensus on the preferred terminology.

The use of objective tools to document airways obstruction and reversibility, as well as airways inflammation with noninvasive markers, represents the goal of future studies.

Diagnostic approach to preschool children with recurrent wheeze and dyspnoea

Wheeze is a nonspecific symptom, which may be caused by a range of clinical conditions. The initial diagnostic approach to a preschool child with wheeze is aimed at excluding serious underlying conditions, which usually present in the form of "atypical wheeze" (table 3). A detailed history and thorough physical examination when the child is symptomatic are usually sufficient to exclude atypical wheeze. If

Table 3. Atypical wheeze: warning signs and possible underlying conditions

Warning sign	Underlying causes (examples)
Persistent symptoms from birth	Tracheobronchomalacia, PCD
Productive wet cough as a main symptom	PCD, CF, protracted bacterial bronchitis, immune deficiency, TB
Never completely symptom free	Tracheobronchomalacia, vascular ring, foreign body aspiration, BPD
Failure to thrive	CF, immune deficiency
Recurrent pneumonia	CF, immune deficiency

history and physical examination suggest the possibility of atypical wheeze, specific further diagnostic testing is indicated.

The majority of preschool children presenting with troublesome wheeze and dyspnoea will have "typical wheeze", after exclusion of the unlikely causes listed in table 3. Because parents differ from physicians in their understanding of the term "wheeze", confirmation of the presence of wheeze by a physician is recommended before initiating therapy. In children with confirmed typical wheeze, the only potentially useful diagnostic test is a test of allergic sensitisation (either skin-prick test or measurement of specific IgE to a panel of allergens in blood) for classification purposes (table 1).

Treatment of acute episodes

The initial treatment of choice in episodes of acute wheeze is an inhaled bronchodilator such as salbutamol, preferably by metered-dose inhaler/spacer combination because this is more effective than treatment delivered by a nebuliser.

The use of oral corticosteroids in preschool children with acute wheezing continues to be debated. Oral corticosteroids are less effective in preschool children with an episode of acute wheeze than in older children with asthma, and are only recommended in children who require hospitalisation and supplemental oxygen for a severe exacerbation, or those with atopic wheeze. Pre-emptive high-dose ICS for viral-induced wheeze, at the start of a viral upper airway infection and continued until this is resolved, although effective, is not recommended because of its effect on growth.

Maintenance treatment

Principles of maintenance treatment are outlined in table 4, and these are in line with asthma guidelines in older children and adolescents. Based on the realisation that parental cooperation is necessary to ensure optimal effects of therapy, the first, and perhaps most important, step of maintenance therapy is to achieve and maintain a therapeutic alliance with patients and parents. Tailored self-management education is needed to ensure that parents understand how and why treatment works, and is most effective when it is delivered repeatedly, addresses parental concerns and cognitions, and incorporates parents' treatment goals for their child. Because wheezing in preschool children largely occurs during discrete episodes with sometimes relatively long symptom-free intervals, parents should understand that the effect of maintenance therapy can only be judged after the child has had one or more subsequent upper respiratory tract infections. A recommendation to reduce exposure to tobacco smoke can only be achieved if this is discussed with parents in a constructive and non-judgemental fashion. If sensitisation to aeroallergens has been demonstrated, reducing the exposure to these allergens is likely to be effective, although evidence in this area is lacking.

Table 4. Principles of maintenance treatment of preschool children with recurrent wheeze

Therapeutic alliance with parents and patient
Non-pharmacological therapy
Self-management education
Maximal reduction of passive smoke exposure
When sensitised to aeroallergens, reduce aeroallergen exposure
Repeated scheduled follow-up
Pharmacological therapy
Inhaled salbutamol on demand
Train and maintain correct inhalation technique
If repeated troublesome symptoms and parents motivated for maintenance therapy, then start low-dose ICS or montelukast[#]
If low-dose ICS do not control symptoms
Check inhalation technique and adherence to treatment
Exclude relevant comorbidity or alternative diagnosis
Add additional controller (ICS, montelukast[#] or long-acting β-agonist)

[#]: because of the risk of serious mental health side-effects, the benefits of montelukast may not outweigh the risks in some patients; the US Food and Drug Administration (FDA) advises assessment of such risks.

The choice of whether to initiate maintenance therapy in preschool children with wheeze depends primarily on the severity and frequency of episodes. The evidence suggests some benefit in the use of ICS in preschool children with recurrent wheezing episodes. These patients, with elevated blood eosinophils and/or aeroallergen sensitisation, may benefit from ICS treatment.

After a systematic review of all available studies using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology, the Dutch Paediatric Respiratory Society, in collaboration with the Dutch Cochrane Centre, recommended ICS as maintenance treatment in preschool children with troublesome wheeze, irrespective of wheezing phenotype. A recent meta-analysis evaluated the efficacy of ICS treatment in children aged ≤6 years with asthma or recurrent wheezing (at least two episodes in the last year). The analysis confirmed daily ICS as the first-line therapy in preschool children with persistent recurrent wheezing.

Although ICS do not alter the long-term outcome or persistence of wheeze, they are effective in controlling symptoms, which is why their use in preschool children with troublesome wheezing symptoms is justified. There is no preference for any specific ICS preparation. The assumed superiority of ICS preparations with ultrafine particles is theoretical, with no evidence from randomised trials to support their use. Although data on side-effects of long-term use are lacking, ICS in this age group appear to be safe.

The Global Initiative for Asthma (GINA) guidelines suggest a stepwise approach in children aged ≤5 years (figure 1). At step 1, this approach advises the use of a short-acting β_2-agonist (SABA) bronchodilator for use as needed during wheezing episodes until symptoms disappear. At step 2, daily low-dose ICS treatment is indicated for symptoms that suggest diagnosis of asthma, such as uncontrolled respiratory symptoms, severe or frequent episodes (three or more in a season), or frequent use of SABA. Montelukast, a leukotriene receptor antagonist (LTRA), is a reasonable alternative as a controller therapy, although it is less effective than ICS in children with recurrent wheeze. However, the US Food and Drug Administration (FDA) has advised that, because of the risk of mental health side-effects, including suicidal thoughts or actions, the benefits of montelukast may not outweigh the risks in some patients,

	Step 1	Step 2	Step 3	Step 4
Preferred controller		Daily low-dose ICS	Double low-dose ICS	Continue controller and refer for specialist assessment
Other controller options		Daily LTRA or intermittent ICS‡	Low-dose ICS + LTRA Consider specialist referral	Add LTRA or increase ICS frequency or add intermittent ICS
Reliever	SABA as needed			

Figure 1. Stepwise treatment approach to asthma management in preschool children. LTRA: leukotriene receptor antagonist; SABA: short-acting β_2-agonist. ‡: intermittent short courses of ICS at onset of respiratory illness. Reproduced from the GINA guidelines (2020) with permission.

particularly when the symptoms of disease may be mild and adequately treated with other medicines. The FDA recommends that healthcare professionals consider the benefits and risks of mental health side-effects before prescribing montelukast.

If symptoms fail to improve sufficiently during ICS or montelukast maintenance treatment, physicians should exclude reasons for failure of such therapy before starting additional medication. Treatment failure can often be explained by insufficient adherence to medication, poor inhalation technique, an alternative diagnosis such as bronchomalacia, or relevant comorbidity such as allergic rhinitis. If these are properly addressed and treated, and symptoms remain problematic for >3 months, doubling the initial low dose of ICS or addition of LTRA can be considered (step 3). There is no evidence from randomised trials to prefer any add-on treatment schedule over another, although studies on montelukast in young children demonstrate benefit, particularly in the setting of viral-induced wheezing.

Most cases of troublesome preschool wheeze can be controlled effectively by ICS or montelukast alone, or by a combination of controller medications. For patients not well controlled at step 3, the recommendation is to refer the child to expert advice (step 4). Other therapeutic options are addition of regular LTRA doses or increasing dose/frequency of ICS.

Because of preschool wheezing's favourable natural history, maintenance treatment should be tapered off when the child is completely symptom free for 3–6 months, or for 12 months in children who have had a serious exacerbation requiring long-term hospitalisation or admission to intensive care.

Macrolides are sometimes prescribed in the treatment of recurrent wheezing but are not part of the current guidelines. Their use could be considered to prevent the progression to more severe complications in preschool children with respiratory illness.

Summary

Recurrent wheeze in preschool children is common. Due to the limited amount of evidence on its complex and multifactorial pathophysiology, different classification systems with associated treatment recommendations have been proposed, none of which can be recommended for universal use at present. Since not all children respond in the same way to conventional asthma therapies, defining the endotype and phenotype of wheezing children is essential to guide the clinician in management therapy. After excluding cases with atypical features, most patients with severe

recurrent wheeze in this age range can be managed effectively by ICS or montelukast, either alone or in a combination regimen. Mild intermittent wheeze can be treated with an inhaled bronchodilator only. New therapies such as allergen-specific immunotherapy and biological agents are being further evaluated for prevention of asthma in some children with recurrent wheezing.

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Asthma

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Asthma is the leading chronic disease in children in the Western world, affecting 5–20% of school-age children in Europe. Asthma prevalence has increased during the last two decades, although this trend seems to be levelling off, at least in high-income countries. A discrepancy between a lower prevalence of asthma but higher prevalence of signs/symptoms such as wheeze is found in low- to middle-income countries. Childhood asthma is a serious public health problem for several reasons. First, even though mortality is rare, asthma causes considerable morbidity and healthcare utilisation. High frequencies of sleep disturbances due to asthma (up to 34%), absence from school (23–51%) and limitation of activities (47%) have been reported in several studies. Asthma is the third-highest cause of hospitalisation in children and the most common cause of school absenteeism due to chronic disease among children in the USA. Paediatric asthma imposes a significant economic burden to healthcare systems, with average annual costs per child ranging between USD 3076 and USD 13612. Besides pharmacy costs, emergency visits and hospitalisations are

Key points

- There is no universally accepted definition of asthma, although reversible airway obstruction, airway hyperresponsiveness and chronic inflammation are key features. Airway remodelling is a common feature in adult severe asthma but this is less clear in childhood, particularly regarding when it starts and what elicits the process.
- There is accumulating evidence that the interaction between respiratory viral infections, environmental factors and atopy is important in the course and pathogenesis of atopic asthma.
- The ultimate goals of asthma treatment are to achieve and maintain clinical control with a minimum of side-effects and to reduce future risks to the patient.
- Asthma should be managed in a step-up/step-down approach, with inhaled corticosteroids as the main controller treatment. Before every step up, adherence to treatment, inhaler technique and exposure to triggers should be assessed. Monitoring includes a continuous cycle of assessing asthma control and future risks, adjusting treatment accordingly and assessing response to interventions.

the main contributors to healthcare costs. In Europe, unscheduled emergency visits to healthcare centres accounted for 47% of total asthma costs in infants and 45% in children; 7% of all children reported at least one hospitalisation. Secondly, as asthma is associated with reduced growth of lung function, and lung function at a young age is a determinant of lung function in adult life, optimal treatment is of major concern for long-term prognosis.

The main characteristics of asthma are reversible airway obstruction and airway hyperresponsiveness; chronic inflammation of the airways plays a central role in the pathogenesis of asthma and anti-inflammatory treatment with inhaled corticosteroids (ICS) is the treatment of choice. A stepwise approach to asthma management has been suggested by all international guidelines, and the ultimate goals of asthma treatment are to achieve and maintain clinical control with the least possible unwanted effects and to reduce future risks.

The underlying mechanisms of asthma are poorly understood. However, there is accumulating evidence that the interaction between respiratory viral infections, against a background of atopy and environmental factors, is important in the course and pathogenesis of atopic asthma.

Diagnosis

Diagnosing asthma may be challenging, particularly in infants and preschool children, and no universally accepted definition of asthma exists that embraces children from infancy to post-puberty. Difficulty in studying asthma arises from the fact that asthma is not a single disease but probably a compilation of aetiologies presenting as a syndrome or a collection of signs/symptoms. Particularly in childhood, reversible bronchial obstruction may be a final common feature of a number of different diseases with distinct aetiologies, and different environmental and genetic associations. However, most cases of asthma start in childhood and the severity and number of obstructive episodes in early childhood appear to be reasonable predictors for later ongoing childhood asthma.

Several phenotypes of asthma have been described and are being identified, commonly based upon the time of presentation of "wheeze" within the first part of childhood, on the presence or absence of allergic sensitisation, on whether there is eosinophilic or non-eosinophilic inflammation, or on response to treatment.

With this background, various definitions are used, and common to them all are reversible airway obstruction and chronic airway inflammation. Thus, a descriptive and pragmatic approach is necessary in the clinic, as the diagnosis will elicit targeted treatment. The proposed definition of asthma in children is that it is a disease including signs/symptoms (wheeze, cough and/or difficulty in breathing), reversible airways obstruction, airway inflammation and/or bronchial hyperresponsiveness (BHR), but it is not necessary that all of these are present in each individual patient at all time-points.

Classical signs/symptoms of asthma are wheeze, cough (particularly at night or during exertion), dyspnoea and chest tightness. It is important to note that asthma rarely presents with cough as a single symptom. If wheeze is absent on anamnesis, alternative diagnoses should be considered first.

The main features for diagnosing asthma are:

- History taking
- Objective documentation of reversible bronchial obstruction

- Allergy and BHR testing
- Assessing exhaled nitric oxide fraction (F_{ENO}) whenever possible

The medical history should focus on signs/symptoms of bronchial obstruction or cough, triggers of these signs/symptoms, and should include all items in figure 1, with attention to the age-specific questions. Furthermore, triggers of signs/symptoms are distinct from inciters of asthma development, mechanisms of the latter being less clear. Common triggers of signs/symptoms are viral infections, exercise, allergen exposure and irritants such as tobacco smoke.

In the case of airways obstruction (FEV_1 <1.69 z-scores or FEV_1/FVC ratio <80%), bronchodilator reversibility should be tested. When positive (FEV_1 increase of ≥200 mL and/or 12%), asthma diagnosis is confirmed. In children with fixed airway obstruction, alternative diagnoses should be considered. In children with normal spirometry but elevated F_{ENO} (>25 ppb), an asthma diagnosis is probable. If both F_{ENO} and spirometry are normal, a bronchial challenge test (*i.e.* exercise challenge test or methacholine challenge test) or an assessment of peak flow variability over a fixed time period should be performed.

Differential diagnosis

Alternative conditions must be taken into account before a diagnosis of asthma is made. Alternative causes of recurrent episodes of wheezing, especially in early childhood, are shown in table 1. The main differential diagnoses are respiratory tract infections, congenital and structural problems, foreign body aspiration and GOR. In children with severe, recurrent wheezing that is nonresponsive to ICS, leukotriene receptor antagonists (LTRAs) and/or bronchodilators, other diagnoses should be considered.

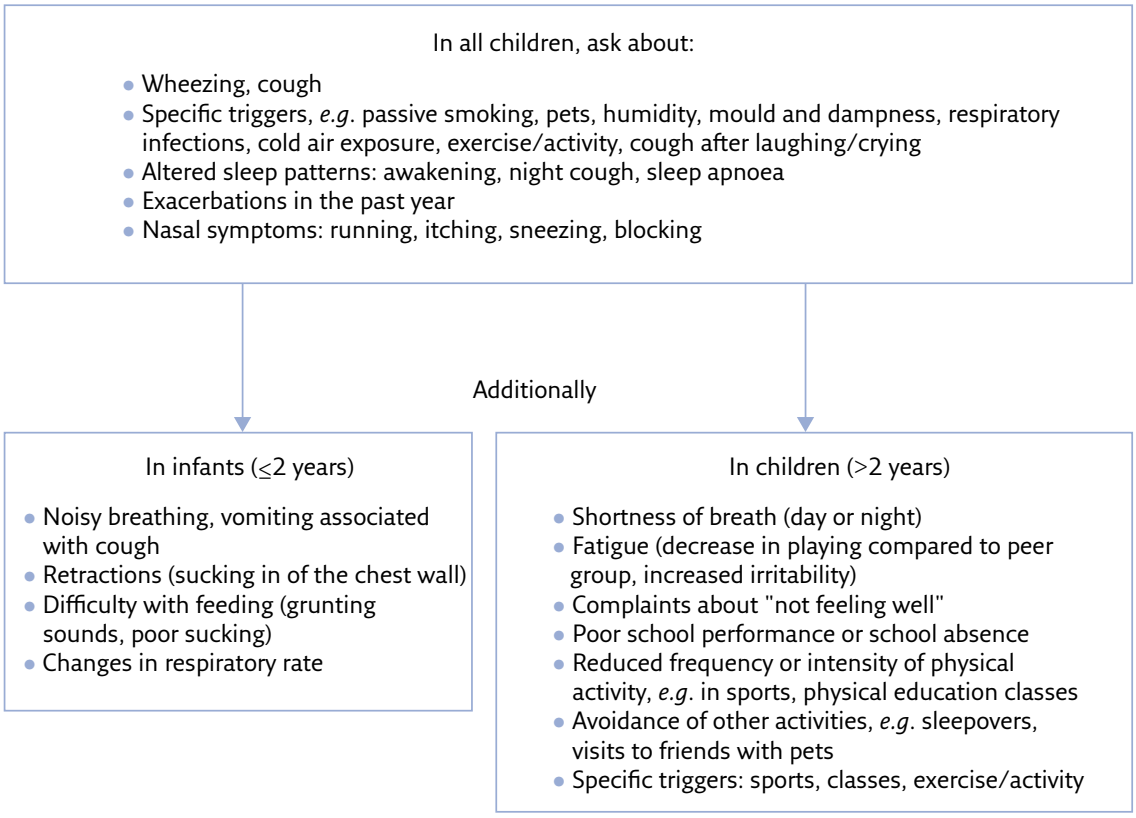

Figure 1. Specific signs and symptoms that should be asked about in assessing asthma diagnosis. Information from Bacharier et al. *(2008).*

Table 1. Differential diagnosis in bronchial asthma

	Signs, symptoms and history	Medical findings
Respiratory tract infections	Fever Cough with respiratory distress Relatives with the same signs/symptoms	Wheezing Rales Rhonchi
GOR disease	Frequent regurgitation Post-prandial vomiting Crying in supine position Nocturnal signs/symptoms	Failure to thrive Loss of weight
Foreign body aspiration	"Cough/suffocation" with sudden onset Sudden cough	Wheezing
Inducible laryngeal obstruction	Shortness of breath, wheezing, stridor or cough	Truncation of inspiratory flow–volume loop
Laryngomalacia	Inspiratory stridor present from birth	"Tooth" deflection of inspiratory flow–volume loop
Cardiovascular causes of airway compression	Recurrent respiratory difficulty, dyspnoea, dysphagia, wheezing, stridor Present from birth	Wheezing
Genetic disease	Recurrent dyspnoea Recurrent infections	Wheezing, dyspnoea
Congenital malformations of the lower respiratory tract	Respiratory symptoms at birth, but can remain asymptomatic for long periods	Malformations on radiological/endoscopic investigation

Respiratory tract infections

In children with persistent wheezing that does not respond to adequate ICS treatment, viral and bacterial infections are frequent. The main pathogens involved are viruses, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*. Chronic cough is also a frequent symptom in young children that could be confused with asthma. In sinusitis, purulent rhinorrhoea, sneezing and post-nasal drip are related to chronic cough. Chronic sinusitis requires a long course of antibiotics (10–15 days). Other respiratory tract infections causing wheezing and cough in children (*e.g.* pertussis) could also be confused with asthma. Cough and other respiratory signs or symptoms could also be related to TB, which may manifest without the typical symptoms (night sweats, haemoptysis, weight loss and fatigue). In this case it is necessary to perform adequate diagnostics.

Gastro-oesophageal reflux disease

Infant wheezing that is unresponsive to bronchodilator therapy may be related to GOR disease or silent aspiration. GOR disease has been shown to be associated with chronic respiratory symptoms, including reactive airways disease, recurrent stridor, chronic cough and recurrent pneumonia. The gold standard for investigation of GOR disease is 24-h pH monitoring.

Foreign body aspiration

In children with sudden onset of cough and wheezing, inhalation of a foreign body should be considered. In this case, it is important to analyse the history and look for temporal relationships with onset of signs/symptoms. Although chest radiography could be helpful if the foreign body is radiopaque or if indirect signs develop, such as consolidation or mediastinal dislocation, the diagnostic and therapeutic gold standard is bronchoscopy.

Inducible laryngeal obstruction

Inducible laryngeal obstruction is a disorder characterised by an episodic and involuntary upper airway obstruction caused by adduction of the vocal cords and/or false cords, primarily on inspiration. This disease is often confused with refractory asthma as symptoms are intermittent shortness of breath, wheezing, stridor or cough, which may lead to unnecessary therapy or step up in medication. Diagnosis should be suspected when there is a truncation of the inspiratory flow–volume loop. Direct visualisation during an attack permits definitive diagnosis.

Congenital abnormalities

Laryngomalacia

Laryngomalacia is the most common congenital abnormality and cause of inspiratory stridor in children. The manifestations can vary from mild noisy breathing with feeding to life-threatening airway obstruction and failure to thrive. The flow–volume loop is characterised by a "tooth" deflection in the inspiratory phase.

Lower respiratory tract malformations

Congenital malformations of the lower respiratory tract are rare anomalies and include a wide spectrum of conditions with a broadly varying clinical presentation. Individuals with congenital lung malformations can present with respiratory symptoms at birth or can remain asymptomatic for long periods. Usually, the diagnosis requires radiological and/or endoscopic evaluation. Depending on the pathophysiological mechanisms and structures involved, lung malformations can be divided into several categories: bronchopulmonary anomalies, combined lung and vascular anomalies, and vascular anomalies. Section 10 of this *Handbook*, "Congenital malformations", describes these abnormalities in detail.

Cardiovascular causes of airway compression

Compression of the airways is a relatively common complication of congenital vascular malformation in children. The main signs/symptoms are recurrent respiratory difficulty, dyspnoea, dysphagia, wheezing and stridor. Confirmation in general requires chest radiography, echocardiography, MRI, CT and/or bronchoscopy.

Genetic diseases

Genetic conditions such as PCD and CF may be relevant in the differential diagnosis in children presenting with recurrent dyspnoea.

Bronchopulmonary dysplasia

Another differential diagnosis that should be considered is BPD. It is an important cause of morbidity and mortality in preterm infants. Its incidence ranges with gestational age and birthweight, affecting approximately 70% of children born after 24 weeks gestational age and 25% at 28 weeks gestational age. BPD is discussed in detail in section 11 of this *Handbook*.

Pathophysiology

Asthma is a chronic inflammatory airway disease characterised by reversible airway obstruction and BHR. However, there is no current consensus on the underlying pathophysiology of asthma throughout childhood. This said, the underlying chronic inflammation is often characterised by eosinophilic activity and allergic inflammation, but non-allergic asthma is not uncommon in childhood.

Bronchial obstruction

Bronchial obstruction is a result of bronchial muscle constriction, acting particularly through the β-receptors, as well as mucosal oedema and increased airway secretions resulting from airway inflammation. All contribute to reduced airway flow, which is reflected in reduced lung function and classical signs/symptoms such as wheezing, dyspnoea and coughing. Reversibility of the bronchial obstruction may occur spontaneously or with bronchodilators (particularly β_2-agonists), whereas anti-inflammatory medications, such as corticosteroids, are necessary to reduce the underlying pathophysiological causes of bronchoconstriction.

Airway inflammation

The underlying airway inflammation in asthma is generally considered to be eosinophilic. However, the strength of the association between atopic sensitisation and asthma varies, and most sensitised subjects do not have asthma. Allergen exposure may, in some, lead to a break in natural tolerance, triggering allergic inflammation, and an allergen-specific immune response involving T- and B-lymphocytes. The innate immune system is, in effect, the barrier between the organism and the external environment, being the important first line of defence against infections and intruders. The adaptive immune system, however, classically involves (T-)cellular responses to antigens (or allergens), typically with production of specific IgE antibodies from B-cells, and adapts to environmental challenges.

The allergic response is initiated when an allergen binds to the high-affinity receptor for IgE (FcεRI) on the antigen-presenting cells that facilitate presentation to the T-cells. IgE is synthesised in the presence of interleukins (ILs) (*e.g.* IL-4 and IL-13) and other cytokines. The allergic inflammation is characterised by a T-helper cell (Th) type 2 cascade involving Th2 cytokines and other immune mediators. It is currently believed that directing naïve T-cells to Th1 *versus* Th2 immunity involves regulatory T-cells, a process which is important in tolerance development and suppression of allergic inflammation. In addition, dendritic cells in the airway epithelium facilitate uptake of allergens bound to FcεRI. Such mechanisms are probably propagated through defects in barrier function that have recently been shown in the airway epithelium of asthmatic subjects.

Viral infections are important triggers of signs/symptoms and exacerbations of asthma in childhood, whereas many children with "viral wheeze" may later not have asthma. Recent studies suggest that respiratory viruses, possibly (subtypes of) human rhinovirus in particular, may play a role in triggering the immune system. The mechanisms are currently not known, although several hypotheses exist, including an immune circle in asthma development in which repeated airborne irritant stimuli (such as allergens or viruses) evoke cycles of inflammation, giving intermittent inflammation resulting in episodic symptoms at first. However, with repeated insults, the inflammatory resolution becomes less complete, leading to tissue repair and regeneration that may set off prolonged periods of pathological changes. These periods may progress to deterioration in respiratory function and, perhaps, to remodelling.

A potential causal association between allergic sensitisation and viral infection is currently the focus of research, and it has been suggested that allergic sensitisation precedes rhinovirus-induced wheezing. Another aspect of the damaged epithelium in asthma is the reduced ability to handle viruses in an optimal way. It appears that reduced ability of airway epithelial cells to produce interferon-γ may lead to cytotoxic cell death and subsequent dissemination of viruses, rather than apoptosis, possibly explaining the prolonged symptomatic viral infections observed in asthmatics.

BHR is a common, but not obligate, feature of childhood asthma. It typically presents as a general liability to develop symptoms after exposure to various physiological or environmental stimuli, exercise being a classical childhood asthma symptom trigger. The underlying mechanisms for BHR development are not clear but may involve barrier dysfunction as well as possibly neural parasympathetic mechanisms involving heat and fluid exchange over the epithelium. BHR is a modest, but significant, risk factor for later asthma and tends to decrease through childhood.

The role of lung function reductions in the development of asthma, in contrast to lung function decline with chronic asthma, is not entirely clear. There is no doubt that asthma is associated with reduced lung function as well as a more rapid decline in lung function compared to healthy individuals. In a few birth cohorts, reduced lung function has been found to precede asthma in some, but not all, children with asthma. However, reduced lung function in infancy is predictive for asthma persistence in young adults.

Airway remodelling, being a common feature in adult asthma, is less clear in childhood, particularly as to when it starts and what elicits the process. Due to the lack of invasive longitudinal or intervention studies, the relationship between asthmatic airway inflammation and airway remodelling cannot be determined.

Management

Several national and international guidelines address asthma treatment in adults and children, the most commonly used being the British Thoracic Society (BTS)/ Scottish Intercollegiate Guidelines Network (SIGN) guideline and the Global Initiative for Asthma (GINA) report. This section discusses management of asthma in children aged ≥5 years. For children aged <5 years, see chapter "Preschool wheezing", and for difficult to treat and severe asthma, see chapter "Difficult and severe asthma". Details on aerosols, delivery of drugs to the lung, inhaler devices and instructions on optimal inhaler technique can be found in section 17 of this *Handbook*, "Inhalation therapy".

Nonpharmacological management

Most nonpharmacological interventions in asthma have limited effect and often lack sufficient evidence, except for avoidance of active or passive smoking. Exposure to environmental tobacco smoke is associated with decreased lung function from birth, increases the risk of asthma development, increases the frequency and severity of asthma symptoms, decreases asthma-related quality of life and is associated with persistent asthma in adults. Smoking cessation by parents/caregivers or children themselves should be vigorously encouraged and supported.

In obese patients, weight reduction may increase general health and improve asthma control, although studies in children are scarce. It has been suggested that rapid weight gain during early life is associated with increased risk of developing asthma.

A Cochrane review showed that single and combined measures are unlikely to reduce exposure to house dust mite (HDM) allergens and have not been effective in reducing asthma symptoms or other asthma outcomes. A more recent study in a selected group

of HDM-allergic asthmatic children, after an emergency hospital visit because of an asthma exacerbation, showed a reduction in hospital visits for asthma exacerbations but not in prednisone courses, with the use of mite-impermeable encasings. In general, in pet-allergic children with uncontrolled asthma, removal of animals from the home is advised, in order to gain adequate asthma control, although this has been questioned.

There is no evidence that dietary interventions with fish oil, antioxidants or probiotics improve asthma outcomes in children. Randomised controlled trials provide some low-quality evidence that supplementation with vitamin D may reduce asthma exacerbations in children with low baseline levels.

Aims of asthma treatment

The ultimate goals of asthma treatment are to achieve and maintain clinical control and to reduce future risks to the patient. The level of clinical control is defined as the extent to which asthma manifestations have been reduced by treatment. The future risks to the patient include loss of control, exacerbations, accelerated decline in lung function or impaired lung function growth, and side-effects of treatment. Ideally, treating patients with asthma should take into account both these goals.

The GINA guidelines suggest discerning three asthma control levels (controlled, partly controlled and uncontrolled), which guide step-up or step-down asthma treatment. The asthma control level is determined by asking whether, in the past 4 weeks, the patient has had:

- Daytime symptoms more than twice per week
- Any night-time waking due to asthma
- Need of a reliever more than twice per week
- Any activity limitation due to asthma

If the patient has had none of these, the asthma is classed as well controlled; if they have had one or two of these, the asthma is partly controlled; if they have had three or four of these, the asthma is classed as uncontrolled.

For the second goal, to reduce future risks, it is recommended to assess risk factors for poor asthma outcomes, to assess exacerbations and monitor FEV_1. Factors that should be assessed in poorly controlled asthma, before step-up treatment is considered, are as follows:

- Adherence to treatment
- Inhaler technique
- Exposure to triggers (tobacco smoke, allergens)
- Allergic rhinitis
- Correct diagnosis of asthma
- Comorbidities

A stepwise treatment approach

A stepwise approach to asthma treatment has been proposed by all international guidelines (figure 2). Both BTS and GINA suggest a difference between the management of younger children (aged 5–12 years or 6–11 years, for BTS and GINA, respectively) and older children (>12 years). In patients with uncontrolled asthma, step-up treatment should be considered. However, as mentioned in the previous section, before stepping up treatment there is an absolute need to check adherence to treatment, inhaler technique and ongoing exposure to triggers. In a patient unresponsive to treatment, one should confirm that the symptoms are due to asthma

	Step 1	Step 2	Step 3	Step 4	Step 5
Preferred controller		Daily low-dose ICS	Low-dose ICS–LABA or medium-dose ICS	Medium-dose ICS–LABA and refer for expert advice	Refer for phenotypic assessment ± add-on therapy, *e.g.* anti-IgE
Other controller options	Low-dose ICS whenever SABA taken#, or daily low-dose ICS	LTRA, or low-dose ICS whenever SABA taken#	Low-dose ICS + LTRA	High-dose ICS–LABA, or add-on tiotropium, or add-on LTRA	Add-on anti-IL-5 or add-on low-dose OCS, but consider side-effects
Reliever	SABA as needed				

Figure 2. Stepwise management of asthma treatment in children aged 6–11 years. At each step, a short-acting β_2-agonist (SABA) should be provided for quick relief of symptoms. LABA: long-acting β_2-agonist; OCS: oral corticosteroids. #: off-label; separate ICS and SABA inhalers; only one study in children. Reproduced from the GINA guidelines (2020) with permission.

and consider comorbidities like untreated allergic rhinitis, obesity or GOR disease. Step down should be considered if patients are well controlled for 3–6 months, and the lowest step and dose of treatment that maintains control should be sought.

Based on indirect evidence, GINA now recommends low-dose ICS whenever a short-acting β_2-agonist (SABA) is taken, or daily low-dose ICS in step 1 for children aged 6–11 years and as-needed low-dose ICS–formoterol for children aged ≥12 years. The reason for this is that patients with apparently mild asthma, and in particular those who have a high use of SABA, are at risk of serious adverse clinical outcomes, which may be prevented by ICS. Therefore, for safety reasons, GINA no longer recommends SABA-only treatment in step 1.

If children have symptoms and/or need rescue SABA more than twice a week, wake up at least one night a week or have had any asthma exacerbation during the last year, maintenance treatment with ICS should be started (step 2). GINA recommends step 2 treatment in children with symptoms more than twice a month or if risk factors for exacerbations exist. ICS at a very low or low dose is the recommended controller treatment for patients of all ages in step 2. The starting dose of ICS may depend on severity of disease and will usually be 200–400 $\mu g \cdot day^{-1}$ for budesonide and beclomethasone preparations, 200–250 $\mu g \cdot day^{-1}$ for fluticasone, mometasone and ultra-fine beclomethasone preparations and 160 $\mu g \cdot day^{-1}$ for ciclesonide. One should be aware that, although ICS are highly effective in reducing asthma symptoms, improving lung function and reducing airway hyperresponsiveness, these effects do not persist when discontinuing treatment.

Less effective controller medications are leukotriene modifiers, which may be appropriate for patients who are unable or unwilling to inhale ICS, although the US Food and Drug Administration (FDA) has advised that, because of the risk of mental health side-effects, including suicidal thoughts or actions, the benefits of montelukast (an LTRA) may not outweigh the risks in some patients, particularly when the symptoms of disease may be mild and adequately treated with other medicines. As an alternative to daily ICS, GINA suggests low-dose ICS whenever SABA is taken, as a controller option in step 2.

If children are uncontrolled at low doses of ICS, there are three treatment options: 1) add an inhaled long-acting β_2-agonist (LABA), 2) increase the dose of ICS to medium

doses, or 3) add an LTRA. At present, there is no evidence for superiority of one of these strategies over the others, although most children show a differential response to one of these treatment options. While the inter-individual response may vary significantly, no predictors of response to any of the three options have been identified, highlighting the need to regularly monitor and appropriately adjust each child's asthma therapy.

The BTS and GINA guidelines favour the addition of inhaled LABA in step 3 treatment, although increasing the dose of ICS in children aged 6–11 years is suggested to be an equally effective treatment by GINA. LABA should always be an add-on treatment to ICS therapy and should never be used as a single agent. If effective, LABA should be continued, and if ineffective, LABA should be stopped and the dose of ICS should be increased. If LABA–ICS treatment is partly ineffective, ICS dose can be increased or LTRA can be added. In step 3 and higher, GINA recommends giving ICS–formoterol as rescue treatment in children aged ≥12 years. It is important to note that individual variations in the susceptibility to side-effects of steroids may render some children, even those on low doses, at risk of adrenal axis suppression.

National guidelines may differ from the BTS and GINA guidelines and should be consulted on a local level. In addition, side-effects, the convenience of use of prescribed medication, individual patient preferences and costs may guide treatment choices in individual patients.

Although healthcare varies between and within countries, it should be emphasised that children who are not controlled on step 3 treatments should be referred to a paediatrician specialised in asthma care. Assessment of a possible wrong diagnosis, lack of treatment adherence or persistent exposure to untoward environmental factors should be considered. In step 4, ICS dose should be optimised to 800 $\mu g \cdot day^{-1}$ beclomethasone dipropionate or equivalent, together with LABA and/or LTRA. Low-dose, sustained-release theophylline may provide some benefit in addition to medium- to high-dose ICS and LABA, although generally the clinical effects have been small. Add-on tiotropium is an alternative option in step 4.

Step 5 treatment should be confined to paediatric specialists in asthma management. For treatment of children with severe therapy-resistant asthma, see chapter "Difficult and severe asthma".

Treatment of asthma exacerbations

For treatment of asthma exacerbations, consultation of (inter)national guidelines is highly recommended as local policies may differ between countries and settings, and guidelines are not uniform on all points. Most mild–moderate exacerbations might be treated in a community setting, whereas moderate–severe exacerbations should be treated in acute care settings.

The severity of the asthma exacerbation is assessed by a brief history and physical examination. Important signs and symptoms are the ability to talk in sentences, pulse rate, respiratory rate, breath sounds, use of accessory muscles, retractions, oxygen saturation, degree of agitation, conscious level and (if possible) peak expiratory flow (PEF) or FEV_1 (table 2). Scoring systems for the severity of an asthma exacerbation, like the Paediatric Respiratory Assessment Measure (PRAM) score, may be helpful in assessing the course of an attack and response to treatment.

Children with an asthma exacerbation who do not respond adequately to β_2-agonists and/or are in need of supplemental oxygen and/or have severe asthma should be admitted to hospital. A follow-up visit within a short time after discharge by a general practitioner or asthma specialist should be arranged.

Table 2. Assessment of severity of asthma exacerbation in children aged >5 years

Moderate exacerbation	Severe exacerbation	Life-threatening exacerbation
Able to talk	Too breathless to talk	Agitation
S_{pO_2} ≥92%	S_{pO_2} <92%	Drowsiness, confusion
Heart rate ≤120 beats·min^{-1}	Heart rate >120 beats·min^{-1}	Risk factors for near fatal asthma
Respiratory rate ≤30 breaths·min^{-1}	Respiratory rate >30 breaths·min^{-1}	Silent chest
PEF ≥50% best or predicted	PEF <50% best or predicted	PEF <30%
	Use of accessory muscles	P_{CO_2} >45 mmHg
	Chest retractions	P_{O_2} <60 mmHg

With moderate or severe exacerbations, treatment should be initiated immediately. P_{CO_2}: carbon dioxide tension; P_{O_2}: oxygen tension.

There is no absolute limit at which oxygen therapy should be instituted. However, oxygen *via* a facemask or nasal cannulae should be administered if oxygen saturation is <94%.

In children with mild–moderate exacerbations, β_2-agonists delivered *via* a pressurised metered-dose inhaler (pMDI)–spacer combination are usually sufficiently effective. Two to four puffs of β_2-agonists (up to 10 may be used in moderate exacerbations) should be administered one at a time and inhaled *via* tidal breathing, and repeated at 10–20-min intervals for the first hour as needed. However, nebulised β_2-agonists should be considered in moderate–severe exacerbations if there is insufficient effect from pMDI–spacer administration. Addition of an inhaled anticholinergic, like ipratropium bromide 0.5 mg, may be beneficial.

Severe or life-threatening exacerbations should be treated with nebulised salbutamol 5 mg or terbutaline 10 mg at intervals of 10–20 min. Systemic steroids should be given in all but the mildest exacerbations. After starting inhalation therapy, oral prednisolone is as effective as parenteral prednisolone; however, in children with altered consciousness or who vomit, intravenous corticosteroids are preferred. In children, the advised dose is 1–2 mg·kg^{-1} prednisolone for 3–5 days up to a maximum of 40–60 mg. Alternatively one or two doses of oral dexamethasone of 0.3–0.6 mg·kg^{-1} may be used with similar effectiveness. Intravenous magnesium sulfate in a dose of 40 mg·kg^{-1} (maximum 2 g) administered over 15 min may be considered in children unresponsive to 1 h of adequate treatment.

If the response to intensive nebulised treatment and prednisolone is poor, children should be referred to a paediatric intensive care unit (PICU). Intravenous salbutamol or terbutaline may be considered even before transport to the PICU under close monitoring of heart rate, arterial blood gases and serum potassium. The starting dose is 0.1 µg·kg^{-1}·min^{-1} continuously; there is controversy about the usefulness of giving an intravenous loading dose of 15 µg·kg^{-1}.

Monitoring

Asthma is a chronic disorder with a variable course, which makes regular follow-up of asthmatic children necessary. Monitoring of children with asthma requires a continuous cycle of assessing asthma control and future risks, adjusting treatment and reviewing response to adjustment. A European Respiratory Society task force on monitoring asthma in children recommended assessing, at every visit, the type and pattern of symptoms, the impact on daily life including limitation in physical activity

and school absenteeism, exacerbations and oral corticosteroid use, and use of rescue medication. Additionally, inhaler technique and adherence to treatment should be checked. As mentioned earlier, before stepping up treatment, one should consider low adherence, poor inhaler technique, adequate avoidance of risk factors, allergic rhinitis, (passive) smoking, other aggravating factors and comorbidities.

Validated questionnaires may be of help in the standardised assessment of asthma control in the clinic and for research purposes, but their use does not improve asthma outcomes. There are several questionnaires available, such as the Asthma Control Questionnaire (ACQ), the Asthma Control Test (ACT) and the Childhood Asthma Control Test (C-ACT), the Asthma Therapy Assessment Questionnaire (ATAQ) and the three-item Royal College of Physicians (RCP3) questionnaire. In routine monitoring of asthma there is no place for quality of life questionnaires.

Traditionally, more objective measures such as spirometry, PEF and BHR are used to assess asthma control and disease activity. In patients older than 5–6 years, spirometry or PEF should be measured during clinic visits to assess asthma control and detect possible decline in lung function. FEV_1 is preferred over PEF, as PEF may be completely normal while severe airway obstruction is present. The presence and degree of airway obstruction have short- and long-term prognostic value for asthmatic children, and are independent predictors of future risk. Guidelines recommend assessing lung function at diagnosis, 3–6 months after starting controller therapy and then at least yearly. More frequent monitoring with spirometry is recommended if a child experiences uncontrolled asthma, has poor symptom perception, or after admission or exacerbation.

Contrary to adults, in children, adjusting the dose of ICS to symptoms and BHR does not result in more symptom-free days compared to titrating treatment to symptoms only. However, in a subgroup of children with few symptoms but hyperreactive airways, monitoring BHR resulted in improved lung function.

Much attention has been paid to markers of inflammation, like the F_{ENO} and eosinophil count in induced sputum, as objective tests to monitor asthmatic patients. As the evidence that F_{ENO} can be used to guide treatment is mixed, guidelines do not recommend routine monitoring of F_{ENO}. However, a recent Cochrane review showed a significant reduction in exacerbations for titrating ICS based on F_{ENO} levels. Contrary to results in adults, adjusting treatment to sputum eosinophils has not been shown to be effective in improving asthma outcomes in children.

In all children treated with inhaled or systemic corticosteroids, height should be monitored.

Self-management

Although self-management education, including written action plans, clearly leads to improved outcomes in asthmatic adults, this has not been shown for children. To date, there is a lack of studies comparing the effect of providing a written action plan *versus* no written action plan in children and adolescents. However, symptom-based action plans seem superior to peak flow-based action plans for preventing acute care visits in children. There is some evidence that combined interventions aimed at self-management (*e.g.* information, self-monitoring and action plan, or educational and environmental measures) may reduce asthma exacerbations in children who visited the emergency room for asthma. The optimum setting and content for such educational interventions and relative effectiveness of the various components are largely unknown. Self-management using e-health is promising, although it remains to be shown if monitoring *via* digital methods improves asthma outcomes in children.

Poor symptom perception may be a challenge for adequate self-management and more frequent spirometry may be needed in that case.

In general, a written personal action plan is recommended for all children with asthma and, in particular, for children with poorly controlled asthma. Furthermore, parental education in asthma is recommended, to improve assessment of the child's disease as well as adherence to treatment.

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Difficult and severe asthma

Andrew Bush and Louise Selby

When an airway disease such as asthma is apparently not responding to treatment, the reasons should be sought in three domains: the airway pathology itself, extrapulmonary comorbidities, and social and environmental factors. Each domain should be explored for treatable traits, and what treatment success would look like should be determined. Difficult and severe asthma are rarely due to difficult and severe airway pathology; most children with asthma will respond to low-dose inhaled corticosteroids (ICS) if these are administered regularly through an appropriate medication delivery device. This chapter will discuss the approach to the school-age child who is not responding to asthma treatment, and is summarised in figure 1.

Definition

Difficult and severe asthma are conventionally defined solely according to levels of prescribed medication, according to the following points:

- Children who remain chronically symptomatic despite the prescription of >800 µg beclomethasone equivalent ± long-acting β_2-agonist ± leukotriene receptor antagonist (LTRA) ± low (anti-inflammatory) dose theophylline (or failed trials of these add-on therapies), or require these high doses to remain symptom free.

Key points

- Most children with asthma are easily treated if basic management is right; only very few of those referred to a specialist clinic actually need "beyond guidelines" therapy.
- A multidisciplinary team is essential for the assessment of those referred with asthma not responding to therapy.
- Most asthma attacks are preventable, and should potentially be considered a "never event"; they may represent a dangerous failure of management, like amputation of the wrong leg during surgery, and need a detailed and focused response and reassessment.
- A systematic approach to assessment should be used to characterise children with apparent severe asthma, to delineate the problems and determine an appropriate treatment regime on an individual basis.

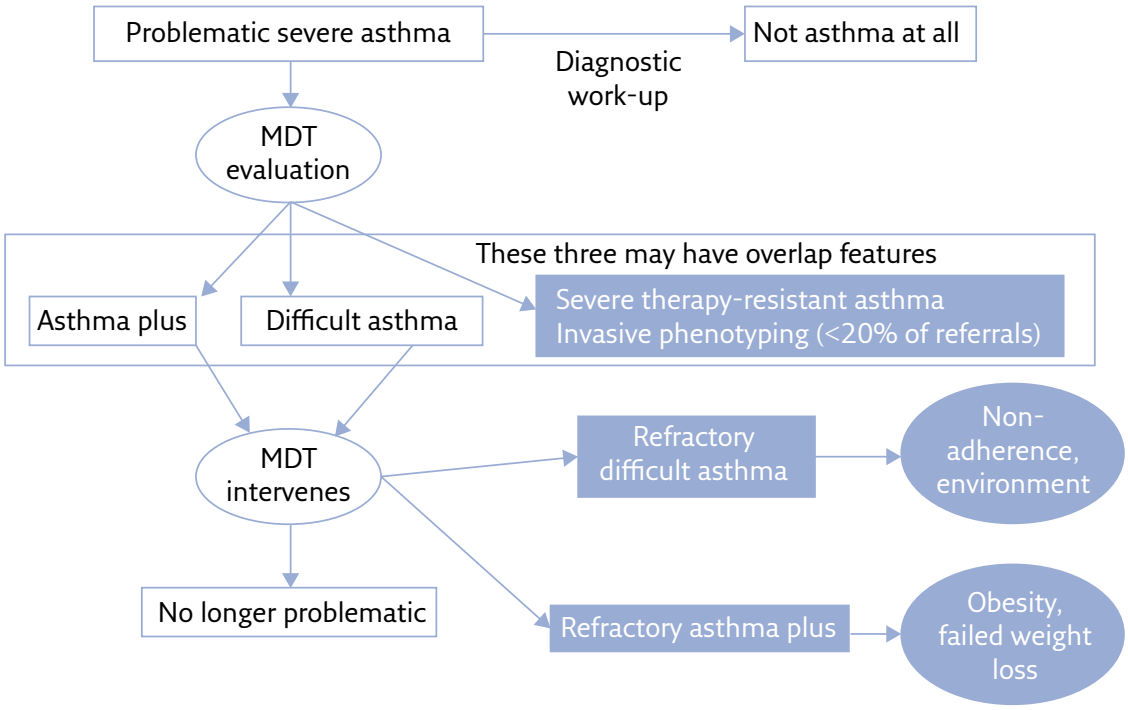

Figure 1. Assessment protocol for children referred for difficult and severe asthma. MDT: multidisciplinary team. Reproduced and modified from Bush et al. *(2017) with permission.*

- Children who have serious exacerbations (or serious asthma attacks), defined as at least one hospitalisation, intensive care unit stay or mechanical ventilation in the previous year, or >2 prednisolone bursts per year for acute severe asthma (prescription for ≥1 day), despite the prescription of high-dose medication (as in the previous point).
- Children who have airflow limitation, either FEV_1 <80% (or FEV_1 <1.96 z-scores (standard deviation scores) below normal) after short-acting β_2-agonist withhold, or FEV_1 <80% despite steroid trial and short-acting β_2-agonist administration (persistent airflow limitation).

However, this definition is too narrow, as the UK National Review of Asthma Deaths identified that around 60% of asthma deaths were in patients who did not meet the criteria for severe asthma. So it is essential to include a category of "increased risk of future attacks". This is captured to some extent by including serious asthma attacks in the definition, but should also include those consistently over-using short-acting β_2-agonists (>6 cannisters per year), those under-using ICS, and those frequently attending the emergency department but not attending asthma reviews. All these children should be evaluated in specialist centres with dedicated severe asthma clinics.

Initial evaluation

The first step in the approach to difficult and severe asthma is the initial evaluation. There are two important initial questions that need to be asked:

- Does the child have an airway disease at all? The answer may be obvious for a child who has undergone prolonged intubation and ventilation for an asthma attack, but 50% of those with chronic dyspnoea have neither asthma nor exercise-induced laryngeal obstruction (EILO) but are deconditioned. This question may need a formal exercise test to resolve.

- Is another diagnosis such as a vascular ring being missed? There needs to be a detailed history and physical examination, including determining whether true polyphonic whistling wheeze is being described or has ever been heard by a paediatrician. If an alternative diagnosis is found, this is treated on its own merits, and will not be discussed further.

Evaluation by the multidisciplinary team

The next step is evaluation by the multidisciplinary team, which involves assessment by respiratory nurses and a clinical psychologist, and a breathing pattern assessment by a respiratory physiotherapist. If not already done, we recommend documenting spirometry and bronchodilator responsiveness (BDR), atopic status (total and specific IgE, skin prick tests) and evidence of airway eosinophilia (exhaled nitric oxide fraction (F_{ENO}) and peripheral blood eosinophil count), as well as urinary cotinine as a measure of nicotine exposure (passive and active, tobacco and vaping). We assess adherence by giving the child a Smartinhaler (Adherium, Auckland, New Zealand) or other similar electronic device, which records the time and date of inhaler actuation for a 3-month period, and obtain prescription records. In addition, home and school visits are arranged. The physiotherapist assesses the child for evidence of hyperventilation, EILO and dysfunctional breathing patterns. The psychologist assesses (among other aspects) child and carer anxiety and depression. The home visit assesses adverse environmental exposures, and often allows more open discussion than in the clinic, for example about sensitive psychosocial issues. We also try to determine how much, if at all, the child's medications are supervised by the family. In particular, if it is suspected that symptoms are being exaggerated, the school visit may be illuminating; one "steroid-dependent asthmatic" turned out never to use his inhaler at school and was captain of football! We also try to document asthma attacks, and assess whether objective measures were made or whether corticosteroids were prescribed because the emergency paediatrician was told the child had "very severe asthma" but in fact was hyperventilating.

Multidisciplinary team intervention

The child is next reviewed in the clinic with repeat spirometry, BDR and F_{ENO}, and is categorised as having features of difficult asthma (basic management steps not correct) and/or asthma plus (with comorbidities) (table 1), or severe therapy-resistant asthma (STRA; children who have persistent symptoms and attacks despite optimised basic management). Difficult asthma and asthma plus are clearly not mutually exclusive. The adherence data identify four patterns, which will require different management interventions:

- Previous poor control and attacks, high F_{ENO}, low FEV_1, BDR at the start of monitoring, good adherence during monitoring and normal spirometry and F_{ENO} at the end of the period; adherence previously poor, improving during monitoring. Difficult asthma with poor adherence needs to have ongoing adherence supported.
- Good (>80%) adherence but ongoing poor control, F_{ENO} and spirometry. This is likely to be true STRA.
- Poor adherence and poor control. This is either a child with STRA who does not take the medications because they do not work, or ongoing poor adherence despite

Table 1. Difficult asthma and asthma plus

	Adverse factor	Management
Difficult asthma	Poor adherence	Support adherence; directly observed therapy[#]
	Nicotine exposure	Smoking cessation referral
	Allergen exposure	Remove any possible allergens, *e.g.* pets
	Psychosocial factors	Referral for help to local services
Asthma plus	Obesity	Dieting; consider bariatric surgery
	Food allergy	Exclusion diet; injectable adrenaline
	EILO	Physiotherapy, psychology, speech therapy
	Rhinosinusitis	Topical nasal steroid; consider referral to ENT specialist

Note that there is no evidence that GOR is a component of asthma plus, and it is not known whether food allergy is a cause or a marker of severe asthma. [#]: *e.g.* at school.

monitoring (refractory difficult asthma). These can be distinguished by seeing the response to a period of directly observed therapy (DOT).

- Poor adherence, but control, F_{ENO} and spirometry good; likely over-treated in the past, treatment can be weaned.

As a result of the assessment, a plan is made for those with difficult asthma and asthma plus (table 1).

Other strategies: admission to hospital

On occasion, it may be difficult to understand fully how bad the child's asthma really is, especially if there is a disconnect between objective measurements and symptom reporting. In such cases, a 2-week admission to hospital may be useful. The child has DOT, frequent measurements of spirometry and BDR, F_{ENO}, formal exercise testing and informal exercise sessions (*e.g.* playing football), and short-acting β_2-agonists are withheld until the child's need for the medication has been assessed by a paediatrician along with peak flow measurement. There is also an opportunity for more detailed multidisciplinary assessments to be made. Most frequently, all abnormal parameters normalise, and the child is fit and active without using short-acting β_2-agonists.

It is also important to note that child safeguarding concerns are present in approximately 10% of patients referred to us. Hospital admission demonstrates that, in a good environment with regular administration of medication, the child lives a normal life. It is of course one thing to identify such concerns and another to address them, but there should be a low threshold for seeking advice from the safeguarding team. It cannot be over-stressed that asthma still kills children, and children whose asthma is mismanaged at home, either willfully or through lack of parental capacity, are at risk of actual physical harm and even death. This is frequently not appreciated.

Severe therapy-resistant asthma: determining the airway pathology

Those thought to have STRA next undergo bronchoscopic airway phenotyping, to answer the following questions. It should be stressed that only around 10–20% of those referred for "beyond guidelines" therapy actually have true STRA.

- Does the child have persistent airflow limitation (in which case, escalating therapy to try to correct the uncorrectable is not useful)? There is no accepted definition of persistent airflow limitation; we define it as FEV_1 <1.96 z-scores (standard

deviation scores) below normal after an injection of triamcinolone (see details in next section) and administration of a short-acting β_2-agonist.
- Does the child have ongoing inflammation, and if so, what is its nature (eosinophilic, non-eosinophilic)? Is there discordance between symptoms and inflammation? There seems little point in giving anti-inflammatory medications if there is no evidence of airway inflammation.
- Is the child corticosteroid resistant?

The child is admitted, and we assess symptoms and use of rescue medication, and perform spirometry and BDR, induced sputum and F_{ENO}. The child undergoes bronchoscopy, BAL and endobronchial biopsy, and while anaesthetised has a single intramuscular injection of triamcinolone to ensure adherence to the steroid trial (40 mg if weight <40 kg, 80 mg if >40 kg). 4 weeks later, steroid responsiveness is assessed noninvasively (by spirometry and BDR, induced sputum and F_{ENO}), and a treatment plan is made (see below).

New concepts: refractory difficult asthma and refractory asthma plus

Many children respond well to multidisciplinary intervention when the problems are clearly formulated and support to address them is put in place. Symptoms and asthma attack prevalence are reduced, as is the dose of prescribed medication. However, for some, despite the problem being identified, the family is not able or not willing to address this, for which issue we have introduced the term "refractory". For example, there are children and families who will not adhere to treatment, despite support, and will not cooperate with DOT. For some, the SMART (single maintenance and reliever therapy) regime may help, and should certainly be considered if not already tried, *e.g.* single combined inhaler of budesonide and formoterol for preventive and reliever therapy. Those cases where either large numbers of furry pets remain in the home, despite the fact that the child is sensitised, or those where nicotine exposure is ongoing, are termed "refractory difficult asthma". An example of "refractory asthma plus" would be the obese child with failure of weight loss. We now believe that these children should also be offered "beyond guidelines" therapy, since we have to find a way to keep the children alive. Those with refractory asthma would undergo airway phenotyping as described. This is particularly important in obese children, as in such children there is evidence that the airway phenotype may be very different from atopic, allergic asthma in lean children (see chapter "Effects of systemic and extrapulmonary conditions on the respiratory system"); therefore, different treatment strategies are appropriate. The administration of biological treatments in children with refractory asthma has the further advantage that regular review is ensured.

Treatment of severe therapy-resistant asthma and refractory asthma

Beyond routine therapy, the two biological treatments currently licensed for children are the anti-IgE omalizumab, and the anti-interleukin (IL)-5 mepolizumab. The use of these monoclonals means that steroid-sparing agents such as methotrexate and cyclosporine are hardly ever prescribed, and children on long-term oral steroid therapy are rarely seen. Unfortunately, there is a paucity of strategies for non-eosinophilic asthma, in which type 2 inflammation is not a feature, as well as for other phenotypes like severe asthma with fungal sensitisation. It should also be noted that, at least as judged by sputum cytology, asthma phenotypes may be less stable in children than in adults.

Omalizumab

Omalizumab is a medication that has been available for many years. It is given by subcutaneous injection every 2–4 weeks, depending on total IgE and body weight for children aged ≥6 years with an IgE in the range 30–1500 IU·mL^{-1} (consult local recommendations for exact range), although the evidence base for these restrictions is weak and based on extrapolation of adult data. Children must be sensitised to a specific aeroallergen, although non-atopic adults with elevated IgE also respond. To be eligible in the UK, the child must have had at least four oral corticosteroid bursts in the preceding year (prescription for ≥1 day), but again there is no evidence base for this restriction. Omalizumab is most successful in reducing asthma attacks in those with a high blood eosinophil count and F_{ENO}, especially in the latter group if F_{ENO} normalises with triamcinolone. As well as binding the high-affinity IgE receptor, omalizumab has anti-viral effects that contribute to the reduction in attacks. We give an initial 16-week trial, with measurement at monthly intervals of spirometry and BDR, F_{ENO}, induced sputum, Asthma Control Test, quality of life scores and number of asthma attacks. These parameters are collated after 16 weeks, when a decision is made as to whether to continue therapy. Those on chronic therapy are reassessed in the same way every 16 weeks.

Mepolizumab and other monoclonals

Mepolizumab is a monoclonal that binds circulating IL-5. It is now licensed for children aged >6 years, and is given *via* subcutaneous injection at monthly intervals. Data in young children are limited, but on the basis of adult studies it would be reasonable to recommend mepolizumab for children with a blood eosinophil count of ≥300 cells·μL^{-1} at registration, or ≥150 cells·μL^{-1} in the preceding year, or, if the licensing authorities permit, evidence on BAL or induced sputum of ongoing airway eosinophilia. The main benefit is reduction in asthma attacks. We use mepolizumab in children whose IgE levels preclude the use of omalizumab, or omalizumab treatment failures, with the same 16-week cycles of monitoring as for omalizumab. It is likely that other anti-type-2 medications such as dupilumab will soon be licensed, at least for older children.

Severe asthma with fungal sensitisation

There is no paediatric definition of severe asthma with fungal sensitisation. We use the adult one, but do not have an upper limit of IgE because allergic bronchopulmonary aspergillosis is so rare in paediatric asthma (see chapter "Allergic bronchopulmonary aspergillosis"). There is evidence that this form of asthma is mediated through the steroid-resistant epithelial alarmin IL-33, but there is no currently available monoclonal targeting this cytokine or its receptor. The literature is conflicting, but a trial of an antifungal should be considered. It must be remembered that itraconazole inhibits the catabolism of budesonide, and the two in combination can cause iatrogenic Cushing's syndrome.

Non-eosinophilic asthma

The endotypes leading to non-eosinophilic asthma are unknown, and treatment options are very limited. We do not see neutrophilic severe asthma in children, unlike in adults, in whom it is common. Indeed, in our hands, children with severe asthma who have intra-epithelial neutrophils have better outcomes (in terms of symptoms and spirometry) with less prescription of ICS, suggesting that the neutrophils are beneficial. We use azithromycin treatment without it being clear which, if any, of the multiple effects of this medication lead to any benefit. The data on long-acting anti-muscarinic agents are not particularly encouraging. More research is needed to develop strategies for these children.

Asthma attacks should be a "never event"

An area of unacceptable complacency is using the trivialising term "exacerbation" instead of "asthma attack". When did you last hear a cardiologist talking about "heart exacerbations"? Prescribing a short course of prednisolone with no follow-up and no reassessment of asthma management is clearly unacceptable. An asthma attack is a sign of serious management failure, and indicates a child at risk of further attacks and death if something is not done. It is essential that the child is reviewed to ensure the attack has resolved, that adherence and trigger factors are re-evaluated, and that the asthma plan is modified. The approaches are discussed in detail elsewhere; for examples see the further reading list.

Long-term consequences of severe asthma

The study of the Melbourne Asthma Cohort was the first to draw attention to COPD as a long-term consequence of severe asthma, with an even stronger signal than adult-life smoking. Impaired lung function at birth and low lung function trajectories carry a risk of later COPD, and both are prevalent in severe asthma. Currently we have no treatment strategies beyond general lung health measures, which should be applied to all, but this is another risk that requires further research.

Summary

It cannot be over-emphasised that most children with asthma can lead a normal life if the basic management steps are right. If the child is not responding to low-dose treatment, rather than slavishly following stepwise guidelines and prescribing ever more treatment, the diagnosis should be re-visited, and, if it is correct, all aspects of management should be reviewed. The importance of multidisciplinary review in a specialist severe asthma clinic cannot be over-stated. The number of those actually needing monoclonals to control their asthma is greatly exceeded by the number referred for monoclonals to be considered.

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Anaphylaxis

Antonella Muraro and Stefania Arasi

Anaphylaxis is a severe, life-threatening systemic hypersensitivity reaction characterised by being rapid in onset with potentially life-threatening airway, breathing or circulatory problems, and is usually, although not always, associated with skin and mucosal changes. This is the definition provided by the recently updated version of the International Classification of Diseases (ICD-11). It represents a great step forward as the previous ICD (ICD-10) did not include proper coding. A recent systematic review showed that the incidence of anaphylaxis in children worldwide varied widely, ranging from 1 to 761 per 100 000 person-years for total anaphylaxis and 1 to 77 per 100 000 person-years for food-induced anaphylaxis. However, the epidemiology of the disease is hindered by difficulties in timely assessment of symptoms alongside the lack of unambiguous coding. In addition, anaphylaxis in infants and children might be even more difficult to recognise and needs a high degree of suspicion. Furthermore, reports in developing countries are underrepresented. In 2014, the European Academy of Allergy and Clinical Immunology (EAACI) task force on anaphylaxis provided evidence-based recommendations for the recognition, risk factor assessment and management of patients who are at risk of anaphylaxis or have already experienced it.

Triggers

The most common causes of anaphylaxis are food allergens, medications and hymenoptera venoms. Less frequently, anaphylaxis can be triggered by physical exercise, aeroallergens and contact with latex, radiocontrast media and ethanol. Almost all episodes are IgE-mediated reactions, although sometimes other, non-IgE-mediated, immunological mechanisms might be involved, or there may be direct

Key points

- Anaphylaxis is a serious allergic reaction that is rapid in onset and may result in death.
- The most common causes are food allergens, medications and hymenoptera venoms.
- Infants are usually not able to describe symptoms; therefore, physicians need to have a high index of suspicion in order to diagnose anaphylaxis.
- Adrenaline is the medication of choice for anaphylactic episodes.

mast cell activation such as in physical exercise. Idiopathic anaphylaxis, *i.e.* when the cause is unknown, is also relatively common.

In contrast with older patients, in which drugs and hymenoptera venom are the main causes, food allergens are the most common triggers of anaphylaxis in children. Among them, cow's milk, egg, peanuts, tree nuts and seafood are most frequently reported.

Clinical manifestation and diagnosis

The diagnosis of anaphylaxis is primarily based on clinical symptoms and signs, as well as a detailed description of acute episodes, including antecedent activities and events occurring within the preceding minutes to hours.

Typically, exposure to a triggering allergen is followed by rapid development of symptoms over minutes to several hours. Investigation is mandatory, especially if exposure to a likely allergen is reported. Sudden onset of urticaria, swelling of the oropharynx, rhinorrhoea, cough, breathing difficulties, vomiting and progressive abdominal pain, pallor, irritability and sleepiness (*i.e.* hypotension) should be carefully evaluated in any allergic child. In infants, anaphylaxis may be even more difficult to recognise because they are usually unable to describe the symptoms. Moreover, some signs of anaphylaxis, such as irritability, flushing, hoarseness, drooling, regurgitation, loose stools, colicky abdominal pain and somnolence, may be difficult to interpret since they are quite common in this age group.

The US National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network have established three diagnostic criteria, allowing 95% of anaphylaxis events to be diagnosed (table 1).

Table 1. Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria are fulfilled:
1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (*e.g.* generalised hives, pruritus or flushing and swollen lips–tongue–uvula), and at least one of the following:
Respiratory compromise (*e.g.* dyspnoea, wheeze-bronchospasm, stridor, reduced PEF and hypoxaemia)
Reduced BP or associated symptoms of end-organ dysfunction (*e.g.* hypotonia (collapse), syncope and incontinence)
2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
Involvement of the skin-mucosal tissue (*e.g.* generalised hives, itch-flush and swollen lips–tongue–uvula)
Respiratory compromise (*e.g.* dyspnoea, wheeze-bronchospasm, stridor, reduced PEF and hypoxaemia)
Reduced BP or associated symptoms (*e.g.* hypotonia (collapse), syncope and incontinence)
Persistent gastrointestinal symptoms (*e.g.* cramping abdominal pain and vomiting)
3) Reduced BP after exposure to a known allergen for that patient (minutes to several hours):
Infants and children: low systolic BP[#] (age specific) or >30% decrease in systolic BP
Adults: systolic BP <90 mmHg or >30% decrease from that person's baseline

PEF: peak expiratory flow; BP: blood pressure. [#]: defined as <70 mmHg at 1 month to 1 year of age, <70 mmHg+(2×age) at 1–10 years of age and <90 mmHg at 11–17 years of age. Reproduced and modified from Sampson *et al.* (2006) with permission.

In both adults and children, the time course of the reaction may be:

- Uniphasic, occurring immediately after exposure and resolving with or without treatment in minutes to hours
- Biphasic, recurring after the apparent resolution of initial symptoms, usually about 8 h after the first reaction
- Protracted, persisting for hours or days following the initial reaction

Role of laboratory tests

The diagnosis is hampered by the lack of reliable markers of the disease both for predicting who would be at major risk and for appropriate diagnosis of the acute episode. Recently, the use of component-resolved diagnostics has provided some help in identifying epitopes linked to severe reactions (*e.g.* Arachis hypogaea 2 (Ara h 2) for peanut and lipid transfer proteins for fruits and vegetables). At the onset of the symptoms, measuring serum tryptase, which should be obtained after 15 min to 3 h, can be helpful in anaphylaxis triggered by hymenoptera stings or drugs. It has overall low sensitivity and specificity, and its level is typically normal in food anaphylaxis. Histamine blood levels obtained 15–60 min after onset may also be useful. However, these tests are not universally available, especially on an emergency basis, and are not specific for anaphylaxis. Some reports highlight the possible role of platelet-activating factor in the pathogenesis of more severe reactions.

Management

The management of anaphylaxis encompasses both the treatment of acute episodes and the preventive strategies in the community to avoid recurrences and new cases.

Basic management

As with the treatment of any critical patient, the treatment of anaphylaxis begins with a rapid assessment and maintenance of airway, breathing and circulation. Patients experiencing acute anaphylaxis should be kept in a position of comfort, which usually involves a recumbent or semi-recumbent position. This accomplishes two therapeutic goals:

- Preservation of fluid in the circulation (the central vascular compartment), an important step in managing distributive shock
- Prevention of empty vena cava/empty ventricle syndrome, which can occur within seconds when patients with anaphylaxis suddenly assume or are placed in an upright position

Patients with this syndrome are at high risk for sudden death and unlikely to respond to adrenaline, regardless of route of administration, because it does not reach the heart and therefore cannot be circulated throughout the body.

After removing exposure to the trigger (if possible), if any of the three criteria of anaphylaxis outlined in table 1 are fulfilled, the patient should receive adrenaline immediately.

Adrenaline is the medication of choice for anaphylactic episodes; all other medications should be regarded as ancillary. Prompt injection of adrenaline has been associated with better outcomes. A severity score can be helpful in the diagnosis and in ensuring the timely administration of adrenaline (table 2).

The intramuscular route is acknowledged as the optimal route for adrenaline administration. Adrenaline at a concentration of 1 $mg \cdot mL^{-1}$ should be used in a dose

Table 2. Grading of severity of an anaphylactic reaction

Grade	Skin	GI tract	Respiratory	Cardiovascular	Neurological
Mild	Sudden itching of eyes and nose, generalised pruritus, flushing, urticaria and angioedema	Oral pruritus, oral "tingling", mild lip swelling, nausea or emesis, mild abdominal pain	Nasal congestion and/or sneezing, rhinorrhoea, throat pruritus, throat tightness and mild wheezing	Tachycardia (increase >15 beats·min^{-1})	Change in activity level plus anxiety
Moderate	Any of the above	Any of the above, cramping abdominal pain, diarrhoea and recurrent vomiting	Any of the above, **hoarseness, "barky" cough, difficulty swallowing, stridor, dyspnoea and moderate wheezing**	As above	"Light headedness" and a feeling of "impending doom"
Severe	Any of the above	Any of the above, loss of bowel control	Any of the above, **cyanosis or saturation <92%**, respiratory arrest	**Hypotension[#] and/or collapse, dysrhythmia, severe bradycardia and/or cardiac arrest**	Confusion, loss of consciousness

The severity score should be based on the organ system most affected. Bold indicates a mandatory indication for the use of adrenaline. GI: gastrointestinal. [#]: defined as systolic blood pressure <70 mmHg at 1 month to 1 year of age, <70 mmHg+(2×age) at 1–10 years of age and <90 mmHg at 11–17 years of age.

of 0.01 mg·kg^{-1} body weight (maximum single dose 0.5 mg). This dosage can be repeated at short intervals (every 5–10 min) until the patient's condition stabilises.

Although frequently administered, the role and efficacy of antihistamines and corticosteroids in anaphylaxis has not yet been clarified. These medications should not be considered as first-line treatments for anaphylaxis as they do not act quickly. The efficacy of corticosteroids in reducing the risk of late-phase reactions has not been proven. High-flow oxygen should be given to any patient with respiratory symptoms or evidence of shock. Volume support with crystalloid solution or colloid expander is mandatory in the case of hypotension.

Long-term management

Identification of triggers

In order to identify the allergen, patients with a history suggestive of an anaphylactic reaction need urgent referral to an allergy clinic for a diagnostic assessment, based on clinical history and *in vivo* and *in vitro* examinations (*e.g.* skin-prick test, intradermal test, prick-to-prick with raw food, IgE against the suspected allergens, including molecular diagnostics, and oral challenges for food or drugs).

Risk reduction

Strategies to avoid the precipitants should be customised, taking into consideration factors such as age, occupation, activities, hobbies, living conditions and access to medical care. As most episodes of anaphylaxis occur in the community, children and their caregivers must know how to prevent further reactions and how to promptly recognise and appropriately manage any anaphylactic reactions that occur outside the hospital. Allergists, emergency physicians and general paediatricians/practitioners, as well as teachers and caregivers, need to develop a coordinated approach, including actions for primary and secondary prevention and emergency response, in order to prevent fatalities and improve quality of life of patients and families.

Prescription of self-injectable adrenaline

The decision about whether to prescribe a self-injectable adrenaline device involves analysis of the risks of experiencing anaphylaxis, the benefits of a self-injectable adrenaline device, the risks associated with it and its cost on health services and individual families. Absolute and relative indications for prescribing adrenaline are shown in table 3.

In January 2017, the European Medicines Agency (EMA) issued a recommendation valid in all European Union member states to prescribe two adrenaline auto-injectors to any patients at risk of anaphylaxis.

Table 3. Indications for prescribing a self-injectable adrenaline device

Absolute indications	Relative indications
A previous cardiovascular or respiratory reaction to a food (or to other triggers, *e.g.* insect sting or latex)	Any reactions to small amounts of a food including airborne or contact with the food allergen only *via* skin
Exercise-induced anaphylaxis (often also related to food)	History of previous, even mild, reactions to peanut or tree nuts
Idiopathic reaction	Remoteness of home from medical facilities
Child with food allergy and asthma	Food allergy reaction in a teenager

Immunomodulation

Venom immunotherapy is 95–100% and ~80% successful in wasp and bee sting allergies, respectively. Desensitisation protocols have also been established for some medications (*e.g.* a few antibiotics and nonsteroidal anti-inflammatory drugs), although they are only recommended when an alternative drug cannot be put in place.

Food-induced anaphylaxis could theoretically be modulated by allergen desensitisation through immunotherapy, similar to hymenoptera sting anaphylaxis, in centres with professional training in food allergy care with the expertise, competencies and full resuscitation facilities to safely deliver this treatment and manage any complication, including anaphylaxis.

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Allergic rhinitis

Michele Miraglia del Giudice, Annalisa Allegorico, Fabio Decimo and Anna Maria Zicari

The allergic pathologies are frequent and bothersome diseases. Allergic rhinitis affects 10–40% of the population. It reduces quality of life and school and work performance, and is a frequent reason for visits to general practitioners. Medical costs are large, but avoidable costs associated with lost work productivity are even larger than those incurred by asthma. Allergic rhinitis is the most frequent allergic, chronic disease in the paediatric population and is often associated with other allergic diseases. The prevalence of self-reported allergic rhinitis has been estimated to be approximately 2–25% in children and from 1% to >40% in adults.

Definition

Allergic rhinitis is defined as a symptomatic disorder of the nose characterised by:

- Itching
- Nasal discharge (rhinorrhoea)
- Sneezing
- Nasal airway obstruction

These signs and symptoms are induced by an IgE-mediated immune reaction after allergen exposure. It is accompanied by inflammation of the nasal mucosa and nasal airway hyperreactivity. Although it is not life threatening, it can have a significantly

Key points

- Allergic rhinitis is characterised by itching, nasal discharge, sneezing and nasal airway obstruction induced by an IgE-mediated immune reaction after allergen exposure.
- According to ARIA guidelines, allergic rhinitis is divided into intermittent or persistent disease and the severity is classified as mild or moderate/severe depending on the severity of symptoms and their impact on social life, school and work.
- The diagnosis of allergic rhinitis is based on the concordance between a typical history of allergic symptoms and diagnostic tests.
- The therapeutic strategies for allergic rhinitis are patient education, pharmacotherapy and allergen-specific immunotherapy.

detrimental effect on a child's quality of life, and it may exacerbate a number of common comorbidities, including asthma and sinusitis.

Mechanisms

Allergic rhinitis is the result of IgE-mediated allergy and nasal mucosa inflammation. IgE is produced in the lymphoid tissues and locally in the nasal mucosa in response to common environmental allergens. When allergens bind to mast-cell-bound IgE, mast-cell degranulation occurs. Degranulation of mast cells results in the release of a myriad of biochemical mediators that regulate and/or mediate the different aspects of allergic inflammation.

Among other preformed mediators, histamine is released into the surrounding tissues binding to H1-receptors on various target cells and eliciting a powerful allergic response (figure 1). This response is characterised by an increase in vascular permeability and by stimulation of local nerve endings and mucus-secreting cells. Thus, histamine is the key player in the acute allergic response.

Other important mediator classes involved in the acute-phase allergic response include prostaglandins (*e.g.* prostaglandin D_2 (PGD_2)) and leukotrienes (*e.g.* LTC_4). Prostaglandins, of which PGD_2 appears to be the most important, have vasodilatory and bronchoconstrictive properties. PGD_2 produces nasal inflammation in the acute phase, but does not appear to play a key role in chronic inflammation. Evidence derived from topical application of cysteinyl leukotrienes (cysLTs) in the nose and from the effects of leukotriene receptor antagonists (LTRAs) indicates that cysLTs contribute to nasal mucous secretion, congestion, and inflammation. CysLTs promote allergic inflammation by enhancing immune responses and the production, adhesion, migration and survival of inflammatory cells such as eosinophils.

Late-phase allergic reactions and chronic inflammatory changes involve many cell types including T-cells, mast cells and eosinophils. Eosinophilic inflammation also plays an important role. A T-helper (Th)2 response ensues with the release of interleukin (IL)-4 and IL-5. Eosinophils are increased in numbers and activated in the nasal mucosa of symptomatic allergic patients. They release pro-inflammatory

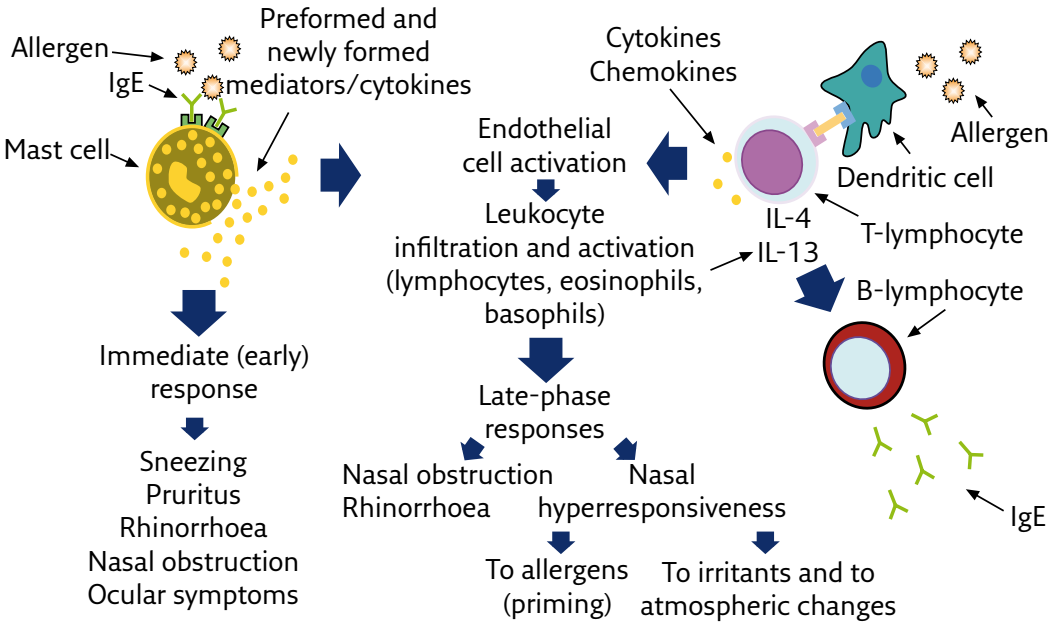

Figure 1. The nasal allergic response. Reproduced from Van Cauwenberge et al. *(2003) with permission.*

mediators, including granule-stored cationic proteins, newly synthesised eicosanoids and cytokines. The major basic protein (MBP) is highly cationic and lacks enzymatic activity; its toxicity is believed to be mediated by enhanced membrane permeability resulting from interactions of the cationic protein with the plasma membrane. After allergen exposure, rhinitis can persist for several weeks. Eosinophils release mediators that can induce tissue damage, and pre-treatment with topical glucocorticoids reduces eosinophil infiltration and cytokine release.

Classification

The classification of allergic rhinitis was previously based on the time of exposure into seasonal or perennial. Perennial allergic rhinitis is generally caused by indoor allergens such as dust mites, moulds and animal danders. Seasonal allergic rhinitis is most frequently related to pollens or moulds.

Recently, an expert panel proposed a new classification of allergic rhinitis. In this classification allergic rhinitis was divided into "intermittent" or "persistent" disease and the severity of allergic rhinitis was classified as "mild" or "moderate/severe" depending on the severity of symptoms and their impact on social life, school and work (figure 2).

This classification was proposed in the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, the first evidence-based guidelines for allergic rhinitis.

Another important aspect of the ARIA guidelines was to consider comorbidities of allergic rhinitis. The eye, ear and lower airways are involved in allergic rhinitis. Interactions between the lower and the upper airways are well known; over 80% of patients with asthma suffer from rhinitis and 10–40% of patients with rhinitis have asthma.

Diagnosis

The diagnosis of allergic rhinitis is based on the concordance between a typical history of allergic symptoms and diagnostic tests. Typical signs and symptoms of allergic rhinitis that are reversible either spontaneously or with treatment include:

- Rhinorrhoea
- Nasal obstruction
- Nasal itching
- Sneezing

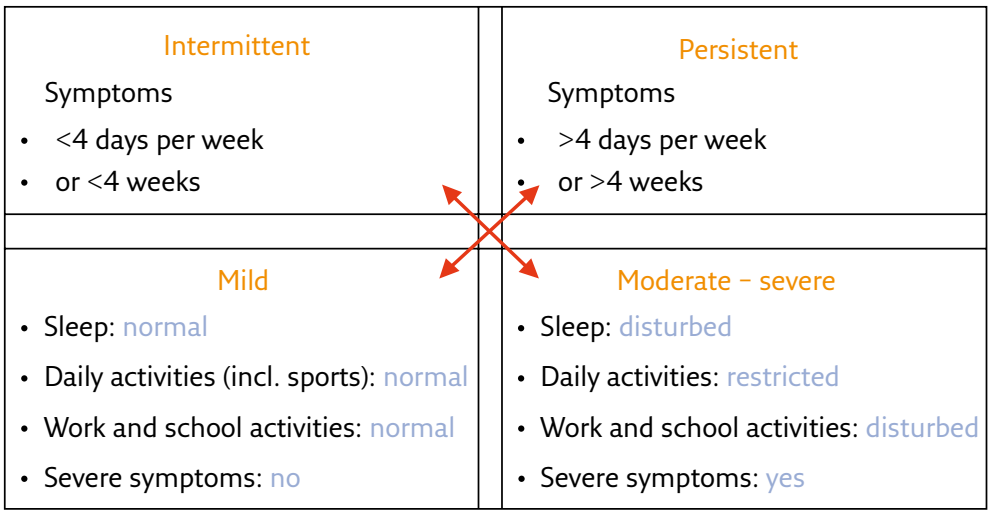

Figure 2. Allergic rhinitis classification, according to Bousquet et al. *(2001).*

Other concurring signs and symptoms may affect the eyes, such as:

- Lachrymation
- Conjunctival itching
- Swelling

Ocular symptoms are common, in particular in patients allergic to outdoor allergens. Allergic rhinitis due to pollen allergy occurs in the relevant seasons and there are large geographical differences. Apart from season and pollen exposure, other factors are also important for severity of symptoms, including the weather: rain reduces the exposure and mild wind in dry weather may increase exposure; in addition, wind may result in exposure far away from the source. Perennial allergens may be house dust mites (HDMs) as well as animal danders. The major cat allergen (Fel d 1) is transported in the air by particles <2.5 µm and can remain airborne for long periods. Fel d 1 is also adherent and can contaminate an entire environment for weeks or months after cessation of allergen exposure. HDMs are most often found in bedding, especially in humid environments. Since HDM allergy often induces late reactions, these children often experience nasal congestion and may also have symptoms during the daytime and seldom specifically in early morning. Allergic rhinitis due to HDM allergy also occurs most often in older children, although even young children may have allergic rhinitis and allergy to pollen as well as HDMs.

The main symptom of allergic rhinitis caused by perennial allergens is nasal congestion; however, conjunctival swelling, itching and watery discharge can occur. The congestion is a consequence of the inflammation that involves the entire upper airways. Nasal congestion can result in chronic mouth breathing, associated with the development of a high-arched palate, an elevated upper lip and overbite. In fact, children often suffer from a sore throat caused by oral respiration. Other symptoms may include coughing caused by post-nasal drip, cephalalgy caused by oedema of the nasal mucosa, and hearing impairment caused by tympanic dysfunction. Sudden night awakening and apnoea can affect sleep. This alteration of sleep phase can affect the child in their everyday life and activities.

In children suffering from allergic rhinitis, social problems can occur with embarrassing repeated actions, such as blowing their nose, grimacing in order to relieve their nasal itching or producing “strange noises”.

Children with allergic rhinitis may have swelling and dark discolouration under the eyes due to congestion of small blood vessels beneath the skin in this area.

In children with persistent allergic rhinitis, the habitual manipulation of the nose due to chronic obstruction and itching is typically accomplished by pushing the tip of their nose with the palm of their hand in an upward motion: this action is known as the “nasal salute” or the “allergic salute”. This may result in a persistent transverse hyperpigmented or hypopigmented line extending across the junction of the lower and middle thirds of the bridge of the nose named “nasal crease”.

Clinical testing

Diagnostic tests are based on the demonstration of allergen-specific IgE *in vivo* or *in vitro*. A skin-prick test (SPT) is recommended as the “gold standard” method for the diagnosis of IgE-mediated allergies in allergic rhinitis. It has advantages of relatively high sensitivity and specificity, rapid results, low cost and good tolerability. However, the quality of the allergens is very important and only standardised extracts should be used. Moreover, the skin of very young children may not be as reactive as that of older children and adults.

In children, the number of allergens to be tested may be limited. The most important allergens in early childhood are HDM and animal dander, but in older children pollens and moulds must be investigated.

The measurement of allergen-specific IgE in serum is available using either radio- or enzyme-labelled anti-IgE. This test has a diagnostic value similar to SPTs, but it is more expensive. For this reason, the measurement of allergen-specific IgE in serum is recommended if the history of allergic symptoms and SPTs disagree, or in children affected by dermographism or widespread skin lesions, or during treatment with drugs affecting the reactions to SPTs (*e.g.* antihistamines).

However, the diagnosis of allergic rhinitis is based upon the association between a typical history of allergic symptoms and results of diagnostic tests. No diagnosis can be based solely on responses to SPTs, the results of *in vitro* tests or nasal challenges. In some cases with a very clear history, *e.g.* those with clear seasonal symptoms or mild symptoms and the child being well treated on symptomatic treatment (*e.g.* antihistamines in normal doses), further diagnosis with SPTs, specific IgE or even nasal challenges may not be necessary.

Local allergic rhinitis (LAR) is a phenotype of rhinitis that has been poorly studied in children. It is characterised by the same symptoms as allergic rhinitis but with the absence of markers of systemic atopy. The nasal allergen provocation test has been needed to identify LAR. This new entity is a localised nasal allergic response in the absence of systemic atopy characterised by local production of specific IgE antibodies, a Th2 pattern of mucosal cell infiltration during natural exposure to aeroallergens, and a positive nasal allergen provocation test response with release of inflammatory mediators (tryptase and eosinophil cationic protein). Several non-allergic conditions can mimic allergic rhinitis symptoms, but because management differs in each case, it is very important to differentiate between allergic rhinitis and non-allergic rhinitis.

Recently, it has been reported that cytological examination of the nasal mucosa offers the possibility of a noninvasive study of cellular changes within the nasal mucosa. This method does not induce tissue stress or pain or immunological changes. Using this analysis, the presence of eosinophils and basophils supports the diagnosis of allergic disease, while an increased percentage of neutrophils supports the diagnosis of bacterial infection. A viral infection can be diagnosed if cilia with separated tufts are visible in the sample. It has been reported that nasal cytology using light microscopy can identify biofilms, which appear as cyan-stained “infectious spots”. Currently cytological examination of the nasal mucosa is a useful tool in the diagnosis of allergic rhinitis, NARNE (non-allergic rhinitis with neutrophilia), NARES (non-allergic rhinitis with eosinophilia), NARMA (non-allergic rhinitis with mast cells) and NARESMA (non-allergic rhinitis with eosinophilia and mast cells).

Management of a child affected by allergic rhinitis

The control of the nasal mucosa allergic inflammation is the goal of all therapeutic strategies in the management of allergic rhinitis. The key points for management of allergic rhinitis are patient education, pharmacotherapy and allergen-specific immunotherapy (figure 3).

A lot of perennial allergens have been associated with allergic rhinitis, of which HDM and animal dander are the most important. Mould spores can also provoke rhinitis and asthma. Patients allergic to furred pets may benefit from allergen avoidance at home, but they may encounter allergens on public transportation, and in schools and public places. A systematic review of dust mite allergen avoidance has shown that

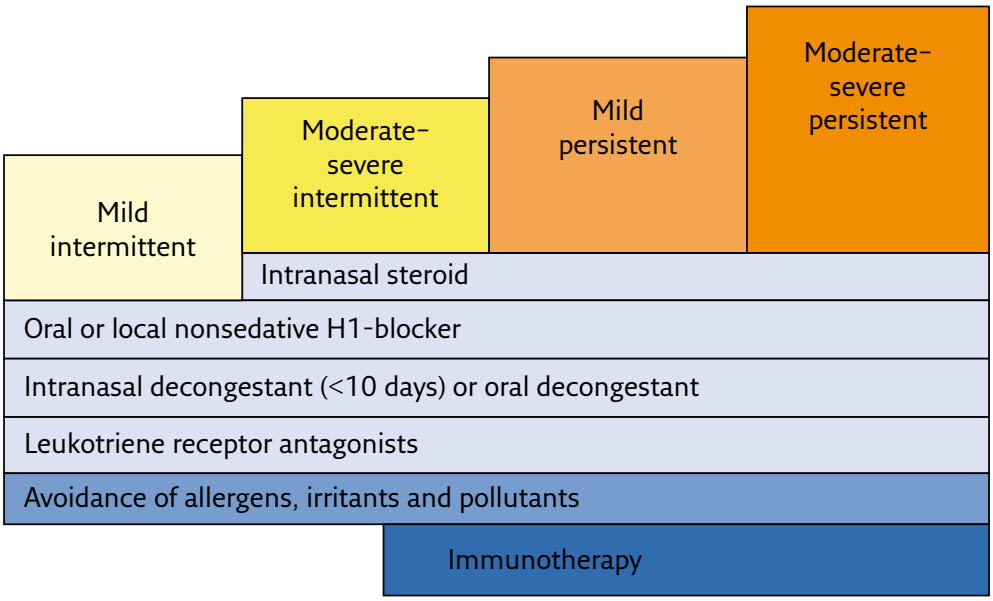

Figure 3. Management of allergic rhinitis: ARIA guidelines. Data from Bousquet et al. *(2001).*

single measures are not effective in reducing symptoms of allergic rhinitis, although the general consensus is that allergen avoidance should lead to an improvement of symptoms. However, improving air quality by ventilating airtight homes to prevent a build-up of biological pollutants and volatile organic compounds may be useful.

Medications used for the treatment of allergic rhinitis in children are antihistamines (oral or topical), glucocorticoids, chromones and antileukotrienes. Antileukotrienes are particularly useful when the allergic rhinitis is associated with asthma. Nasal glucocorticoids can also contribute to the reduction of asthma symptoms.

Antihistamines

H1-antihistamines are inverse agonists that combine with and stabilise the inactive conformation of H1-receptors. Thus, they interfere with actions of histamine at H1-receptors. They are widely used for treatment of allergic rhinitis, allergic conjunctivitis, urticaria, coughs, colds and insomnia. H1-antihistamines are classified into an older "first generation" and a newer "second generation". First generation H1-antihistamines have poor H1-receptor selectivity and cross the blood–brain barrier. They have a lot of adverse events, such as anti-muscarinic, anti-α-adrenergic, anti-serotonin and sedative effects. By contrast, second generation H1-antihistamines are highly selective for the histamine H1-receptor, do not cross the blood–brain barrier and have minimal adverse events. The risks of first-generation H1-antihistamines have been clearly underestimated, particularly when purchased as nonprescribed over-the-counter medications by the public. Oral H1-antihistamines are effective against symptoms mediated by histamine (rhinorrhoea, sneezing, nasal itching and eye symptoms), but have nearly no effect on nasal congestion. Oral H1-antihistamines have been shown to be safe and effective in children, including for long-term treatment.

Glucocorticoids

The rationale for using intranasal glucocorticoids in the treatment of allergic rhinitis is that high drug concentrations can be achieved at receptor sites in the nasal mucosa with a minimal risk of systemic adverse effects. Topical corticosteroids stabilise the membranes of mast cells and exert most of their effects *via* such membranes and

partial blocking of the late-phase reaction. The current intranasal preparations are well tolerated and can be used on a long-term basis without atrophy of the mucosa. Side-effects are generally mild (crusting, dryness and minor epistaxis).

Due to their mechanism of action, efficacy appears 7–8 h after dosing, but maximum efficacy may require up to 2 weeks to develop. They are generally safe, and there is little evidence to support suppression of the hypothalamic–pituitary–adrenal axis (HPA axis) with prolonged use. The safety of intranasal corticosteroids is particularly relevant in paediatric and adolescent patients because these agents are widely used in this population. The effect of 6 weeks of once-daily treatment with beclometasone dipropionate (BDP) nasal aerosol on HPA axis function, as measured by 24-h serum cortisol concentrations, has been evaluated in children with perennial allergic rhinitis. The results of this randomised, double-blind, placebo- and active-controlled study indicated that in paediatric patients with perennial allergic rhinitis, 24-h serum cortisol profiles were comparable for BDP nasal aerosol and placebo, indicating that once-daily BDP nasal aerosol treatment did not significantly affect HPA axis function.

The newer formulations of topical corticosteroids for allergic rhinitis, such as ciclesonide, fluticasone furoate and mometasone furoate, which have less systemic bioavailability, may be safer for long-term use. Fluticasone furoate nasal spray is a topical intranasal corticosteroid with enhanced affinity for the glucocorticoid receptor and low systemic exposure. A recent randomised, double-blind clinical trial demonstrated that a 14-day course of 200 µg per day nasal fluticasone propionate was superior to placebo in relieving ocular symptoms associated with allergic rhinitis.

The treatment of rhinitis reduces asthma severity: asthma and allergic rhinitis commonly occur together, and treatments for one condition could potentially alleviate the coexisting condition. The use of nasal corticosteroids in patients with rhinitis and asthma reduces not only rhinitis symptoms but also asthma symptoms and airway reactivity to methacholine challenge.

It should be made very clear that systemic treatment with corticosteroids for allergic rhinitis in children is not standard treatment, although a short course with low-doses prednisolone in some severe cases can be necessary. Patients with severe symptoms who do not respond to other drugs or those who are intolerant to intranasal drugs may need to be treated with systemic glucocorticoids (*e.g.* prednisolone, starting dose 10–15 mg per day) for a short period of time.

Allergen-specific immunotherapy

Allergen immunotherapy (AIT) is a proven therapeutic option for the treatment of allergic rhinitis and/or asthma. The decision to prescribe AIT should be individualised and based on the relevance of the allergens and the persistence of symptoms despite appropriate medications according to guidelines, as well as on the availability of good-quality and efficacious extracts. Allergen extracts cannot be regarded as generics. AIT is selected by specialists for stratified patients. There are no currently available validated biomarkers that can predict AIT success. In adolescents and adults, AIT should be reserved for patients with moderate/severe rhinitis or for those with moderate asthma who, despite appropriate pharmacotherapy and adherence, continue to exhibit exacerbations that appear to be related to allergen exposure, except in some specific cases. AIT may be even more advantageous in patients with multimorbidity.

In children, AIT may prevent asthma onset in patients with rhinitis.

AIT is the only therapy that alters the allergen immune response, resulting in fewer symptoms upon natural exposure.

In current clinical practice, immunotherapy is delivered as either subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT). Most meta-analyses and reviews concluded a trend that SCIT was better than SLIT in reducing symptoms of allergic rhinitis and rescue medication use; however, SLIT has a better safety profile than SCIT. In addition, the absence of pain on administration of therapy is a characteristic of SLIT that is well suited for children. The immunological mechanism that underlies SLIT has only started to be investigated. Oral mucosal tissue displays high permeability for allergens. It is conceivable that the sublingual administration route might induce immunological tolerance towards allergens involving cells and mediators specific to the oral and intestinal mucosa.

SLIT tablets are now commercially available for grass and ragweed allergy and appear to have a superior safety profile to SCIT with similar long-term effectiveness, because, as with SCIT, symptom improvement persists after the SLIT course is completed.

Comorbidities and complications

Allergic rhinitis cannot be considered as an isolated pathology. The inflammation that affects the nasal mucosa will consequently affect the eye mucosa, paranasal sinuses, ear and lower airways.

Chronic exposure to perennial allergens, especially in domestic environments, induces a gradual nose occlusion that will be very subtle in its manifestation, therefore the subject will physically adapt to the symptoms. Permanent signs found in allergic rhinitis subjects can be malocclusion or misalignment of teeth and jaws and adenoidal face (long face syndrome). For subjects affected by allergic rhinitis the coexistence of multiple diverse conditions, such as deviated septum, nasal turbinate dysfunction, sinusitis and adenoid hypertrophy, can occur. Physical examination of the allergic rhinitis subject should also include an otoscopic examination. Children affected by allergic rhinitis are more prone to otitis media with or without effusion. A probable mechanism is that allergic inflammation in the respiratory epithelium at the entrance to and inside the Eustachian tube can result in tube dysfunction due to swelling in this region and possibly cause secondary inflammation in the middle ear. In some cases, there is a difficulty in the interpretation of the symptoms of nasal occlusion caused by allergy and often these symptoms get confused with the physical inflammatory cause (*e.g.* dental malocclusion combined with adenoidal obstruction).

Integrated handling of the allergic rhinitis may require the prevention of complications; therefore, predicting the best treatment may require the expertise of an otolaryngologist, surgeon or an orthodontist. Referring a patient for surgical treatment is the only solution in order to correct certain anatomical anomalies of the nasal bones, or for removal of enlarged tonsils or adenoids. Referral should only occur in cases in which, along with the allergic inflammation, they aggravate nasal obstruction and breathing.

Numerous studies have demonstrated that allergic rhinitis may be a risk factor for both the onset and the worsening of asthma. The nose and lung are both part of the respiratory tract. Often the diseases affecting the nose and/or the bronchi are treated separately. However, in recent years, numerous studies have highlighted the fact that the respiratory system is a single entity and the concept of "united airway disease" has become more and more important. The unity of the respiratory tract is confirmed both from a morphological and from a functional point of view. This concept is also

confirmed for the respiratory immune system, innervation and vascularisation, integrating all along the tract, from the nose to the bronchioles.

Finally, in relation to the close connection between lower and upper airways, the physical examination should always carefully investigate the breathing condition of the patient and consider lung function testing. Patients with allergic rhinitis who do not report symptoms of bronchial asthma may show signs of bronchial hyperresponsiveness (BHR) on spirometry, which could indicate the presence of subclinical inflammation of the lower airways. The presence of BHR and concomitant atopic manifestations in childhood increases the risk of developing asthma and should be recognised as a marker of prognostic significance, whereas the absence of these manifestations predicts a very low risk of future asthma. Measurement of the exhaled nitric oxide fraction (F_{ENO}) may be considered a surrogate marker for airway inflammation. Allergic rhinitis patients may frequently have high F_{ENO} values, exceeding 50 ppb. This might be associated with an impaired lung function, BHR, a perceived worsening of respiratory symptoms, and potential progression to asthma. Increased F_{ENO} has been associated with a significantly longer allergic rhinitis duration, impaired lung function, more severe symptoms, and more frequent BHR.

Impaired forced expiratory flow at 25–75% of FVC (FEF_{25-75}) values might predict severe BHR, and BHR is related to F_{ENO} in adolescents. Therefore, BHR should be suspected in adolescents with low FEF_{25-75} values. Moreover, an impaired FEF_{25-75} value (<65% predicted) may be considered a reliable marker of bronchial reversibility, mainly in children with allergic rhinitis.

Patients with allergic rhinitis due to pollen often display adverse reactions upon the ingestion of plant-derived foods as a result of IgE cross-reactive epitopes shared by pollen and food allergen sources. The signs and symptoms of such pollen–food syndromes range from local oral allergy syndrome to severe systemic anaphylaxis. The best-known association is between birch pollen and a series of fruits (including apple), vegetables and nuts.

Allergic rhinitis can often be a debilitating condition which, if untreated, can result in considerable health-related and economic consequences. For example, numerous studies have demonstrated that poorly controlled symptoms of allergic rhinitis contribute to decreased health-related quality of life, reduced sleep quality, daytime fatigue, impaired learning, impaired cognitive functioning and decreased long-term productivity.

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Allergic bronchopulmonary aspergillosis

Andrew Bush and Dominic Hughes

Unlike in adults, and for reasons which are not clear, in children, allergic bronchopulmonary aspergillosis (ABPA) is virtually always seen in the context of CF. ABPA complicating paediatric asthma has only been the subject of isolated case reports. Other even more rarely reported associations in children include hyper IgE syndrome, chronic granulomatous disease, bronchocentric granulomatosis, previous TB, and treatment of sarcoidosis with infliximab. In adults, it has been described in association with COPD. Unsurprisingly, late diagnosis after a prolonged clinical course is common in this rare setting. If ABPA is suspected in the context of another paediatric respiratory illness, three steps are essential:

- Ensure that atypical forms of CF have been excluded. Even if the sweat test is unequivocally normal, genetic testing and measurement of transepithelial potential differences should be considered.
- Consider alternative differential diagnoses, such as mucus plugging and atelectasis, GOR disease, eosinophilic or other non-infective pneumonias, and collagen vascular disease.
- Finally, consider the possibility of the aforementioned rare associations.

Aspergillus fumigatus is ubiquitous in the environment. Two features make it particularly prone to infecting the human lower airway: 1) the spores have a mass median diameter in the range of 2–5 µm, meaning that they are the ideal size for impacting in the lower airway; and 2) they grow at 37ºC, *i.e.* body temperature. However, an ABPA-like picture has rarely been reported as being caused by other fungi, for example other strains of *Aspergillus* or non-*Aspergillus* species such as *Scedosporium apiospermum*. These are not covered further in this chapter. Manifestations of

Key points

- Allergic bronchopulmonary aspergillosis in children is almost exclusively seen in the context of CF.
- Diagnosis should be considered in all cases of increased respiratory symptoms in CF, especially where lung function has sharply declined.
- Symptoms and lung function often respond quickly to treatment with corticosteroids and antifungals, but complications of disease can be marked if left untreated.

Table 1. Manifestations of Aspergillus fumigatus *lung disease*

Disease	Manifestation
CF	ABPA Positive sputum culture, which may be associated with worse lung function and more pulmonary exacerbations Allergen provoking wheeze, analogous to severe asthma with fungal sensitisation in the non-CF patient Large airway plugging Mycetoma Invasive aspergillosis
Asthma	Isolated positive skin test Allergen provoking wheeze due to atopic sensitisation Severe asthma with fungal sensitisation
Immunocompromised host (congenital or acquired)	Invasive aspergillosis
Lung cavity (congenital thoracic malformation, TB, post-pneumonic)	Mycetoma
ILD	Hypersensitivity pneumonitis

A. fumigatus lung disease are summarised in table 1. The rest of this chapter discusses ABPA in the context of CF.

Definition

ABPA is the clinical manifestation of a T-helper cell (Th) type 2-driven hypersensitivity response within the airway to *A. fumigatus* and its exoproducts.

Prevalence of ABPA

The prevalence of ABPA is difficult to determine due to the different diagnostic criteria used (*e.g.* IgE >500 IU·mL^{-1} in Europe, >1000 IU·mL^{-1} in the USA) and the different indices of suspicion prevailing in the various clinics. The latest European Cystic Fibrosis Society (ECFS) registry report (which contains data from nearly the whole of Europe), using the diagnostic criteria shown in table 2, reported prevalences which varied from 0.6% (Hungary) to 13.9% (Luxembourg). Whether these differences reflect different levels of diagnostic suspicion, differences in diagnostic testing or a genuine geographical variation in disease prevalence is not clear. The UK Cystic Fibrosis Registry

Table 2. Summary of diagnostic criteria for ABPA used in the ECFS Patient Registry

Acute or subacute clinical deterioration, no other aetiology found
Total IgE >500 IU·mL^{-1}
Positive skin-prick test (>3 mm) or specific IgE for *A. fumigatus*
Either: 1) IgG precipitins or *in vitro* demonstration of IgG antibody response to *A. fumigatus*; or 2) new or recent imaging abnormalities (chest radiograph or CT) not clearing with standard therapy

From Zolin *et al.* (2019), with reference to Stevens *et al.* (2003).

report (10 509 registered patients) gave a total of 722 (prevalence 7.3%) cases of ABPA in 2018, of which 219 were new (incidence 2.2%). Both the prevalence and the incidence of new cases were higher for those aged >16 years than those <16 years (prevalence 9.6% *versus* 3.9%, incidence 2.5% *versus* 1.8%, respectively).

There are two other older but still useful registry studies, from the USA and Europe. The study from the USA (281 (2%) ABPA patients out of a total of 14 210 registered patients, almost certainly an underestimate) reported an increasing prevalence up to age 20 years, which thereafter declined. 10% of ABPA patients had a normal FEV_1, and >80% did not report wheeze. Infection with *Pseudomonas aeruginosa* was common (~70%). The European registry study (967 ABPA patients out of a total of 12 447 CF patients in the registry) reported a peak between 13 and 18 years, and ABPA was rare below age 6 years. There is no convincing sex difference in prevalence when the two databases are combined. ABPA was associated with a poorer general clinical condition (10% lower FEV_1, lower weight z-score, more commonly infected with *P. aeruginosa*, *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, and, surprisingly, *Haemophilus influenzae*, but not with *Staphylococcus aureus*) and there was an association with pneumothorax and massive haemoptysis, presumably related to the underlying severe lung disease. There were no associations with particular genotypes or mutation classes.

Pathophysiology

A. fumigatus may provoke an intense allergic response leading to secondary airway damage, but proteolytic and other enzymes may lead to nonallergic, direct pulmonary toxicity. ABPA is the result of a skewed $CD4^+$, Th2 response to *A. fumigatus* leading to interleukin (IL)-4 and IL-5 production and hence elevation of serum IgE, and airway eosinophilia. *A. fumigatus* may lead directly to the production of pro-inflammatory cytokines from bronchial epithelial cells. The importance of genetics has been suggested by the occurrence of familial cases. Important factors include human leukocyte antigen (HLA)-DR and HLA-DQ (the latter protective). Alleles in the HLA class II region are associated with susceptibility to ABPA in CF as well as in asthma. Also, polymorphisms in the genes for IL-4 receptor alpha (*IL 4RA*), IL-10, surfactant protein A and Toll-like receptor 9 are important. Recently, elevated levels of the co-stimulatory molecule OX40 ligand (OX40L) have been shown to be important in driving the Th2 response to *A. fumigatus* in peripheral $CD4^+$ T-lymphocytes. Of possible therapeutic interest, OX40L levels fell with *in vitro* addition of vitamin D. However, *A. fumigatus* downregulates the vitamin D receptor, which may affect the response to vitamin D therapy.

Presentation

There are multiple causes of increased respiratory symptoms and deterioration in lung function in CF patients, of which reduced adherence to treatment and a pulmonary exacerbation are among the most important. In such patients, all aspects of standard therapy should first be checked, including airway clearance, mucolytics and antibiotic treatment for chronic or new pathogens in the upper and lower airway. ABPA should be at least suspected in CF children with increased respiratory symptoms, particularly if there is wheeze, chest tightness or pleuritic chest pain and an audible pleural rub. Exceptionally, pleural effusion and pneumomediastinum have been described in ABPA. There may be a sharp decline in spirometry, and the chest radiograph typically shows one or more new soft fluffy shadows (figure 1), with a "gloved finger" appearance of mucus impaction in the airways, which are very unusual in a CF pulmonary exacerbation. HRCT is not usually necessary for diagnosis, but is useful in atypical cases, especially when the

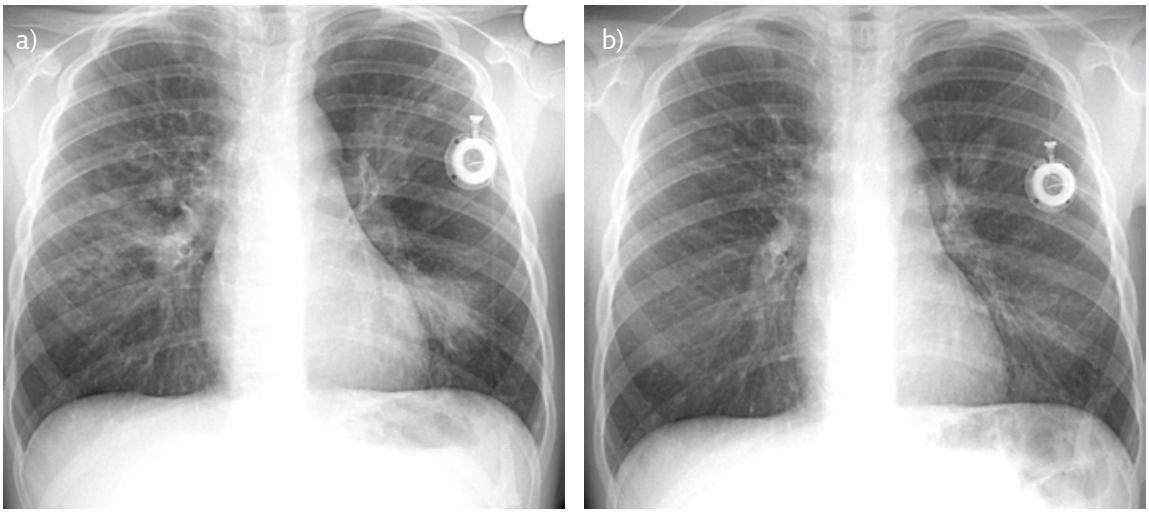

Figure 1. Patient with known CF and recently diagnosed ABPA. a) Chest radiograph showing a combination of widespread indistinct nodular opacities, ring shadows (bronchiectatic airways) in the right mid zone, and consolidation in the left lower lobe. b) Several months later, most of the shadowing has resolved but there is a new elliptical opacity (a plugged bronchiectatic airway) just above the left hilum.

cause of deterioration in the clinical state is not known. Less than half the patients will have a positive sputum culture for *A. fumigatus*.

Confirming the diagnosis of ABPA

Making the diagnosis of ABPA in the context of CF may be difficult; there is no single diagnostic test. The classical case is easy to diagnose. However, many of the symptoms and signs of ABPA are common to the underlying CF. Furthermore, markers of sensitisation to *A. fumigatus* and positive sputum cultures are frequently seen in otherwise uncomplicated CF, and true cases of ABPA may be culture negative for *A. fumigatus*. We find that the single most useful test is an abrupt, ≥4-fold rise in total IgE to >500 IU·mL^{-1}. IgE may sometimes but not always fall with treatment, so serial IgE measurements should be used with caution in monitoring response. A high level (>90 mg·mL^{-1}) of IgG precipitating antibodies to *A. fumigatus* may also be suggestive; multiple positive precipitins are more suggestive of mycetoma. Major and minor criteria for ABPA have been proposed, but atypical cases may not meet classical criteria yet still require treatment, which should not be delayed if the index of suspicion is high but "classical" criteria are not met. In doubtful cases, many would initially give a trial of intravenous antibiotics and then treat for ABPA if there was no response.

The tables of major and minor criteria are useful guides to the diagnosis of ABPA, but are no more than guides, and atypical cases will continue to be diagnosed on an individual clinical basis. The Cystic Fibrosis Foundation Consensus Conference in the USA proposed criteria for classical ABPA, minimal diagnostic criteria, and recommendations for screening (table 3). These are a useful guide to the clinician and are very helpful for ensuring uniformity of diagnosis in registries, but cannot be considered definitive under all circumstances.

Novel, more sophisticated testing has been proposed. Cytoplasmic *A. fumigatus* antigens may be elevated in ABPA. Initial studies using targeted allergy testing to specific purified *A. fumigatus* antigens (including Asp f1, f3, f4 and f6, and serum thymus and activation-regulated chemokine (TARC) levels) looked promising. Only TARC has been studied in a second prospective cohort, but its measurement currently remains in the research domain.

Table 3. Diagnostic criteria for ABPA in the context of CF

Classical ABPA
Acute or subacute clinical deterioration not attributable to another cause
Serum total IgE >1000 IU·mL^{-1} in the USA (>500 IU·mL^{-1} in Europe) in a patient not receiving oral corticosteroids
Positive skin-prick test to *A. fumigatus*
Positive IgG precipitins to *A. fumigatus*
New or recent chest radiograph abnormalities not clearing with conventional therapy such as physiotherapy and antibiotics
Minimal diagnostic criteria for ABPA
Acute or subacute clinical deterioration not attributable to another cause
Serum total IgE >500 IU·mL^{-1} (retest in 1–3 months if 200–500 IU·mL^{-1})
Positive skin-prick test to *A. fumigatus*
Either: 1) positive IgG precipitins to *A. fumigatus*; or 2) new or recent chest radiograph abnormalities not clearing with conventional therapy such as physiotherapy and antibiotics

From the Cystic Fibrosis Foundation Consensus Conference, Stevens *et al.* (2003).

Lung function testing in ABPA

There are no changes in lung function that are specific to ABPA. Characteristically, there is an acute worsening of pre-existing airflow obstruction, or its *de novo* development. This is initially at least partially reversible, but becomes fixed with low lung volumes if the disease progresses. Diffusing capacity may be low in an acute exacerbation, and remain low in end-stage disease. Spirometry is probably the most useful marker of response to treatment, being better than serum IgE or more sophisticated biomarkers.

Screening

An annual measurement of total IgE is recommended, with further investigation if IgE is >500 IU·mL^{-1}, or 200–500 IU·mL^{-1} and the index of suspicion is high. The possibility of ABPA should be considered in all pulmonary exacerbations, in particular if there are fresh chest radiographic infiltrates or response to treatment is poor; an admission measurement of total IgE is routine in our CF unit.

Management

Prevention

Playing or working in damp places, such as stables, where *A. fumigatus* spores are in high concentrations, must be discouraged. Although there is less evidence, it would seem sensible to ensure there are no moulds in the house and to check that *A. fumigatus* (or indeed other organisms) are not cultured from the nebuliser, by maximising hygiene. Recent immunological work suggests that optimising vitamin D levels may be helpful.

Treatment

As with much of paediatric respiratory medicine, there are no randomised controlled trials to inform treatment decisions, and no satisfactory evidence base on which to recommend the nature and duration of treatment of ABPA. If there is any doubt about the diagnosis, then intravenous antibiotics should be given first. Treatment is aimed

at reducing the inflammatory and tissue-damaging consequences of fungal infection, and also at reducing the burden of the fungal infection.

Corticosteroids

Conventionally, the mainstay of treatment is oral prednisolone, which may need to be given in a high dose for a prolonged period of time. A typical regime would be 2 $mg \cdot kg^{-1}$ for 2 weeks (maximum 60 mg), then 1 $mg \cdot kg^{-1}$ for 2 weeks, then 1 $mg \cdot kg^{-1}$ on alternate days for 2 weeks, followed by a slow taper, but many patients need a prolonged course. The alternative to oral corticosteroids is pulsed methylprednisolone, 500 $mg \cdot m^{-2}$ on three successive days every 4 weeks. It is suggested that there is improved efficacy and fewer side-effects. Certainly, the use of pulsed therapy means that adherence is not an issue, provided the child is brought to the hospital. There is no evidence base for the use of steroid-sparing agents.

Antifungal therapy

The Cochrane review by Elphick *et al.* (2016) identified only four trials of antifungal therapy in ABPA, none of which were suitable for inclusion in the review. We use itraconazole in combination with steroid treatment, for two reasons. First, in ABPA complicating asthma there is clear evidence that this is beneficial, and there is weak retrospective evidence of benefit in CF. Secondly, rare cases of invasive aspergillosis complicating CF have been described and, at least in theory, itraconazole may prevent this. Oral absorption of itraconazole is poor, and serum levels should be measured and the dose adjusted. Furthermore, at least in adults, azole resistance in *A. fumigatus* is common. Itraconazole inhibits the cytochrome p450 enzyme CYP3A, which can lead to Cushing's syndrome and iatrogenic adrenal suppression in patients also taking inhaled budesonide or fluticasone and oral methylprednisolone (but not prednisolone). Other antifungal options include nebulised amphotericin (liposomal if the standard preparation cannot be tolerated) with or without nebulised budesonide, voriconazole, posaconazole and intravenous liposomal amphotericin. *In vitro* sensitivity testing may help antifungal selection. The evidence for usage of these agents is minimal.

Other current treatment options

There are small case series reporting the use of the anti-IgE monoclonal antibody omalizumab in ABPA. Inhaled corticosteroids are commonly employed, but there is only the most limited evidence that they are beneficial. There are occasional anecdotal reports of bronchoscopic airway toilet in recalcitrant airway plugging.

The future

The evidence of Th2-driven responses suggests that monoclonal antibody-directed signature Th2 cytokines (IL-4, IL-5 and IL-13), which are already researched in asthma, may also be useful in ABPA.

Complications of ABPA

The complications of ABPA are the complications of the disease itself, as well as complications of treatment:

- Disease-specific complications are severe proximal bronchiectasis (figure 2) and, in some but not all series, accelerated decline in lung function. ABPA is a risk factor for infection with atypical *Mycobacteria*, although whether because of steroid therapy rather than the underlying disease is not known.
- Complications of treatment are generic to the medications used but, for CF, loss of bone mineral density and precipitation of CF-related diabetes are particularly important.

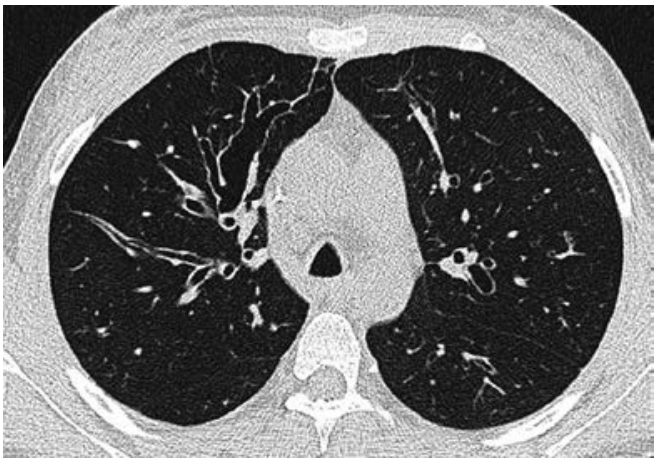

Figure 2. HRCT through the upper lobes showing bilateral bronchiectasis; the varicose pattern of bronchiectasis in the anterior segment of the right upper lobe is typical of ABPA.

Table 4. Stages of ABPA

1: Acute phase	There are acute infiltrates, which clear completely with prednisolone
2: Remission	No prednisolone therapy or infiltrates for 6 months
3: Recurrent exacerbation	Similar in type to stage 1; isolated single episodes are rare
4: Steroid-dependent asthma	
5: Fibrotic disease	No longer completely responds to prednisolone therapy

Prognosis

Mild cases of ABPA may resolve spontaneously, but the majority relapse after treatment. Accelerated decline in lung function is reported in patients treated for ABPA. ABPA has been divided into five stages with different prognoses (table 4), but it is arguable whether these are clinically useful. They are not a chronological progression in clinical practice. Prolonged and recurrent ABPA is common, so prognosis must be guarded.

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Diagnosis and basic management of associated allergic conditions

Maurizio Mennini, Stefania Arasi, Vincenzo Fierro, Maria Cristina Artesani and Alessandro Giovanni Fiocchi

The term "atopy" was originally used by Coca and Coole in 1923 to describe the predisposition to develop hypersensitivity to common allergens associated with an increase of IgE, and with clinical manifestations such as wheal-type reactions, asthma and hay fever. Todays, the term atopy is commonly used to define a disorder involving IgE antibody responses to allergens that are associated with several clinical disorders such as atopic dermatitis, allergic rhinitis, asthma and food allergy. From studies of the epidemiology and heritability of allergic diseases, it is clear that the interaction between genetic and environmental factors plays a role in the development of clinical symptoms.

Since the first report of linkage between chromosome 11q13 and atopy in 1989, there have been thousands of published studies of the genetics of asthma and other allergic diseases. Susceptibility to allergic disease is likely to result from the inheritance of many gene variants but the underlying cellular defects are unknown. By undertaking research into the genetic basis of these conditions, these gene variants and their gene products can be identified by the anomalous phenotypes they produce. In addition, genetic variants may also influence the response to therapy and the identification of individuals with an altered response to current drug therapies. Overlapping sets of genes have been reported in genome-wide association studies (GWAS) for asthma, rhinitis, serum IgE levels and atopic dermatitis, supporting a common genetic element within the mechanisms predisposing individuals toward different allergic disease phenotypes.

Key points

- The main tools for the diagnosis of allergic diseases are the patient's clinical history and physical examination. When the clinical history identifies allergic symptoms with a temporal relationship to a definable and relevant allergen exposure, *in vivo* and *in vitro* tests are used to confirm sensitisation.
- One of the main objectives of allergy therapy is education. Patients should be educated on what sources are causing their individual symptoms and trying to reduce symptoms by limiting exposure.
- The therapy for allergic rhinitis, asthma and atopic dermatitis should be decided based on the most recent guidelines, but adapted to the characteristics of the individual patient.

Gene therapy for allergic disease has not been demonstrated in humans, and application in a clinical setting is not expected soon. However, genetic understanding of allergic disease and the ability to manipulate genes continues to improve.

The important role of epigenetics as a mechanism by which the environment can alter disease risk in an individual is being increasingly recognised (post-translational acetylation and methylation of histones, DNA methylation and microRNA).

Diagnosis of allergic conditions

The diagnosis of allergic disease begins and ends with the patient's clinical history and physical examination.

Theoretically, only controlled allergen challenge can confirm the cause–effect relationship between allergen exposure and clinical symptoms. However, in daily allergy diagnostics it is common to use other kinds of investigations. When the clinical history identifies allergic symptoms with a temporal relationship to a definable and relevant allergen exposure, allergic sensitisation must be confirmed using *in vivo* skin tests or *in vitro* blood tests.

In vivo *testing*

Skin testing is the preferred method for *in vivo* detection of IgE-mediated sensitisation, due to its objective end-point and the ability to test for multiple sensitisations in one session.

There are two approaches to allergen skin testing:

- Percutaneous introduction of allergen through a break in the skin by pricking or puncturing
- Intracutaneous testing with a hypodermic syringe and needle for drugs

Reaction of the skin to extracts of environmental allergens is common, but not invariable in patients with atopic diseases. There is no lower age limit for performing a skin-prick test (SPT). In the past, a lower age limit of 3 years has wrongly been recommended.

The allergen panel used should be modified according to allergen-related symptomatology and local allergen exposure (indoor as well as outdoor). In early infancy, food allergy with manifestations from the skin, gastrointestinal or respiratory tract is more common than inhalant allergy. For children less than 3–4 years of age, recurrent wheezing/asthma and atopic dermatitis are the most common problems. Above 4 years of age, allergies to inhalant allergens develop, especially to indoor allergens (*e.g.* house dust mites, pets, cockroach) and later to outdoor allergens like pollen and moulds.

In vitro *testing*

Total and specific serum IgE

Historically, total serum IgE was used as diagnostic marker for allergic disease. However, the wide overlap in the total serum IgE levels between atopic and non-atopic populations caused it to be superseded by allergen-specific IgE. Non-isotopic auto-analysers that employ a two-stage non-competitive immunoassay format quantify their presence. Quantitative IgE antibody results are reported in $kUa \cdot L^{-1}$ (kilounits of allergen per litre) traceable to the World Health Organization IgE reference preparation (1 U = 2.4 ng of IgE). Allergen-specific IgE antibodies are a marker of allergic sensitisation and a risk factor for allergic disease, but alone, they do not make the diagnosis of allergic disease.

Component-resolved diagnostics

Component-resolved diagnostics (CRD) uses purified native or recombinant allergens to detect sensitisation to specific allergen molecules and has become of great importance in clinical investigations of IgE-mediated allergies.

Cross-reactions between allergens of known allergen families are emphasised. In pollinosis, as well as in allergy to hymenoptera venoms or to food, CRD permits (to some extent) discrimination between clinically significant and irrelevant allergen-specific IgE results and establishes sensitisation patterns with different prognostic outcomes (*e.g.* sensitisations to storage proteins, which correlate with clinically severe reactions in peanut allergy). Further improvements in diagnostics are expected from additional, not yet commercially available, recombinant allergen diagnostics identifying specific molecules of risk. Overall, CRD may decrease the need for provocation testing and may also improve the specificity of allergen-specific immunotherapy. CRD is used in laboratory practice as singleplex and multiplex assays. The choice of allergen for a singleplex assay is based on clinical history, clinical findings and SPT results. Multiplex microarray assays simultaneously determine multiple allergen-specific IgE against numerous allergens. The multi-allergen screen is a qualitative assay that measures allergen-specific IgE to multiple aeroallergens and/or food allergens in a single test.

Basophil activation testing

Basophil activation testing (BAT) is an excellent "*in vitro*" method, that is able to simulate the encounter between basophils and the allergen and to assess the subsequent cellular activation by analysing the expression of activation markers on the cell surface by flow cytometry. CD203c (a member of ectonucleotide pyrophosphatase/phosphodiesterase family) and CD63 (a protein associated with intracellular vesicle membranes) are the most reliable markers of basophil activation currently available. The test uses whole blood rather than isolated leukocytes, due to both simpler and faster manipulation of the method, and also the belief that leaving basophils in their natural environment ensures better functionality. Until 10 years ago, BAT was used as a diagnostic method in drug allergy, with controversial results in terms of sensitivity and specificity for different drugs evaluated.

In recent years, several scientists have shown the usefulness of BAT as a functional assay able to analyse the cellular activation threshold towards an allergen. In this way, BAT has been used to monitor the development of tolerance in children with food allergies before oral challenges.

Serum IgG and IgG4

Food antigen-specific IgG and IgG4 antibody levels are not diagnostically useful as they do not correlate with the results of oral food challenges. Patients affected by eosinophilic oesophagitis showed elevated systemic IgG4 serum levels compared with patients with GOR disease, but this evidence is not yet completely clarified.

Implementing guidelines and improving diagnosis

Implementation of evidence-based recommendations for allergy testing in children will differ between countries depending on local organisation of professionals and the level of knowledge within allergology. In general, improved education in allergology, both at undergraduate level at university as well as at postgraduate level, including primary care physicians and their staff, specialists, subspecialists and nurses is

warranted. Furthermore, it is recommended to ensure and strengthen cooperation between the specialist sector/hospitals, general practitioners and the local homecare team to benefit the individual patient.

Management of allergic conditions

Pharmacological management of associated allergic diseases requires an evidence-based approach. The clinician must refer to the most up-to-date treatment guidelines for each condition. Evidence-based guidelines are at the cornerstone of integrated care pathways, structured multidisciplinary care plans that promote translation of guideline recommendations into local protocols and their subsequent application in clinical practice.

Before undertaking any therapy, however, it will be essential to make a precise diagnosis of the present atopic conditions and a definition of the degree of persistence and severity according to defined criteria.

Allergic rhinitis

The most important element in the evaluation of allergic rhinitis is the distinction between "intermittent" and "persistent" allergic rhinitis. It is also important to perform a differential diagnosis between allergic rhinitis and other types of rhinitis due to structural or mechanical factors (*e.g.* deviated septum), infections, inflammatory/immunological causes, drugs or environmental factors.

Specific treatment options for confirmed allergic rhinitis include:

- Environmental controls for allergen avoidance
- Pharmacotherapy (second- and third-generation antihistamines, intranasal corticosteroids, mast cell stabilisers, ipratropium bromide, leukotriene receptor antagonists)
- Immunotherapy

The two main objectives are improvement of quality of life and the prevention of complications.

Asthma

Management of asthma is based on the principle "assess, adjust and review response". When asthma is suspected, a functional assessment through spirometry is required.

Most asthma guidelines focus on defining levels of asthma severity and future risk. Based on the first evaluation, a pharmacological stepwise approach coordinates inhaled bronchodilators, inhaled corticosteroids and leukotriene receptor antagonists.

Biological agents are used in the most severe cases (omalizumab (anti-IgE) and mepolizumab (anti-interleukin (IL)-5) are currently licensed for children). Not only has the use of these monoclonal antibodies led to improved asthma control in patients with severe disease, their use has also provided insights into the mechanisms of severe asthma.

Allergen immunotherapy (AIT) is considered the only aetiological treatment able to prevent asthma development, to improve asthma symptoms in children with allergic rhinitis, and to prevent new sensitisations in already sensitised patients.

Food allergy

The management of food allergy entails the following:

- Dietary avoidance of the identified allergen to prevent chronic and acute food allergic reactions. Patients and their caregivers must learn how to read and interpret product labels to successfully identify and eliminate food allergens. Elimination diets must prevent inadequate nutrient intake and poor growth.
- AIT, which may be effective in raising the threshold of reactivity to a range of foods in children with IgE-mediated food allergy during therapy (*i.e.* desensitisation) and after discontinuation. It is, however, associated with a mildly increased risk of serious systemic adverse reactions and a substantial increase in minor local adverse reactions. More data are needed in relation to adults, long-term effects, the impact on quality of life and the cost-effectiveness of AIT. Omalizumab has been suggested as an "add-on therapy" to AIT, but larger studies are needed to identify patients who would benefit from the addition of omalizumab to AIT, as well as optimal dosing strategies and treatment duration.
- Epicutaneous immunotherapy (EPIT), which is a novel method that involves transdermal administration of peanut allergen with the objective of inducing tolerance. EPIT could lack the rapid mast-cell desensitisation induced by the progressive intake of food in AIT, which explains differences in short-term outcomes and safety profiles. Head-to-head and long-term comparison of real-life efficacy with regards to sustained unresponsiveness will help define its place in the treatment of food allergy.
- Lysosomal-associated membrane protein DNA (LAMP DNA) vaccines and the use of immunomodulatory agents. These are in the early development phase. Depending on results, they could also become important treatment options.

During treatment with omalizumab for severe uncontrolled asthma, it has been demonstrated that in patients with food allergy the food allergen threshold increases to 8.6 times its original value. The quality of life of patients also increased, due to a better asthma control and a reduction in dietary restrictions. From this perspective, it could be interesting to imagine the use of omalizumab instead of AIT.

Atopic dermatitis

Treatment of atopic dermatitis aims to suppress inflammation, restore the skin barrier and control itching. Various strategies and several treatments are available. Optimal management is tailored to the patient and often involves multimodal strategies. Patient education to maximise adherence is essential.

Avoidance of irritants and allergens, emollients, and topical corticosteroids of appropriate potency and duration remain the cornerstone of atopic dermatitis therapy for acute flare-ups. Topical calcineurin inhibitors inhibit the phosphatase activity of calcineurin, blocking the expression of cytokines. They act "downstream" in the glucocorticoid receptor pathway and thus represent a more targeted way to contain inflammation and avoid the possible adverse effects of topical corticosteroids.

Systemic agents are generally reserved for persistent, widespread and severe atopic dermatitis unresponsive to other therapies. Such patients should be treated by experienced specialists and therapies include corticosteroids, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil and, more recently, biological agents (*e.g.* monoclonal antibodies). In particular, dupilumab is the first biological agent approved for the treatment of atopic dermatitis, having received US Food and Drug Administration and European Medicines Agency approval for adults in 2017

and 2018, respectively, and for children aged ≥6 years in 2020. This fully humanised monoclonal antibody targets the IL-4 receptor alpha subunit, which is shared by the IL-4 and IL-13 receptor.

The association between atopic dermatitis, allergic rhinitis, asthma and food allergy is frequent. From this perspective, an approach with potential universal drugs, able to act on common molecules in the pathogenic processes of different atopic conditions, could be very useful. The diagnosis and treatment of allergic disease continue to advance and challenge clinicians with increasing complexity and novel opportunities. CRD, prevention through exposure, local allergy, biological agents and sublingual immunotherapy are among the advances that have entered the literature and are finding clinical application. The next generation of providers who treat allergic diseases will have new tools and treatment options, but will also face greater complexities.

Education

One of the main objectives of allergy management is education. Patients should be educated on what sources are causing their individual symptoms and trying to reduce symptoms by limiting exposure.

Strategies to reduce symptoms through use of dehumidifiers, air filters, dust mite covers, pet washing and other interventions have rarely shown a significant decrease in symptoms, although a reduction of antigen is often demonstrated. Reducing allergen exposure enough to reduce symptoms in an already sensitised individual seems to be difficult to achieve in most situations.

The new atopic march: aeroallergen or food allergen?

A recent systematic review and meta-analysis of 13 birth cohort studies reported that early food sensitisation is associated with subsequent asthma in childhood. However, no previous population-based studies have determined whether children with clinical food allergy, defined as positive oral food challenges in early life, have a greater risk of developing asthma than those with asymptomatic food sensitisation. Eczema in infancy is also associated with an increased risk of asthma, and early-onset eczema is associated with increased risk for food allergy.

In the longitudinal, population-based HealthNuts cohort study, 5276 infants aged between 11 and 15 months were recruited in Australia. Participants underwent an SPT at recruitment to egg, peanut, sesame, and either cow's milk or shrimp and were examined for eczema while their parents completed a questionnaire. When the children turned 4 years of age, all parents were asked to complete a second questionnaire about their child's health and allergies. Questions on key allergic outcomes (asthma, eczema and allergic rhinitis) included those from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. Children with a food allergy at age 1 year were asked to attend an assessment at the hospital at age 4 years, which included an SPT and oral food challenge to test for persistence or resolution of their food allergy. The authors found that both asymptomatic food sensitisation and food allergy in infancy are associated with an increased risk of asthma by age 4 years. The risk of asthma was higher for children with two or more food allergies in infancy than for those with a single food allergy. Both transient and persistent food allergy were associated with a similar magnitude of increase in the risk of asthma. Having both infantile eczema and food allergy almost tripled the risk of having asthma at age 4 years compared with no eczema and no food allergy. This study adds to existing knowledge about the atopic march. Knowing that having food allergy and eczema increases the chance of subsequent asthma makes it possible to identify children

at highest risk, who might benefit from additional screening for asthma to ensure optimal early management.

Another recent study has shown that food sensitisation in the first 2 years, independent of early life eczema and wheeze, predicts asthma and allergic rhinitis in later childhood. Additionally, co-sensitisation to both food and aeroallergen was the strongest predictor at any time-point tested. The findings were mostly consistent across two cohorts, with different populations in relation to co-sensitisation to food and aeroallergen and sensitisation to aeroallergen only.

Considering this evidence, the patient with an allergic pathology is an individual characterised by a family predisposition, who travels under the stimulus of environmental determinants. It therefore appears necessary to carry out primary and secondary prevention activities on allergies in patients at risk.

Summary

The term "atopy" was originally used to describe a predisposition to develop hypersensitivity to common allergens. GWAS support a common genetic element within the mechanisms predisposing individuals towards different allergic disease phenotypes. An integrated approach and the use of therapeutic remedies effective for multiple atopy conditions, in compliance with the most up-to-date guidelines, is a promising approach for the management of atopic diseases.

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In vivo and *in vitro* allergy diagnostics

Gunilla Hedlin and Jon Konradsen

Allergic sensitisation is a major risk factor for asthma and for increased morbidity in children with diagnosed asthma. Accordingly, the possibility of allergic sensitisation should be considered in all children with suspected or diagnosed asthma. Many children who start to wheeze during airway infections in early life will improve with age when infections become less frequent and the airways grow. However, there is a large group of children who start with viral wheeze and continue to develop persistent asthma. In many of these children IgE-mediated allergy will play an important role as a trigger of symptoms. In some, allergy testing will confirm an IgE-mediated sensitisation sometimes preceding the clinically relevant allergy. In others, asthma symptoms at allergen exposure will appear before sensitisation can be confirmed. Thus, although allergy is a common cause of symptoms of asthma and often of asthma exacerbations, it is not always clear what role a specific allergen plays in the severity of the disease. This is particularly obvious when the relationship between exposure and symptoms is unclear. In pollen allergy, the relationship between exposure and symptoms is easy to assess using pollen count reports. The relationship between sensitisation, exposure and symptoms can in most circumstances be confirmed by taking a history and performing a skin-prick test (SPT) and/or an analysis of allergen-specific IgE in serum. In animal dander allergy there could also be a clear relationship between exposure and allergic symptoms, but this may not always be the case. The exposure to animal dander present on clothes, hair or on surfaces at home and school or in other public places is common but constitutes a hidden and very often unrecognised source of allergen. Under these circumstances it can be difficult to evaluate the impact of allergy on a child's symptoms. These examples highlight the importance of performing a careful, thorough diagnosis of allergy before the decision is made to take action on allergen avoidance and/or initiate immunotherapy.

Key points

- Allergy is a common trigger of asthma.
- Allergy can start at any age.
- Allergy testing should be performed in all children with asthma.

Prevalence of allergic sensitisation

The prevalence of allergic sensitisation is increasing and becomes more common as the child gets older. In Sweden, the prevalence of any positive SPT has been reported to be 30% at age 7–8 years and 41% at age 11–12 years. In the US National Health and Nutrition Examination Survey similar prevalences were reported; 36% of children at age 1–5 years and 45% of participants aged >6 years had one or more positive IgE to one or more food or inhalant allergen. Among schoolchildren with asthma the prevalence of allergy has been reported to be 60% and among children with persistent asthma the prevalence is 80%.

Diagnosis of allergy

History

The first and most important step in the evaluation of children with asthma is a careful detailed history. Important questions include: family history of allergic disease; known triggers of symptoms; timing, frequency and severity of symptoms; and other signs of atopic disease, *e.g.* rhinitis not related to a cold, atopic dermatitis and adverse reactions to food. In some children allergic rhinitis may precede asthma and act as a predictor of an increased risk of asthma. Early development of eczema and/or food allergies can also be signs of risk of later allergic asthma in children.

Allergic sensitisation testing: practice and interpretation

The most common mode of allergy testing is *in vivo* testing by SPT; this is usually the test of choice. The alternative is *in vitro* testing, *i.e.* analysis of allergen-specific IgE antibodies in serum. Both tests have advantages and disadvantages (table 1).

SPTs should be performed with well-standardised extracts. Usually a panel of aeroallergens are used. There are some things that need to be considered when performing the SPT. The test is carried out by applying drops of allergen extract on the volar side of the forearm. The drops are then punctured by a needle-like device (figure 1). After 15–20 min any wheal and flare skin reactions are recorded, and the longest diameter of each wheal is measured. A wheal diameter ≥3 mm is considered a significant skin reaction. A false-negative SPT result can be seen when the patient has ongoing antihistamine therapy, ongoing dermatitis and/or when a topical corticosteroid has recently been applied to the skin. A false-negative result can also be seen at an early stage of sensitisation or if sensitisation is weak. A false-positive SPT can be seen if the child suffers from dermographism or when sensitisation does not reflect clinical allergy; in the latter case the history is more important than the test result, although a positive test can precede the clinical allergy. In food allergy that subsides, such as egg and milk allergy, the skin sensitivity can remain after the child has developed tolerance. An SPT can be performed at any age but skin reactions tend to be smaller in young children (table 2).

Table 1. Advantages of in vivo *(SPT) and* in vitro *(serum IgE) allergy tests*

SPT	Serum IgE
No blood sample needed	No need to withhold antihistamines
Reliable with good extracts	Reliable with validated methods
Immediate results	Always available
Visible results	Can be used when skin is impaired
	Many allergens available for testing

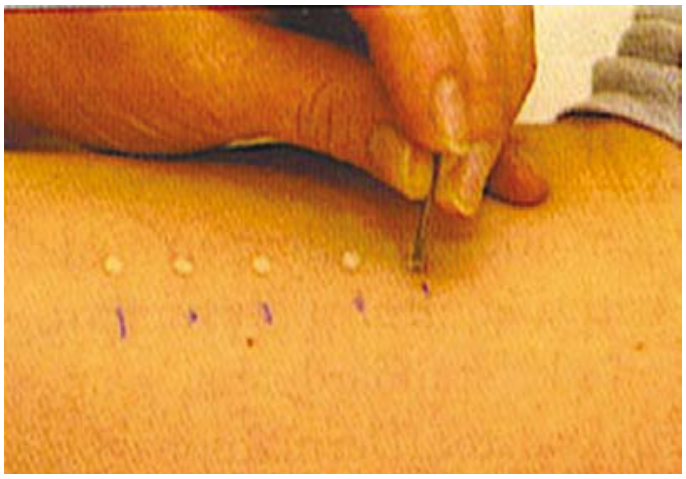

Figure 1. Performance of an SPT.

Table 2. Interpreting allergy test results

Allergy can be an asthma trigger in spite of a negative allergy test
Allergic sensitisation may be unrelated to asthma symptoms
The degree of sensitisation (*e.g.* wheal size and antibody level) may or may not reflect disease severity
SPT and *in vitro* IgE tests often agree but sometimes both tests are needed
When allergy testing and history disagree, an allergen challenge test could be required, if allergy needs to be confirmed or excluded

IgE in serum can be analysed for:

- Single allergens
- Allergenic molecules (components) of single allergens
- A mixture of allergens (mixture of rodents, moulds and dust mites)
- Screening purposes using a multi-allergen test, including the common SPT panel of allergens (table 3)

The *in vitro* IgE measurement and the SPT result usually agree, but not always. If the SPT does not agree with the history, IgE in serum should be measured before ruling out a suspected allergy. Analysis of serum IgE can be performed at any age and at any time; current pharmacotherapy does not interfere with the test result. Negative test results in young children should be interpreted with caution. Low specific IgE levels (0.1–0.35 $kUa \cdot L^{-1}$) can indicate sensitisation. There are a number of companies that provide assays for the *in vitro* IgE antibody tests. Most commonly, a solid phase matrix with allergen extract is used. After adding the patient's serum, an anti-IgE antibody

Table 3. Common panels of allergens included in SPT and/or IgE antibody screening

Tree pollen (relevant for geographical area)
Grass pollen (relevant for geographical area)
Weed pollen (relevant for geographical area)
Animal dander (cat, dog, horse)
Dust mite
Mould (*Alternaria*, *Cladosporium*)

is added and the amount of bound allergen-specific IgE in the patient's serum is analysed. The result is usually expressed in arbitrary mass units per litre ($kUa \cdot L^{-1}$).

Allergen challenge tests

While *in vitro* tests or SPTs are good enough for confirming pollen and animal dander allergy, it may be necessary to perform allergen provocation tests in the eyes and/or the nose to confirm a dust mite or mould allergy. Bronchial allergen challenge is rarely indicated. It can be dangerous in children with asthma, inducing a severe asthmatic reaction, and should be avoided.

Nasal and conjunctival allergen challenges can be important if there is doubt about the impact of the specific allergy on the severity of symptoms. This may be the case when allergen immunotherapy is considered. The rationale is to avoid treating a child whose symptoms are mainly caused by other factors, in spite of confirmed allergen sensitisations.

Food challenges, either open or double-blind, are sometimes warranted to confirm an allergy but also to support development of tolerance, which is common in children with, for example, milk and egg allergy.

Total IgE measurements in serum

Total serum IgE measurements are mainly needed when treatment with anti-IgE (omalizumab) is considered, an injection therapy with monoclonal anti-IgE antibodies. Dosing is based on the patient's age, weight and total IgE level.

Molecular diagnostics

Molecular allergy diagnostics offers new opportunities for refined characterisation and can be particularly useful to separate species-specific IgE antibodies from cross-reacting IgE antibodies from different allergen sources. Assessment of allergen components can be done either by measuring antibodies to individual components or by using an allergen microarray chip. The former approach provides quantitative results on a single allergen component, whereas the latter approach allows simultaneous semiquantitative measurement of IgE antibodies to a large number of components. Some components are recognised as specific markers of an allergen source, and by identifying these allergens it is possible to determine which are the sensitising and which are the cross-reactive allergen sources. Currently, the only commercially available component-resolved microarray diagnostic method is the Immuno-Solid phase Allergen Chip microarray (Phadia, Uppsala, Sweden).

Summary

Allergy diagnostics is an important part of the evaluation and management of children with preschool wheeze and asthma. Together with a careful history, it is one of the first steps in identifying possible triggers in children of all ages. Identification of allergic sensitisation supports asthma diagnosis and indicates which symptom triggers should be avoided. Finally, proven allergy has prognostic value, as allergic children are less likely to grow out of their asthma.

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Prevention measures in allergic disorders

Susanne Halken

The majority of schoolchildren with asthma are allergic to airborne allergens, and allergy is a common trigger of asthma symptoms. The allergens associated with allergic airway disease depend on the age of the child, climatic, seasonal and social factors, and housing conditions. In temperate and humid regions, allergy to house dust mites (HDMs) shows the strongest association with asthma, followed by allergy to furred pets (especially cats). In arid climates, allergy to fungi (*Alternaria* spp.) is prevalent.

Allergic asthma is most often associated with indoor inhalant allergens, whereas allergic rhinitis is most often associated with outdoor allergens such as pollen. In children with allergic asthma, persistent allergen exposure is associated with airway inflammation, bronchial hyperresponsiveness, and an increased risk of persistent and severe asthma.

The aerodynamic characteristics of the allergen-carrying particles vary considerably. Most HDM and cockroach allergens are carried on relatively large particles, whereas most pet allergens are carried on small particles. Therefore, HDM allergen exposure is most commonly associated with chronic inflammation; in contrast, pet allergens may induce acute reactions as well.

Management of allergic rhinitis and allergic asthma includes more or less intensive pharmacological treatment, but also avoidance of the specific allergen(s) and allergen immunotherapy (AIT) with allergens to which the patient has a proven and clinically relevant allergy. This requires a specific allergy diagnosis with sensitisation to allergens that are clinically associated with the symptoms. In clinical practice, allergic sensitisation is documented by a positive skin-prick test (SPT) and/or measurement of allergen-specific serum IgE antibodies (sIgE).

Key points

- Allergen avoidance as well as allergen-specific immunotherapy are relevant treatment options for allergic asthma and allergic rhinitis, along with appropriate pharmacotherapy, but they require proper diagnosis with documented clinically relevant sensitisation.
- Allergen-specific immunotherapy with seasonal and perennial airborne allergens has beneficial effects on allergic asthma and rhinitis.

Recently, it has been shown that sIgE to specific allergen components (component-resolved diagnostics) may be more specific and thereby more useful for evaluating the effects of allergen avoidance and AIT. It is important to be aware that sensitisation in itself is not the same as clinical allergy, for which a clinical response is also required. The effects of allergen avoidance and AIT are still a topic of discussion.

Allergen avoidance

Avoiding exposure to relevant allergens is a logical way to treat allergic airway diseases, when the offending allergen can be identified and effective avoidance is feasible. It is well recognised that avoidance of relevant pollen and food allergens results in fewer and milder or no symptoms in children allergic to these allergens. As regards allergy and exposure to perennial airborne allergens it is more complex, as exposure is not restricted to specific situations, environments or seasons, but may occur throughout the community. Moreover, many children with allergic asthma are allergic to a number of allergens (*e.g.* both HDMs and pets). Pet allergens are, to a high extent, airborne and ubiquitous and significant concentrations are also found in clothes and places without direct contact with pets, even several years after removal of a pet.

A clinical effect of allergen avoidance was first suggested by studies in which children with allergic asthma were removed from their homes to low-allergen, mountain environments. Later, several studies on different measures of environmental control in patients' homes indicated a clinical effect of allergen avoidance. However, much controversy exists regarding the evaluation of results from these studies and from meta-analyses, mainly due to methodological problems. In order to document a cause–effect relationship, avoidance measures should be capable both of reducing the allergen level sufficiently and of resulting in a clinical effect.

Most previous studies on environmental allergen avoidance measures have focused on a single allergen, and the measures for exposure have been concentrations of allergens in dust from mattresses, floors or furniture, which may not represent personal exposure to aeroallergens. Individual differences in sensitivity to exposure may also be important. In addition, the level of anti-inflammatory treatment may be important for evaluation of a possible effect of different environmental measures.

HDM allergen avoidance

HDMs are an important and widely distributed allergen source. HDMs require high humidity and a temperature of ~24ºC for their life cycle and reproduction, and the best conditions are in temperate, humid regions. HDMs mainly live in our bedding, but HDM allergens may also be detected in, for example, clothes, carpets and upholstered furniture, although in lower concentrations. Many different single measures have been recommended for HDM allergen avoidance, most of them focusing on the bedding environment (table 1).

Table 1. Proposed recommendations for children with asthma and HDM allergy

Ensure sufficient ventilation
Avoid damp housing conditions
Encase mattresses with a mattress-encasing product with documented effect
Wash pillows, duvets, blankets and bed pads every 3–4 months (>55ºC)
Wash soft toys and other mite reservoirs

Table 2. Allergen avoidance measures without documented effect

Synthetic filling of pillows and duvets
Foam mattresses
Chemical treatment of mattresses
Special vacuum cleaners
Air filters, ionisers, *etc.*

A Cochrane meta-analysis concluded that current chemical and physical methods aimed at reducing exposure to HDM allergens cannot be recommended for patients with asthma and HDM allergy. However, this conclusion may have many explanations such as heterogeneity in studies, inclusion criteria and the fact that some of the allergen avoidance measures did not sufficiently reduce allergen exposure (table 2).

Well performed, controlled, randomised studies with adequate design and methods have demonstrated that some avoidance measures, such as mattress encasings with mite allergen-impermeable coverings, have proven effective both in reducing the level of HDM allergens and in improving disease control in children, and recently, also in preventing severe asthma exacerbations.

There is no evidence that synthetic fillings for bedding (duvets and pillows) are more beneficial than feather fillings or that foam or water mattresses should result in lower exposure, as compared with sprung mattresses, but the limited available data indicate that using a washable bed pad may reduce exposure from the mattress.

Washing of bedding and clothing at >55ºC kills HDMs and effectively removes allergens. Washing at lower temperatures also removes allergens. However, it is not known whether washing has any clinical effect.

Vacuum cleaning removes allergens and may result in a modest decrease of allergen reservoirs, but it also causes a brief increase in personal aeroallergen exposure while vacuum cleaning, and high-efficiency particulate air (HEPA) filters make only a little difference. Data on the possible reduction in personal allergen exposure and its clinical effect are lacking.

There is no good evidence for possible effects of air filtration or acaricides; for the latter, concerns about human health and environmental toxicity remain.

Different floor coverings may have different effects. Carpeted floors contain particles and allergens to which children playing on the floor are exposed. It has been assumed that hard floors have a beneficial effect, but available data suggest a complex and small effect.

Recently, a clinical effect for the novel concept nocturnal temperature-controlled laminar airflow treatment has been demonstrated, and the results are encouraging, but further studies in children are needed.

A large trial provided evidence of improvement of asthma control by a multifaceted intervention that was tailored to the child's sensitisation and exposure status. This included several measures, such as education, encasing of mattresses and pillows, high-filtration vacuum cleaners, and HEPA filters.

Apart from attempts to reduce the reservoirs of allergens, an obvious target is to try to remove the conditions for the HDMs to live and reproduce by reducing humidity (to below 45–50% relative humidity), avoiding moisture problems and increasing the ventilation of the home, although clinical data are limited.

Table 3. Advice for children with asthma and allergy to pets

The only effective method is removal of the pet
General cleaning and vacuum cleaning is advised, although there is no good evidence
Even after removal of a pet, it may take many months before the reservoir of allergens is reduced sufficiently and it may take 6–12 months before the full benefit is seen
Complete avoidance of pet allergens is impossible as the allergens are ubiquitous and can be found in many environments outside the home, including schools

Pet allergen avoidance

In the case of asthma and allergy to pets, repeated exposure is associated with bronchial hyperreactivity and eosinophilic airway inflammation, even without obvious symptoms. Cat allergens in particular are airborne and sticky, and are found at varying levels in houses and public places without cats. Thus, removal of a pet from the home reduces the allergen level, but does not abolish exposure (table 3). Washing of bedding and clothes might reduce exposure.

Washing of the pet has been tried in some studies, and it has been shown that it may reduce the allergen level but only for a short time. We lack good data on the clinical effectiveness of different measures to reduce pet allergen levels and exposure.

Pest avoidance

Particularly in inner-city environments, cockroach allergy is a major cause of allergic asthma. Approaches include pesticides and sanitation (*e.g.* avoiding making food available to the cockroaches, control of water leaks and control of entrances). After such elimination procedures, thorough cleaning is necessary for a long period to remove the pesticides and allergens.

Likewise, mouse exposure, particularly in bedrooms, is prevalent, especially in inner-city dwellings, and methods for effective rodent control have been shown to reduce exposure and improve symptoms. However, to date, the evidence is limited.

Mould avoidance

Many studies have shown that exposure to and allergy to fungi are often associated with severe asthma. Some fungi (often *Aspergillus*) may colonise and even infest the lungs, thereby causing severe disease. Many other fungi, most often *Alternaria* but also others such as *Cladosporium* or *Penicillium*, appear to play an important role in severe asthma. There is limited evidence about the role of fungal allergen avoidance in asthma. Moisture issues cause most instances of fungal growth in the indoor environment, and control of indoor environmental humidity and removal of contaminated material has been recommended. There are no convincing trials on avoidance of *Alternaria*, which is primarily an outdoor allergen, although it can also be found indoors.

In the case of suspicion of significant problems with fungal growth in the indoor environment, it is often necessary to investigate which fungus is present, and to involve experts and technicians with special expertise in this area.

Allergen-specific immunotherapy

Subcutaneous immunotherapy (SCIT) has been used for more than 100 years and is regarded as a safe and efficacious treatment for allergic rhinitis and allergic asthma. Children with severe allergic asthma are often sensitised to multiple allergens, which

Table 4. Indications for AIT

"Allergic rhinitis/asthma" triggered by allergen exposure
Confirmed specific allergy
Seasonal allergy to pollen
Perennial allergy, especially to HDMs

may make SCIT complicated and less safe to administer. In a previous Cochrane review, it was concluded that SCIT has significant beneficial effects on symptoms and medication use in both children and adults with mostly mild asthma. SCIT in children with moderate and severe asthma is not well documented. Sublingual immunotherapy (SLIT) has also been shown to improve allergic rhinitis and asthma symptoms and decrease medication use. SLIT is safe, although systemic side-effects may occur. The effect and safety aspects of AIT are described in a series of systematic reviews and recommendations on AIT from the European Academy of Allergy and Clinical Immunology (EAACI). It has been demonstrated that the effects of AIT last beyond the cessation of AIT in contrast to other treatment for allergic rhinitis/asthma. Furthermore, AIT has been shown to reduce the risk of development of new asthma in children with allergic rhinitis and grass pollen and/or birch pollen allergy.

The available guidelines have an important role in providing standards for the indications, use and administration of AIT.

Criteria for considering AIT

Before considering immunotherapy, the allergen(s) triggering asthma symptoms must be identified and the allergic sensitisation confirmed (table 4). While *in vitro* tests or SPTs are useful for confirming pollen and animal dander allergy, it may be necessary to perform ocular or nasal allergen provocation tests to confirm other perennial allergies like HDM allergy. More information on the relevant procedures can be found in a position paper published as a Global Allergy and Asthma European Network (GA^{2}LEN)/EAACI pocket guide on AIT for allergic rhinitis and asthma.

AIT to improve and prevent deterioration of allergic asthma

The majority of AIT studies in children (and adults) with asthma have been performed in those with mild allergic asthma, usually combined with rhinitis. Most of the studies have been performed with SCIT using single allergens, the most predominant perennial allergen being HDM and the dominant seasonal allergens being birch, olive/*Parietaria*, grass and ragweed (mostly in the USA). The best evidence of efficacy of immunotherapy in children with asthma also emanates from studies of children allergic to pollen and HDMs (table 5). A few small studies have also indicated a beneficial effect of SCIT with cat allergen extracts; to date, there is no good documentation for dog or horse allergens.

Only a few studies have investigated AIT in children with concomitant seasonal and perennial allergies. One American randomised controlled trial of multi-allergic

Table 5. Documented effects of AIT

Less severe symptoms on allergen exposure
Decreased medication use during the allergy season
Improved quality of life
Lasting effect after cessation of AIT
Asthma-preventive effect in children with pollen allergy (birch/grass)

children demonstrated no significant effect of SCIT on medication use and symptom control. A few other studies have been more successful; thus, AIT may change the severity of asthma by inducing allergen tolerance.

Recent extensive reviews conclude that there is evidence for efficacy of SCIT and SLIT in both children and adults with asthma, especially for AIT with pollen or HDM allergens, whereas evidence for other allergens is not yet well documented. More high-quality studies are needed.

SCIT for asthma

A course of SCIT consists of an up-dosing phase with increasing doses until the optimal maintenance dose is achieved, followed by a maintenance phase where this dose is received every 6–8 weeks for a total treatment duration of 3–5 years. Different up-dosing regimens are used for the up-dosing phase of SCIT, including "rush" and "cluster" regimens and the conventional "one injection per week" regimen. Pre-treatment with antihistamines may reduce the local side-effects.

The highest risk of systemic side-effects has been reported when a SCIT rush regimen is used. However, none of the schedules is without risk of systemic side-effects, which may even include anaphylaxis. Implementation of safety measures and standardised procedures, including measurement of lung function, are mandatory when AIT is administered. Injections should not be given if the subject has ongoing allergic symptoms or a current infection; asthma symptoms have to be controlled and recent allergen exposure should be checked. A standard procedure for required dose adjustments in case of side-effects (major local swelling and/or systemic effects) should be followed. After each injection, the subject should stay at the clinic for observation for ≥30 min, as most systemic side-effects occur within that time. Table 6 provides a comparison of the disadvantages of SCIT *versus* SLIT. It is mandatory that standardised procedures for prompt recognition and treatment for any side-effect, including adrenaline for possible anaphylaxis, are in place.

SLIT for asthma

SLIT has been shown to improve allergic rhinitis and asthma symptoms and medication use, but to date, the effect in children with asthma is less well documented than for SCIT, and mostly concerns pollen and HDM allergens. Some reviews conclude that existing studies show an effect especially for HDM SLIT, but there is a very high degree of heterogeneity. SLIT appears more convenient and safer than SCIT, with less systemic side-effects, although the frequency of transient local side-effects, such as itching in mouth and throat, is high. The first dose of SLIT should be given at a clinic and followed by observation for ≥30 min (table 6).

Table 6. Disadvantages associated with AIT

SCIT	SLIT
Frequent subcutaneous injections	First tablet given in the clinic
Long-term therapy (≥3 years)	Long-term therapy (3 years)
Loss of school attendance for the child and workdays for accompanying relatives	
Risk of systemic side-effects, including anaphylaxis	High risk of local side-effects, although less severe systemic side-effects
Costs	Costs

AIT combined with anti-IgE: safety and efficacy in children with severe allergic asthma

Few studies have addressed this question in children. One study including polysensitised children with seasonal allergic rhinitis and birch or grass allergy showed that the combination of omalizumab and pollen SCIT had superior effects on symptom load in both birch- and grass-allergic children. Other studies performed in groups of children and adults have shown similar results. Pre-treatment with omalizumab in patients with severe multi-allergic asthma was the subject of another study of combined therapy, although omalizumab treatment only overlapped at the start of immunotherapy in symptomatic patients with asthma. The risk of systemic side-effects was reduced, although severe systemic reactions still occurred in the group pre-treated with omalizumab. There is a need for more studies of this combination before it can be considered an additional therapy in children with asthma and severe allergies.

Summary

A pragmatic approach in clinical practice should involve interventions tailored to the patient's sensitisation and exposure in a multifaceted allergen avoidance regime, based on removal of the accumulating allergens. The extent of such avoidance measures should also be tailored to the severity of the disease, and combined with education and other relevant treatment options. Environmental avoidance measures have proven effective as a specific treatment for a specific allergy under the right conditions, but it requires defining specific and clinically relevant sensitisation, education and an overall plan to reduce exposure in the child's home, and its success also depends on the relevance of other allergens and exposure outside the home. Thus, in children with allergic asthma, measures to reduce allergen levels significantly should be included in an individualised treatment plan as well as an appropriate pharmacological treatment and avoidance of exposure to tobacco smoke.

If allergen avoidance is not possible or sufficient, the addition of AIT may be considered, provided it is combined with adequate pharmacotherapy. Studies of SCIT for pollen and HDM allergy have shown significant effects on the specific allergies. Recent reviews have confirmed the utility of SCIT and SLIT for allergic asthma and rhinitis in children. The treatment can improve the quality of life for the allergic child, and decrease symptoms and need for medication. However, an effect in multi-allergic children and children with severe asthma has not been demonstrated.

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Epidemiology, genetics, pathophysiology and prognosis of CF

Caroline Poulter, Iolo Doull and Jayesh Mahendra Bhatt

CF is caused by variants in the gene that encodes CFTR, a cAMP-regulated chloride channel that is crucial for chloride, bicarbonate and sodium transport across cell membranes. In the lung, defective CFTR function is thought to reduce airway surface liquid (ASL) hydration, resulting in a failure to clear airway pathogens and a cycle of infection and inflammation. Median age of death in most developed countries is ~30 years. It is probable that newer disease-modifying therapies will change the landscape and life expectancy of CF.

Epidemiology

CF is the most common inherited life-limiting disease in Caucasians. Worldwide over 80000 people have been diagnosed with CF, although this is probably an underestimate due to under-diagnosis and under-reporting in non-Caucasians. There are comprehensive patient registries that have been powerful tools to advance care for those with CF; between them the US Cystic Fibrosis Foundation and European Cystic Fibrosis Society registries have data on ~75000 people with CF. The incidence of CF varies between one in 2000 and one in 4000 in those of northern European ancestry (including in North America and Australia), but is significantly less common in African Americans (one in 20000) or Japanese individuals (one in 350000). The gene frequency varies between one in 25 in those of northern European descent and

Key points

- CF is the most common autosomal recessive life-limiting condition in the Caucasian population.
- There are around 200 different *CFTR* variants confirmed to cause CF, the majority of which fall into one of six classes based on the underlying mechanism of defective *CFTR* production or function.
- CF is a muco-obstructive disease in which obstruction, infection and inflammation in the lungs are closely linked.
- Life expectancy for people with CF continues to increase, while pulmonary disease remains the major cause of morbidity and mortality.

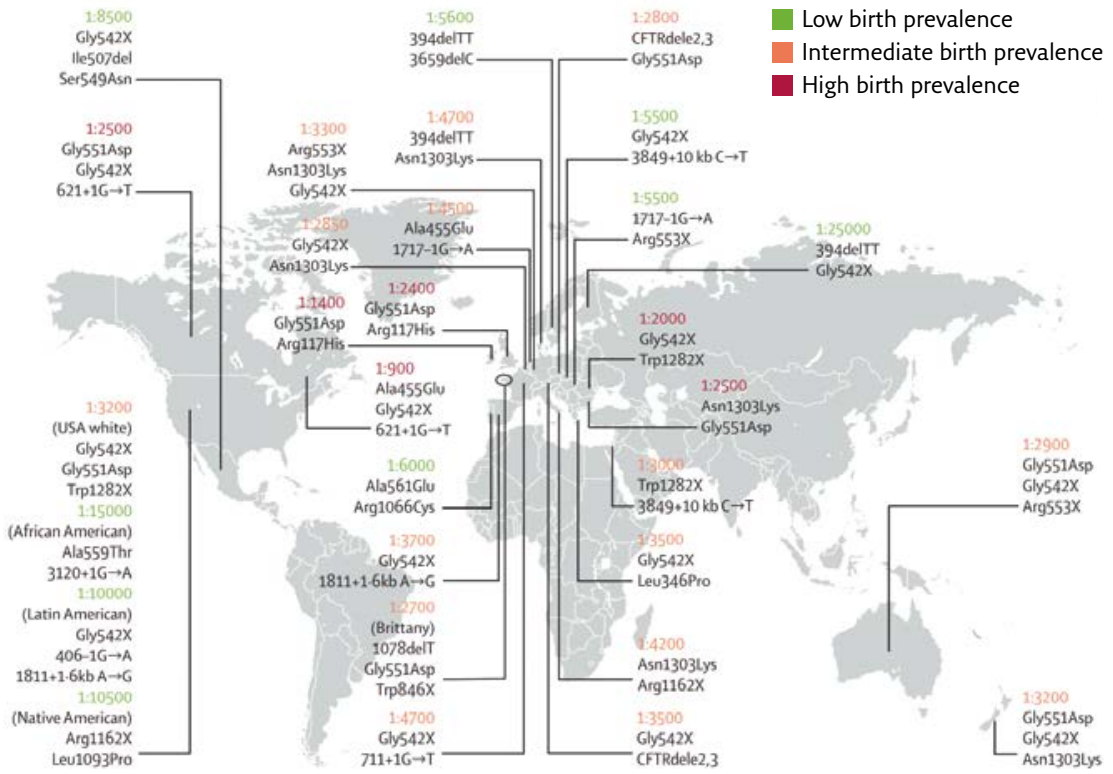

Figure 1. Approximate CF birth prevalence and common mutations for selected countries. Birth prevalence is reported as number of live births per case of CF. Common/important mutations in each region are listed below the prevalence. The birth prevalence can vary greatly between ethnic groups in a country. Reproduced from O'Sullivan et al. *(2009) with permission.*

less than one in 200 in India. The incidence of CF may be higher in countries with high rates of consanguinity (*e.g.* Jordan, incidence one in 2500). Birth prevalence varies from country to country, and with ethnic background (figure 1).

The introduction of CF newborn screening is often associated with a 10% decrease in the incidence of CF. With improved care and advances in treatment, the prognosis of CF has increased incrementally such that in most developed countries adults with CF outnumber children.

The most common *CFTR* variant, F508del, accounts for 60–70% of CF chromosomes worldwide; consequently ~40–50% of patients will be F508del homozygous and 30–40% will be F508del heterozygous. There is a long tail of non-F508del variants, although none are more frequent than 5%. There are some notable population-specific variants, *e.g.* the variant W1282X accounts for nearly 50% of CF chromosomes in Ashkenazi Jews and is the most frequent in Israel (23.0%).

The *CFTR* gene and protein

The gene causing CF, identified in 1989, is located on the long arm of chromosome 7 at position q31.2, spans ~250 kb of genomic DNA and contains 27 exons. It is transcribed into 6.13-kb mRNAs encoding a transmembrane protein of 1480 amino acids known as CFTR.

The CFTR protein is a member of the ATP-binding cassette (ABC) transporter superfamily whose proteins transport various molecules across extra- and intracellular membranes. The CFTR protein consists of five domains:

- Two membrane-spanning domains (MSD1 and MSD2) with six hydrophobic transmembrane helices forming the channel through the membrane

- Two nucleotide-binding domains (NBD1 and NBD2) gating the channel through ATP binding and hydrolysis
- A central, highly charged regulatory domain (R) with multiple consensus sites for phosphorylation by protein kinase (PK)A and PKC; this domain is unique to CFTR as it is not present in other members of the ABC superfamily

Opening of the CFTR channel is initiated by phosphorylation of the regulatory domain by PKA followed by recruitment of ATP to the NBDs, which subsequently dimerise to open the channel pore. ATP hydrolysis causes the NBDs to dissociate to close the channel.

The CFTR protein is predominantly located at the apical membrane of polarised epithelial tissues. Its main function is that of a cAMP-regulated anion channel responsible for the transport of chloride and bicarbonate at the apical membrane of epithelial cells thus generating an osmotic gradient for fluid secretion. It is expressed in several tissues, including the lungs, sweat ducts, pancreas, gastrointestinal tract and vas deferens, accounting for the constellation of clinical symptoms seen in CF. CFTR-mediated chloride secretion across epithelial cells is controlled by both modulating channel activity and regulating the total number of CFTR channels in the membrane.

CFTR variants

Although CF is a monogenic autosomal recessive condition, there is marked phenotypic variability based on residual CFTR function, allele complexity, disease modifying genes and environmental factors.

The significance of individual CFTR variants has been delineated by the Clinical and Functional Translation of CFTR (CFTR2) programme (www.cftr2.org), which assesses disease liability through collating genotypic and phenotypic data from individuals with CF due to both common and uncommon CFTR variants. Three criteria are used to assess the significance of a variant: 1) the clinical characteristics of individuals who have one copy of the variant; 2) functional analysis of the degree of CFTR dysfunction caused by the variant; and 3) population and penetrance analysis of the variant in question. Over 2000 CFTR variants have been identified to date, although not all are clearly disease causing and many are private variants confined to single individuals or families.

The nomenclature of CF variants has changed over time, with many publications referring to the original (legacy) names, but more recently the Human Genome Variation Society (HGVS) DNA and protein names are used. Thus, the most common CF causing variant is F508del (legacy) or c.1521_1523delCTT (HGVS DNA) and p.Phe508del (HGVS protein).

F508del is a 3-bp deletion in exon 10 (current nomenclature: exon 11) that causes the loss of the amino acid phenylalanine at position 508 of the protein. There are another 23 relatively common variants worldwide and a few variants with an unusually high frequency in specific populations indicating founder effect genetic drift. Aside from F508del, there are 10 CFTR variants with a frequency of >1% in people with CF: R117H, G551D, G542X, N1303K, 621+1G→T, 1717-1G→A, 1898+1G→A, P67L, D1152H and 3659delC.

There is a hierarchy of clinical phenotypes dependent on the degree of CFTR dysfunction, with a negative correlation between CFTR function and sweat chloride concentration. The vas deferens appears the most sensitive tissue to CFTR dysfunction and thus minor decreases in CFTR function are associated with male infertility and

normal sweat chloride concentration. With decreasing CFTR function there is a raised sweat chloride concentration with associated pancreatic insufficiency, and finally severe lung disease. A clearer understanding of the form and function of CFTR has resulted in its categorisation into six distinct classes reflecting abnormalities of protein synthesis, structure, and function (table 1 and figure 2).

Class I, II and III variants are associated with minimal CFTR function and patients with these mutations have a more severe phenotype, whereas individuals with class IV, V and VI variants have residual CFTR function (>3% of wild type) and are more likely to be pancreatic sufficient, have mild lung disease and have increased life expectancy. Generally, patients with meconium ileus, distal intestinal obstruction syndrome (DIOS) and CF-related liver disease have two class I–III variants, while those with recurrent pancreatitis have a class IV–VI variant.

Variants can exhibit features of more than one class. For example, although F508del is primarily a class II trafficking variant with only 3% of the protein reaching the apical membrane, once incorporated into the apical membrane it displays both class III and class VI characteristics. Although there are clear differences in phenotype and outcome between the variant classes, there remains significant phenotype variability within classes. For example, although most individuals homozygous for F508del have lung disease, there is marked variability in severity.

The potential of a variant to contribute to the phenotype depends not only on its nature, localisation in the gene and molecular mechanism, but also on its interaction with variants in CFTR in cis (complex alleles) and trans. Complex alleles are single genes that have more than one variant within it. The most notable complex allele is R117H, which has a variable phenotype determined by intragenic modification by the poly-T tract. The poly-T tract occurs in one of three forms dependent on the number of thymidine residues: 5T, 7T or 9T.

Increasing thymidine repeats is associated with increased CFTR function, such that those with R117H/5T usually have diagnostic sweat chloride concentrations but have milder disease and are usually pancreatic sufficient, while those with R117H/7T often have normal or intermediate sweat chloride concentrations and their only manifestation may be infertility in males.

Until recently treatment of CF focused on management of individual organ manifestations of the underlying disease. Advances in technology have led to the emergence of two main categories of disease modifying strategy: those which target the genetic defect, *i.e.* gene therapy; and therapies which target the protein defect, such as CFTR modulators. These small molecule agents target specific CFTR variant classes and as a result, genotyping, which was previously performed to confirm a diagnosis or predict disease severity, has become essential. Three broad classes of treatment have been developed:

- Read-through agents such as ataluren for stop codon variants
- CFTR correctors, such as lumacaftor, tezacaftor and elexacaftor, that improve trafficking of defective CFTR to the cell surface
- Potentiators, such as ivacaftor, that increase CFTR channel function at the cell surface

For variants such as F508del, which has both class II and III defects, a combination of correctors and potentiators is required, such as lumacaftor/ivacaftor, tezacaftor/ivacaftor or elexacaftor/tezacaftor/ivacaftor. Gene therapy is not dependent on variant class (mutation agnostic) and aims to deliver copies of the coding sequence

Table 1. CFTR mutation classification

Class of mutation	Problem	Effect	Examples
I	Production	Leads to a reduction in the quantity of expressed CFTR protein and includes nonsense, frameshift and mRNA splicing defects producing truncated, deleted or elongated protein variants. In effect, virtually no functional CFTR reaches the apical membrane of epithelial cells.	G542X, W1282X, R553X
II	Processing	Includes missense variants as well as in-frame deletions or insertions that cause abnormal CFTR processing. There is failure of the protein to be properly processed to a mature glycosylated form and misfolding of the protein leading to failure of transport to the cell surface.	F508del, N1303K,
III	Regulation	There is aberrant channel function with normal quantities of CFTR. These variants affect the regulation of CFTR function by preventing ATP binding and hydrolysis at the NBDs required for channel activation.	G551D
IV	Conduction	Involves amino acids in the membrane spanning domains. There is normal gating, but there are changes in the conductivity of the channel leading to abnormal chloride and bicarbonate permeability.	R117H, R334W, R347H, R347P
V	Production	There is production of normally functioning CFTR protein; however, mutations located in the promoter or splice sites in the gene cause limitation of transcriptional regulation and lead to reduced protein production.	3849+10kbC→T, 2789+5G→A, A455E
VI	Turnover	There is increased turnover of CFTR at the channel surface (shortened half-life) due to nonsense and frame-shift variants which cause marked instability of an otherwise fully processed and functional protein.	Q1412X, 4326delTC, 4279insA

Information from Elborn (2013), Derichs (2013) and Thursfield *et al*. (2013).

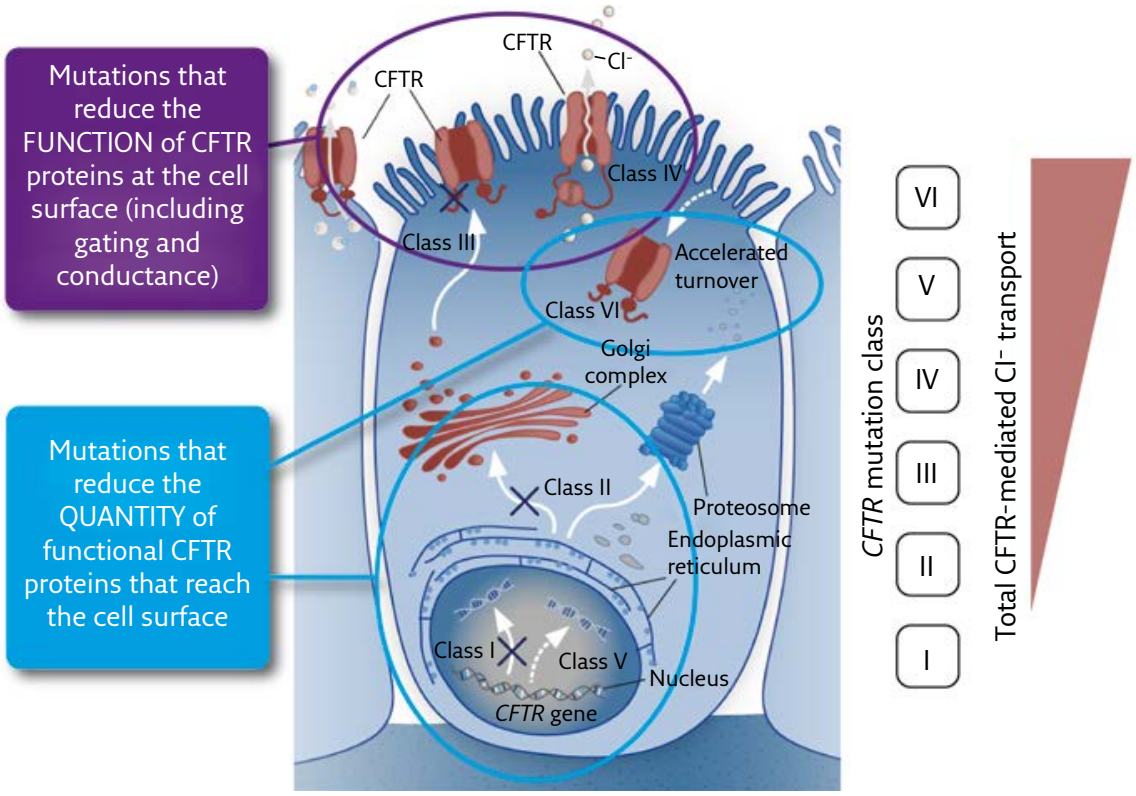

Figure 2. CFTR *gene mutations are categorised into six classes. Mutation classes I, II, V and VI result in an absence or reduced quantity of CFTR protein at the cell membrane, whereas mutation classes III and IV influence the function or activity of CFTR at the cell membrane. Class I mutations are associated with the greatest disruption to CFTR-mediated chloride transport; in general, chloride transport gradually increases through the remaining five classes, with the greatest activity being observed in Class IV–VI mutations. Reproduced and modified from Derichs (2013) with permission.*

of normal *CFTR* DNA to cells. Trials, to date, have shown modest benefits in terms of lung function, but it is likely that improved delivery systems and vectors will be required for significant benefit.

Genotypic and phenotypic heterogeneity

Despite being considered a monogenic disorder, manifestations of CF range from single to multisystem involvement with a wide scale of severity, and studies of the correlation between clinical phenotype and genotype have revealed a complex relationship.

The extent of variability in clinical phenotype without the strong genotype–phenotype correlation to explain this suggests that there are multiple influencing factors. A patient's phenotype is determined by the overall CFTR activity which, in turn, is determined by the combined effect of both disease-causing alleles on the quantity and function of *CFTR*. This is also influenced by a combination of additive effects including modifier genes, complex alleles, variants in alternative genes that produce CF-like phenotypes, environmental influences and epigenetic factors.

There is a close relationship between the *CFTR* genotype and the pancreatic phenotype, revealing "severe" variants to be associated with pancreatic insufficiency and variants with residual function to be associated with pancreatic sufficiency. The development of meconium ileus (predominantly prevalent in patients with pancreatic

insufficiency carrying "severe" *CFTR* mutations), diabetes and liver disease are mainly confined to patients with severe variants without residual function; however, the liver phenotype in CF patients with the same *CFTR* genotype is variable, suggesting that environmental factors or modifier genes might be important in the development of CF-related liver disease.

Because of its complexity and patient exposure to a multitude of endogenous and exogenous factors, pulmonary outcome is the most variable and unpredictable component of the CF phenotype. Several studies have shown significant correlation between *CFTR* genotype and pulmonary status concluding that patients with class I or II variants on both chromosomes have more rapid deterioration in lung function and lower survival rates. F508del homozygous patients were found to present the most considerable variation in terms of severity of pulmonary disease.

Heritability estimates suggest that some features of CF, such as congenital absence of the vas deferens, are highly determined by genetic factors whereas pulmonary pathology is more multifactorial. CF-related diabetes has heritability estimates of nearly 100%; however, in some cases this appears to come from other type 2 diabetes genes rather than *CFTR*.

Modifying factors

Modifying genes act on the clinical variability of CF, particularly in relation to lung disease. The mechanisms by which modifying genes act in the context of lung disease include inflammatory and infectious response, tissue damage and repair, and pharmacogenetic response. Increasingly, modifier genes are identified through genome-wide association studies. Modifiers of clinical phenotype for lung function include mannose-binding lectin (MBL)2, endothelial receptor type A (EDNRA) and transforming growth factor (TGF)-β1.

The impact of these modifier genes is not limited to variability in lung function, as they also contribute towards predisposition to chronic infection with *Pseudomonas aeruginosa*, with the dynactin subunit 4 (DCTN4) gene associated with time to first colonisation, chronicity and mucoid status. In some cases, the influence of gene modifiers downplays the clinical significance of a combination of variants. For example, polymorphisms in the gene encoding TGF-β1 modify the severity of lung disease in homozygous F508del patients. There is marked variability in the incidence of CF-related diabetes in those with a more severe CFTR genotype, with evidence that the gene modifiers are the same as those that increase type 2 diabetes susceptibility in the general population.

Epigenetics

The contribution of epigenetic factors, such as DNA methylation, chromatin remodelling, histone modification and RNA interference, may be substantial. Although several polymorphisms have been reported to lead to alterations in transcription factor binding and, therefore, to be involved in the modulation of *CFTR* transcription, to date, there is no evidence of clinical relevance.

Pathophysiology

In the healthy airway, an osmotic gradient is achieved by an efflux of chloride ions through CFTR channels and an influx of sodium ions through epithelial sodium channels (ENaC). This allows effective mucociliary transport to be maintained by adequate hydration of the ASL. CFTR also transports bicarbonate. The airways are

also defended against infection by mechanical mucus clearance and antimicrobial proteins.

In CF, absent or reduced CFTR activity leads to failure of chloride transport across epithelial cells and upregulation of ENaC. ENaC is negatively regulated by CFTR and it is thought that its increased activity in CF may be due to a combination of excessive proteolytic cleavage of ENaC, dysregulation of ENaC by cAMP and a constitutive increase in ENaC activity. There is also a growing focus on the inhibition of ENaC as a therapeutic target to rehydrate secretions and improve mucus transport. The potential of some of the initial therapies was limited by their systemic side-effects including hyperkalaemia in clinical trials. The most recently developed peptide, SPX-101, is proposed to have a prolonged mechanism of action and avoid the side-effects of its predecessors.

The imbalance of the osmotic gradient due to absent or reduced CFTR activity and upregulation of ENaC results in removal of water from the periciliary gel. This leads to mucus hyper-concentration (increased percentage of solids), compression of the periciliary layer by the mucus layer, decreased mucociliary clearance, and adhesion of dense mucus to the airway walls, the volume depletion hypothesis. ASL rehydrators (hypertonic saline and mannitol) are used in response to the volume depletion hypothesis. These agents produce clinically relevant effects, like increases in FEV_1 and reduced exacerbation frequency. Sputum measurements in CF reveal mucus hyper-concentration with abnormally high total concentrations of the respiratory mucins MUC5B and MUC5AC. The reduced pH of the ASL, resulting from the lack of CFTR-dependent bicarbonate secretion, also prevents mucins from organising normally and leads to reduced bacterial killing. In addition, there is evidence to suggest that CFTR dysfunction itself leads to immune defects with consequent compromised bacterial clearance. CF can therefore be described as a muco-obstructive disease in which obstruction, infection, and inflammation are closely linked.

Roesch *et al.* (2018) have reviewed the role of inflammation in CF very well and the following is a brief summary. The dysregulated host inflammatory response to altered airway conditions and persistent polymicrobial infections is the cardinal feature of lung disease in people with CF. Interestingly, CF patients do not have difficulty containing bacterial infections outside of the lung.

Inflammation begins early in life, persists, and is progressive and unrelenting, and seems excessive relative to the burden of infection. There is increased activation of the inflammatory response with heightened pro-inflammatory signalling; moreover, there is also impairment of anti-inflammatory signalling pathways resulting in an inability to terminate and resolve inflammation. It is not entirely clear whether the abnormal airway inflammation in CF is primary or entirely secondary. Presence of inflammation in the absence of, or prior to, infection may be due to a primary defect in CFTR, which directly increases and prolongs the inflammatory reaction. Alternatively, it could be entirely secondary to altered airway physiology and microbial infection where early, transient infections can induce a host response that persists rather than resolves.

Inflammation impairs host defences, worsens airway obstruction, causes structural damage to the airway wall architecture, and ultimately contributes to progressive loss of lung function. It is complex and involves a multitude of stimuli. These include polymicrobial infections, pro-inflammatory mediators and cells (particularly neutrophils, macrophages and T-lymphocytes), signalling pathways, and products.

The neutrophil is central to the disease process in the CF airway. Massive quantities of neutrophils are present in the CF airway. This is due to a combination of increased influx and decreased clearance. In the CF airway, neutrophils often undergo necrosis rather than clearance by normal apoptotic mechanisms leading to the formation of neutrophil extracellular traps (NETs). NETs form a mesh-like network that consists of neutrophil chromatin complexed with histones, pro-inflammatory mediators and neutrophil granule contents. The majority of human DNA present in the CF airway arises from NETs and the clinical benefits of inhaled dornase alfa relate to its effects on this extracellular DNA. The antimicrobial activity of NETs is of limited value in the more advanced stages of CF lung disease, especially in the face of a chronic, unrelenting bacterial infection. In this situation, NETs are more likely to be harmful and contribute to the immunopathology in the CF airway. Although NETs eventually become ineffectual in killing bacteria over time, they can still incite a vigorous and damaging inflammatory response. The concentration of proteases, like neutrophil elastase, released in the neutrophilic CF airway environment overwhelms natural defence systems. Unopposed elastase (both surface-bound and free) has several deleterious effects. These include:

- Causing structural damage
- Further impairment of mucociliary clearance (as it alters ciliary beating and increases mucus secretion)
- Inducing airway epithelial cells to produce neutrophil chemoattractants
- Activating the apical membrane ENaC, thereby increasing sodium hyperabsorption and further decreasing ASL height
- Degrading macrophage phosphatidylserine receptors, which impairs the resolution of inflammation due to lack of efferocytosis
- Degrading wild-type and mutant CFTR
- Promoting bacterial persistence by cleaving immunoglobulins and complement fragments on the surface of the bacteria and specific receptors on the surface of the phagocytes, thus hindering normal host opsonophagocytic mechanisms

Macrophage function and their ability to resolve inflammation are also defective in CF.

As inflammation plays such a crucial role in the pathogenesis of progressive lung disease, the availability of effective anti-inflammatory drugs for CF lung disease is an important and largely unmet clinical need. To date, most anti-inflammatory therapies considered for CF have involved a direct attack on the activation of the airway inflammatory response. Perhaps, a more prudent approach might be to terminate the inflammatory response by augmenting the body's own counterregulatory mechanisms. Caution must be used when developing anti-inflammatory drugs for CF so as not to exacerbate the coexisting bacterial infection.

The landscape of CF treatment is changing rapidly with the availability of CFTR modulators. Although these modulators address the underlying defect in CF, their impact on downstream consequences such as inflammation are not known and it is unclear to what extent CFTR modulators will impact the inflammatory response. However, recent clinical trials with medications to improve CFTR function have not produced a measurable improvement in airway inflammation, despite better lung function and, at times, reduced bacterial infection.

Improving CFTR function may be unable to repair the structural lung damage already present in many individuals with CF. Even after CFTR function is restored, as in people

with non-CF bronchiectasis, structural lung damage could sustain infection and inflammation.

Several anti-inflammatory drugs are in use or under evaluation (*e.g.* azithromycin, ibuprofen, acebilustat, lenabasum, fenretinide, inhibitors of neutrophil elastase, thymosin α-1, human mesenchymal stem cells). It is likely that people with CF will require antibiotics and anti-inflammatory therapies despite improved CFTR function through drug therapy. Physical exercise may have immunomodulatory effects and have anti-inflammatory benefits.

Pancreatic insufficiency occurs in up to 85% of people with CF. Mucous plugging obstructs the canaliculi of the pancreas and gallbladder leading to defective secretion of digestive enzymes and bile with consequent malabsorption and failure to thrive. Dysfunctional ion transport in the biliary tree leads to an increased risk of gallstones and hepatobiliary disease and pancreatic abnormalities can lead to CF-related diabetes. A more detailed discussion of the pathophysiology for non-respiratory system organ involvement is beyond the remit of this chapter.

Prognosis

There has been an increase in the median survival of people with CF over the past 60 years, thanks to the implementation of newborn screening programmes, multidisciplinary care in specialist centres, mucoactive drugs, anti-inflammatory therapy, antibiotic therapy, optimisation of nutrition and, more recently, the introduction of CFTR modulators. Lung disease remains the major cause of mortality and morbidity, and 80% of patients succumb to respiratory failure or transplant complications. Death in childhood is now rare, and the most frequent age of death in developed countries is close to 30 years. In contrast to median age at death, the calculated median predicted survival for someone born today with CF in developed countries is closer to 50 years. Median predicted survival for males is ~5 years longer than for females. With the increasing life expectancy, extrapulmonary involvement is seen more frequently, with hepatobiliary dysfunction becoming increasingly prevalent and ~25% of patients being affected by CF-related diabetes by the age of 20 years.

The major determinants of survival are pancreatic sufficiency and CFTR class. While the most significant poor prognostic factors are advanced pulmonary disease, as measured by development of a supplemental oxygen requirement and FEV_1 <40%, and malnutrition. It should, however, be noted that FEV_1 does not always accurately reflect the severity of lung disease. It has been known for some time that higher levels of aerobic fitness in patients with CF are associated with a significantly lower risk of dying even after adjustment for other risk factors. This was further confirmed in a recent large, international multicentre study that identified a high-risk phenotype with poor lung function, nutritional status and substantially reduced exercise capacity, a subgroup of patients who may especially benefit from regular monitoring of exercise capacity and exercise counselling. Digital clubbing and chest crackles between 3 and 5 years of age are markers of severe early pulmonary involvement and thus risk factors for childhood death. Recent literature suggests that greater weight at the age of 4 years is associated with better lung function and fewer CF complications in childhood. Other poor prognostic factors include female sex, CF-related diabetes and *P. aeruginosa* infection, although the reason for the gender gap is less well understood. The number of CF-related hospital admissions with pulmonary exacerbations is also a significant predictor of increased morbidity and mortality. Newborn screening for CF is associated with a significant improvement in nutrition, advantages in terms

of pulmonary function and improved survival, and is a cost-effective public health intervention.

Management of end-stage CF should focus not only on quantity but also on quality of life. Attention should be paid to optimising medical therapy, and consideration of adherence to treatment, any adverse environmental and psychosocial factors and any additional diagnoses is crucial.

Adequate nutritional support, often with gastrostomy feeds, good diabetes control and detection and management of GOR are also important. Timely referral for consideration of lung transplant is advised in order to facilitate a thorough assessment by the multidisciplinary transplant team. In most centres, listing for transplant would be considered when there is a <50% predicted 2-year survival.

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Screening and diagnosis of CF

Jürg Barben and Kevin W. Southern

Diagnosis of CF

The diagnosis of CF is based on one or more typical phenotypic features (table 1): a history of CF in a sibling or a positive newborn screening (NBS) result, and a laboratory confirmation of CFTR protein dysfunction and/or identification of two CF-causing mutations. In most cases, the diagnosis of CF will be confirmed by measurement of sweat chloride concentration using quantitative pilocarpine iontophoresis, which measures chloride transport through the CFTR channel, and/or the genetic confirmation of two CF-causing CFTR variants in trans. The 40 most frequent CF-causing CFTR variants will detect >90% of affected CF patients in most European populations. To date, 2102 CFTR variants have been listed in the CF mutation database (www.genet.sickkids.on.ca/cftr/StatisticsPage.html), but so far, only 442 (20%) have been annotated on the CFTR2 website (www.CFTR2.org): 360 are CF-causing, 48 are variants of varying clinical consequence, 11 are variants of unknown significance, and 23 are not CF-causing.

The sweat test comprises three phases: stimulation of the sweat glands (pilocarpine iontophoresis), sweat collection, and sweat analysis. The collection of a sufficient amount of sweat can sometimes be difficult, especially in very young children, but there have been many improvements in the sweat collection method. Newer techniques have reduced the amount of sweat needed, including the Macroduct collection system or the Nanoduct sweat analysing system (figure 1). Sweat tests should not be performed in infants before the age of 3 days, <36 weeks corrected

Key points

- The gold standard confirmation method for a suspected CF diagnosis is the measurement of sweat chloride using pilocarpine iontophoresis.
- A borderline or positive result should always be confirmed with a second sweat test or by CFTR mutation analysis.
- Until recently, the diagnosis has usually been made based on clinical manifestations, but newborn screening for CF has been implemented in many European countries.
- Once CF diagnosis has been confirmed, other family members should be offered screening for the disease using sweat testing, especially all siblings.

Table 1. Age-related signs and symptoms of CF

Age	Common respiratory presentation	Common non-respiratory presentation	Less common presentation
General (any age)	Moist cough with sputum production Respiratory infection with typical CF pathogen (*e.g. Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Burkholderia cepacia*)	Salty-tasting skin	
Neonatal		Diagnosis made by NBS (elevated IRT) Meconium ileus (10–15% of patients with CF) causing bowel obstruction, partly with perforation and peritonitis Abdominal cramps, fatty stool	Protracted jaundice Intestinal atresia Fat soluble vitamin deficiency (*e.g.* bleeding due to vitamin K deficiency) Acrodermatitis atrophicans due to zinc deficiency
Infancy and childhood	Recurrent respiratory symptoms (chronic cough, wheeze, pneumonia)	Failure to thrive due to exocrine pancreas insufficiency with steatorrhoea, diarrhoea and abdominal distension	Rectal prolapse Anaemia, oedema and hypoproteinaemia Dehydration and electrolyte disturbance (Pseudo-Bartter's syndrome, hypochloraemic metabolic alkalosis) Cholestasis Chronic sinusitis
Adolescence and adulthood	Recurrent respiratory symptoms (cough, wheeze) Bronchiectasis Clubbing of finger and toes Chronic pansinusitis, nasal polyps	Azoospermia (secondary to congenital bilateral absence of vas deferens)	Acute pancreatitis Liver disease, portal hypertension Pulmonary infection with atypical mycobacteria Haemoptysis Allergic bronchopulmonary aspergillosis

NBS: newborn screening; IRT: immunoreactive trypsinogen.

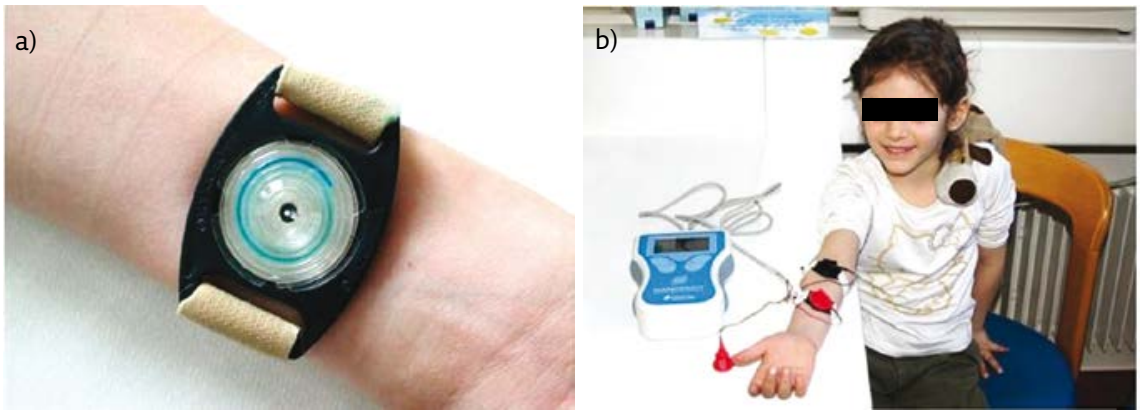

Figure 1. New sweat collection systems. a) Child's arm during sweat test with a macroduct collection system. After pilocarpine iontophoresis to stimulate sweating, the macroduct collection system is firmly attached to the skin of the forearm. Sweat can be seen entering the tube system (blue coloured rings). Chloride analysis can be performed on as little as 15–30 µL sweat. b) A child with a nanoduct system. After pilocarpine iontophoresis to stimulate sweating, a nanoduct analysing system is measuring sweat conductivity while attached to the patient. Measuring conductivity can be performed on as little as 3–5 µL sweat.

gestational age, and with a weight <2 kg. Sweat testing should always be carried out in accordance with the current guidelines and by a trained and experienced professional. Sweat testing is vulnerable to many sources of errors. Table 2 lists some of the common causes of false-negative and false-positive sweat test results.

Sweat chloride concentration increases with age in people without CF, but a sweat chloride concentration of ≥60 mmol·L^{-1} is usually diagnostic for CF (figure 2). Values between 30 and 59 mmol·L^{-1} are intermediate. However, undisputed cases of CF with normal sweat electrolytes have been described. The measurement of other electrolytes (potassium and sodium) is not recommended as they are not diagnostic for CF, but a ratio of sodium:chloride >1 can be supportive for CF. The measurement of conductivity is approved for screening, but a value ≥50 mmol·L^{-1} should always be confirmed with a sweat chloride measurement.

Table 2. Diseases and conditions other than CF associated with raised or lowered sweat electrolytes

Associated with raised sweat electrolytes (false-positive results)	Associated with lowered sweat electrolytes (false-negative results)
Evaporation of the sweat sample	Dilution of sweat sample
Severe malnutrition	Oedema
Anorexia nervosa	Dehydration
Atopic dermatitis (eczema)	Hypoproteinaemia
Familial hypoparathyroidism	Mineralocorticosteroid treatment
Pseudohypoaldosteronism	Some CFTR mutations (*e.g.* R117H, A455E, G551S, 3849+10kbC→T)
Adrenal insufficiency	
Glucose-6-phosphatase deficiency	
Nephrogenic diabetes insipidus	
Mauriac syndrome	
Fucosidosis	
Klinefelter syndrome	
Familial cholestatic syndrome	

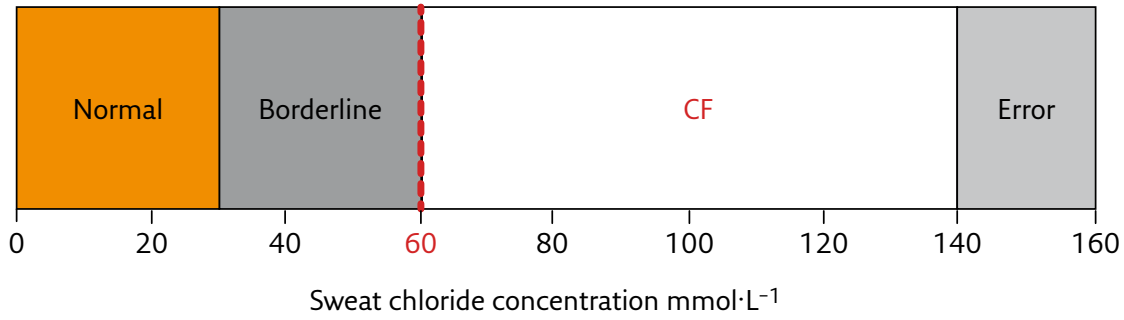

Figure 2. Sweat chloride measurement.

For patients with an unclear diagnosis, there are two main methods of further characterisation of the salt transport defect: nasal potential difference and intestinal current measurement. Both are challenging and only available in a few centres. In certain cases, however, they can provide valuable further information to help support or refute a diagnosis of CF.

Newborn screening

NBS for CF, using immunoreactive trypsinogen (IRT) in dried blood spots taken from infants on the third/fourth day of life, has been implemented in most European countries (figure 3). The first NBS programmes were based on IRT measurements from a heel prick test with repeat testing for infants with an elevated initial measurement 6 weeks later. With the detection of the *CFTR* gene in 1989, many countries introduced DNA analysis as the second tier of analysis. To date, more than 30 screening programmes have been developed, with quite marked variation in protocol design. All screening algorithms rely on testing for IRT as the primary screen for CF. Infants who have an elevated IRT (usually >99th percentile) undergo further assessment either by another IRT measurement (IRT/IRT algorithm), genetic testing for the most common *CFTR* variations (IRT/DNA algorithm) or further screening algorithms. Within these two categories, a variety of modifications are used because no single algorithm is perfect. The screening algorithm of each country depends on programme resources and goals, including mechanisms available for sample collection, regional demographics, the spectrum of disease phenotype that is to be detected and acceptable failure rates.

NBS-positive infants are referred to a CF centre for sweat testing, where the suspected CF diagnosis will be confirmed or rejected. The aim of a NBS programme is primarily to detect as many children with CF and pancreas insufficiency as possible in order to start treatment as early as possible, while avoiding false-positive screening results resulting in unnecessary recalls and sweat tests. The advantages of early diagnosis include nutritional benefits, early substitution of pancreatic enzymes and fat-soluble vitamins, treatment of CF-specific pathogens, access to specialised care, a reduction in the time of diagnostic uncertainty and the ability to counsel parents for prenatal testing. However, screening programmes also have some negative effects. NBS identifies some healthy heterozygote carriers, which can cause anxiety and depression in affected families. In addition, some CF-affected individuals will be missed even in the best NBS programme, depending on the chosen cut-off value of the initial IRT measurement (false negatives in up to 8%).

Most infants with a positive NBS result for CF will have either a clear diagnosis of CF (true positive NBS result) or CF excluded (false positive NBS result); however, a small but significant number will have an inconclusive diagnosis. This is a challenging

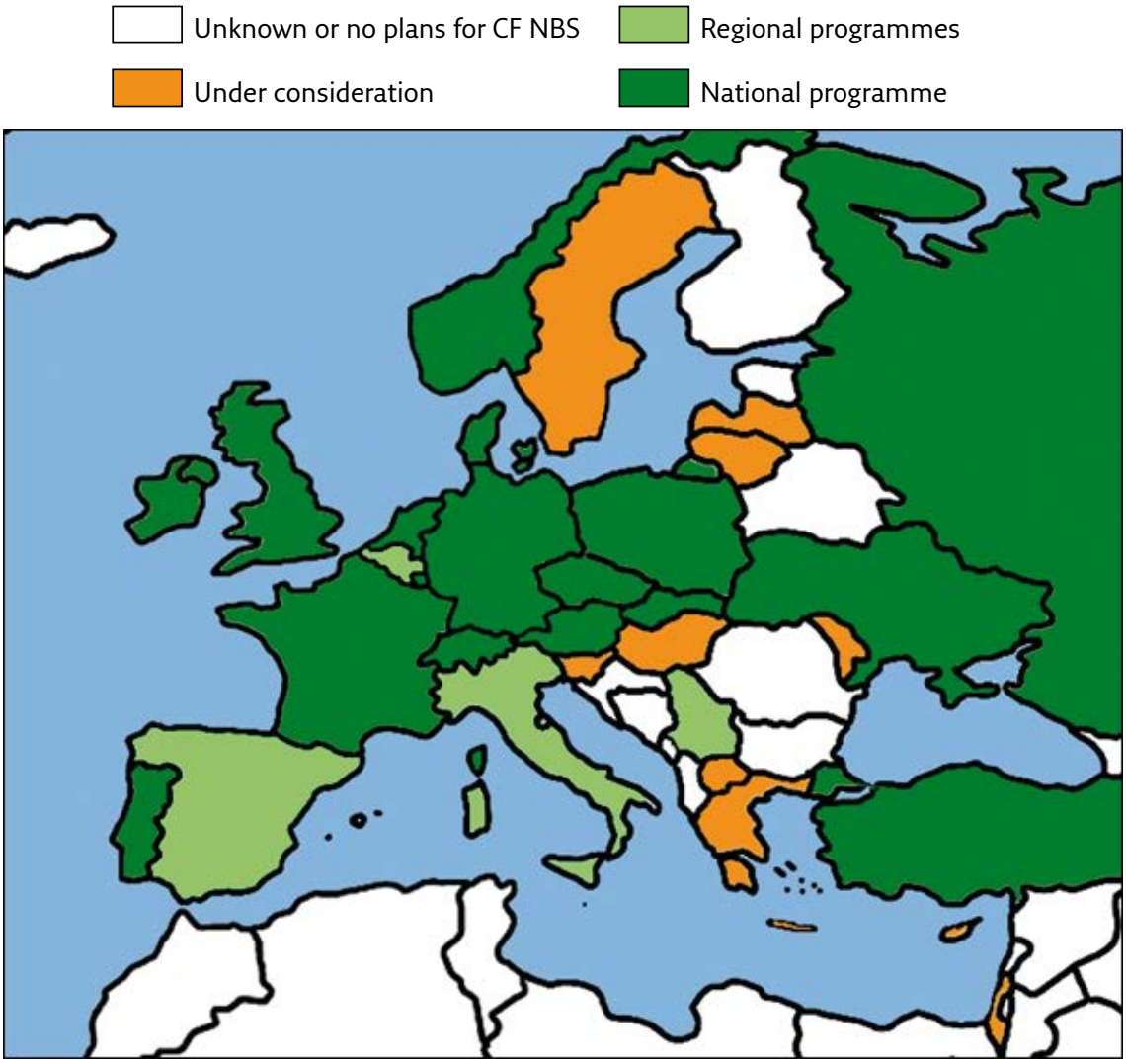

Figure 3. NBS programmes in Europe, 2019.

situation for families and for healthcare professionals. These children are now labelled as CF-screen positive, inconclusive diagnosis (CFSPID); the corresponding term in the USA is CFTR-related metabolic syndrome (CRMS). These children have a positive NBS result for CF and either a sweat chloride value <30 mmol·L^{-1} and two *CFTR* variants (mutations), at least one of which has unclear phenotypic consequences, or an intermediate sweat chloride value (30–59 mmol·L^{-1}) and 1 or 0 CF-causing variants. There is guidance for the early evaluation of infants with an inconclusive diagnosis after a positive NBS result for CF. Key points include the organisation of a second sweat test to measure sweat chloride in a laboratory with a high level of experience, and to repeat the sweat test after 6 months (and later) if the diagnosis is still unclear. Infants with only one *CFTR* variant recognised and a normal repeat sweat chloride (<30 mmol·L^{-1}) should be reported as carriers and no further testing undertaken. Infants with a CRMS/CFSPID designation are well and have no clinical features consistent with a diagnosis of CF. It is important that these infants continue to have regular clinical review by physicians with an interest in CF, as they have a risk to develop significant clinical features consistent with CF.

Once CF diagnosis has been confirmed, other family members may be offered screening. All siblings need to be screened for the disease (sweat test), which may be pre-symptomatic or unrecognised. Asymptomatic adult family members may wish to be screened for carrier status to allow them to make informed choices about prenatal screening.

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CF lung disease

Nicolas Regamey and Giulia Cangiano

Lung disease accounts for most of the morbidity and mortality in CF. CF lung disease begins early in life. It is characterised by impaired mucociliary clearance and mucus obstruction of the small airways, as well as chronic pulmonary infection and inflammation, leading to lung tissue destruction and development of bronchiectasis. There is a progressive decline of lung function with episodes of acute worsening of respiratory symptoms, often referred to as "pulmonary exacerbations". Tissue damage ultimately leads to end-stage lung disease with respiratory failure and death in many patients with CF.

Pathophysiology

The most commonly accepted pathophysiological explanation for airway disease in CF is the "low volume" hypothesis. This hypothesis postulates that CFTR dysfunction leads to a loss of inhibition of airway epithelial sodium channels, which, in turn, leads to excess sodium and water reabsorption. This results in dehydration of the airway surface liquid. Reduced volume of the airway surface liquid causes failure of mucociliary clearance, which leads to mucus obstruction of the small airways. The lungs are unable to effectively clear inhaled bacteria, viruses, fungi and airborne pollutants. The thickened mucus on the epithelium forms plaques with hypoxic areas that can harbour bacteria and other pathogens.

Key points

- CF lung disease begins early in life. It is characterised by impaired mucociliary clearance and mucus obstruction of the small airways, and chronic pulmonary infection and inflammation.
- There is a progressive decline of lung function, ultimately leading to death, with episodes of acute worsening of respiratory symptoms, referred to as pulmonary exacerbations.
- Current management of CF lung disease is predominantly symptomatic. The cornerstones of CF respiratory care are airway clearance and treatment of pulmonary infections. CFTR modulators, which have the potential to revolutionise CF care, have recently been developed.
- Lung transplantation is the final therapeutic option for patients with end-stage lung disease.

The lungs of children with CF appear normal at birth but quickly become infected by organisms that are not adequately cleared. Infants with CF develop persistent endobronchial infections early in life due to *Staphylococcus aureus*, nontypeable *Haemophilus influenzae* and Gram-negative bacilli. By the end of the second decade of life, *Pseudomonas aeruginosa* is the predominant pathogen. Chronic bacterial endobronchial infection is associated with an intense neutrophilic inflammatory response that damages the airway, impairs local host-defence mechanisms and facilitates further infection. For a given bacterial load, a person with CF will have up to 10-times more inflammation than a person with a lower respiratory tract infection but without the disease. This vicious cycle of inflammation and infection with airway damage results in progressive bronchiectasis, gas trapping, impaired gas exchange (hypoxaemia and hypercarbia) and ultimately leads to respiratory failure (figure 1).

Airway disease in CF is present early, even in asymptomatic infants diagnosed through newborn screening. Both infection and inflammation are detected by BAL in CF infants as young as a few weeks of age. CT scans in CF infants show the presence of structural airway wall changes, including thickened airway walls, narrowed airway lumens, air trapping and bronchiectasis. Once present, bronchiectasis persists and is progressive. Lung function has also been shown to be diminished in infants with CF, and lung function declines over time throughout life. Pulmonary insufficiency is responsible for at least 80% of CF-related deaths.

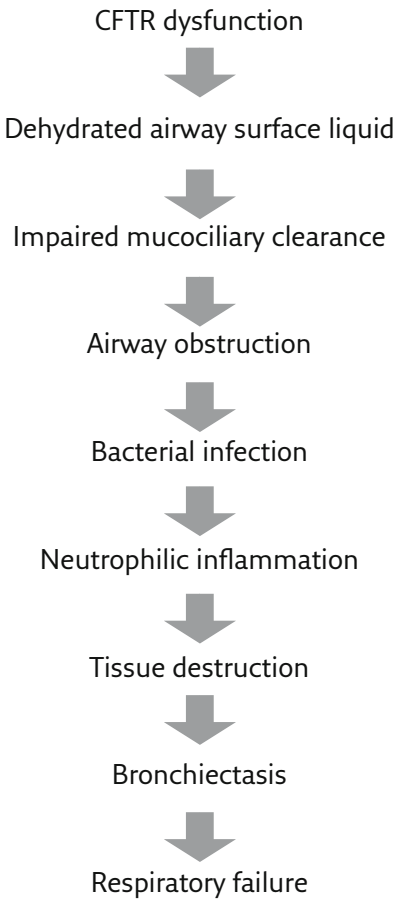

Figure 1. Pathophysiology of CF lung disease. Steps hypothesised to be relevant in the progression of CF lung disease are shown. Note that the steps do not necessarily occur in the order presented; for instance, chronic neutrophilic inflammation leads to further airway obstruction through the accumulation of dead cells and mucus in the airway lumen.

Clinical manifestations

Pulmonary manifestations of the disease appear throughout life with a great variability from patient to patient (table 1; see also table 1 in chapter "Epidemiology, genetics, pathophysiology and prognosis of CF").

In the first months of life, respiratory symptoms can already be present, but gastrointestinal symptoms (meconium ileus, fatty stools and failure to thrive due to pancreatic insufficiency) are predominant. Infants with CF do not experience viral respiratory infections more often than their healthy peers, but the course of viral infections can be severe, especially in the case of an infection with respiratory syncytial virus (RSV). Recurrent cough, tachypnoea and wheeze are the main clinical signs of CF lung disease in the early stages. At first, the cough may be dry but eventually it becomes loose and productive. Some children remain asymptomatic for long periods or seem to have only prolonged acute respiratory infections. Others acquire a chronic cough within the first weeks of life or have repeated pneumonias. High energy consumption due to an increased work of breathing can aggravate failure to thrive.

Older children present with a persistent moist cough and sputum production. Expectorated mucus is usually purulent. Late clinical findings include increased anteroposterior diameter of the chest, localised or scattered crackles and digital clubbing. Chest radiograph abnormalities (*e.g.* infiltrates, atelectasis, bronchiectasis) are pulmonary features of advanced CF lung disease (figures 2 and 3). As airways disease persists and worsens, exercise intolerance and shortness of breath are noted. Exacerbations of pulmonary symptoms eventually require hospitalisation for effective treatment, but what constitutes a pulmonary exacerbation of CF is not clearly defined. Increased cough, change in sputum colour or quantity, decreased appetite or weight, change in respiratory rate and presence of new wheezes or crackles on auscultation of the chest are particularly important features.

With pulmonary disease progression, there is an increased likelihood of respiratory complications. Lobar atelectasis may be asymptomatic and noted only at the time of a routine chest radiograph. Aggressive antibiotic therapy and increased chest physiotherapy may be effective. Allergic bronchopulmonary aspergillosis (ABPA) may present with wheezing, increased cough and shortness of breath. The presence of new, focal infiltrates on the chest radiograph, the recovery of *Aspergillus fumigatus* from sputum, or the demonstration of high immunoglobulin E serum levels or serum antibodies against *A. fumigatus* support the diagnosis. Treatment involves antifungals and steroids to control the inflammatory reaction. Airway infection with *Burkholderia cepacia* may be associated with rapid pulmonary deterioration and death. Nontuberculous mycobacteria, *Stenotrophomonas maltophilia* and *Alcaligenes xylosoxidans* are emerging pathogens in patients with CF. Their clinical impact is not fully understood, but infection with *Mycobacterium abscessus* can be a rapidly progressive process.

Haemoptysis and pneumothorax are complications in advanced lung disease. Endobronchial bleeding is the consequence of airway wall erosion secondary to inflammation and infection. Small volume haemoptysis is relatively common and prompts for intensified antimicrobial treatment and chest physiotherapy. Persistent, massive haemoptysis can be controlled by bronchial artery embolisation. Pneumothorax is rarely encountered in children, but may be a life-threatening complication in older patients. A small pneumothorax is managed conservatively, but a large (distance between the apex and cupola >3 cm) pneumothorax or one under

Table 1. Pulmonary manifestations

Stage	Manifestation	Aim of treatment	Management	Comments
Early	Pre-infection: impaired mucociliary clearance, virus infections	Mucus clearance, prevent bacterial infection Maintain good lung function	Airway clearance techniques: physiotherapy and inhalation with hypertonic saline and rhDNase Influenza immunisation	Early start of treatment before onset of symptoms is recommended
	Intermittent isolation of CF pathogens	Eradication of infection	Different protocols with oral, inhaled and systemic antibiotics	Eradication can usually be achieved, but evidence of long-term benefit unclear
Intermediate	Chronic infection with *S. aureus*, *H. influenzae*, *P. aeruginosa*	Suppression of bacterial load	Oral, inhaled and systemic antibiotics	Segregation of patients with *P. aeruginosa*, BCC, *S. maltophilia* and *A. xylosoxidans* to prevent cross infection is important
	Infection with less common CF pathogens: BCC, *S. maltophilia*, *A. xylosoxidans*	Eradication if early manifestation; suppression of bacterial load	Individual treatment based on antibiotic susceptibility	Confirmation in a reference laboratory essential
	Allergic bronchopulmonary aspergillosis	Reduce allergic response and fungus load, prevent bronchiectasis	Oral steroids and antifungal agents	Long course over several months required
	Non-tuberculous mycobacterial infection	Eradication	Long-term combination therapy for ≥12 months	Treatment started after repeated detection of the same isolate with clinical manifestations
End stage	Haemoptysis	Prevent bleeding, which may be fatal	Intravenous antibiotics, pause airway clearance therapy for a few days, bronchial artery embolisation	
	Pneumothorax		Drainage, pleurodesis if recurrent	
	Respiratory failure		Low-flow oxygen therapy, temporarily continuous positive airway pressure, lung transplantation	

rhDNase: recombinant human doxyribonuclease; BCC: *Burkholderia cepacia* complex; *S. maltophilia*: *Stenotrophomonas maltophilia*; *A. xylosoxidans*: *Alcaligenes xylosoxidans*.

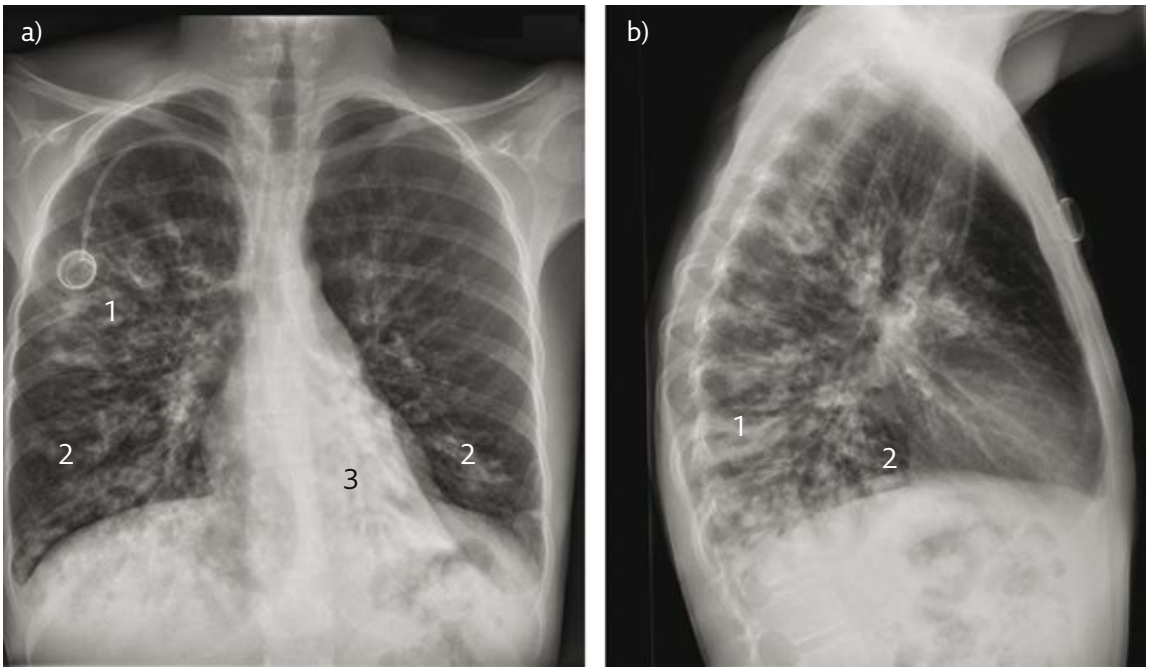

Figure 2. Chest radiograph of a 15-year-old female CF patient with advanced lung disease: a) posteroanterior view and b) lateral view. The radiograph shows pronounced pulmonary hyperinflation with sternal bowing, bronchial wall thickening and bilateral bronchiectasis, infiltrates mainly in the right upper lobe (1) and in the lower lobes on both sides (2) as well as atelectasis of the left lower lobe (3). Note the central venous access (Port-a-Cath system; Smiths Medical, St Paul, MN, USA). Courtesy of E. Stranzinger, Division of Radiology, University Children's Hospital of Bern, Bern, Switzerland.

tension requires rapid treatment with drainage. If recurrent, pleurodesis or surgical intervention must be performed.

Acute respiratory failure rarely occurs and is usually the result of a severe viral illness, such as influenza. Patients eventually progress to chronic respiratory failure from slow deterioration of lung function. Chronic right-sided heart failure (cor pulmonale) is a

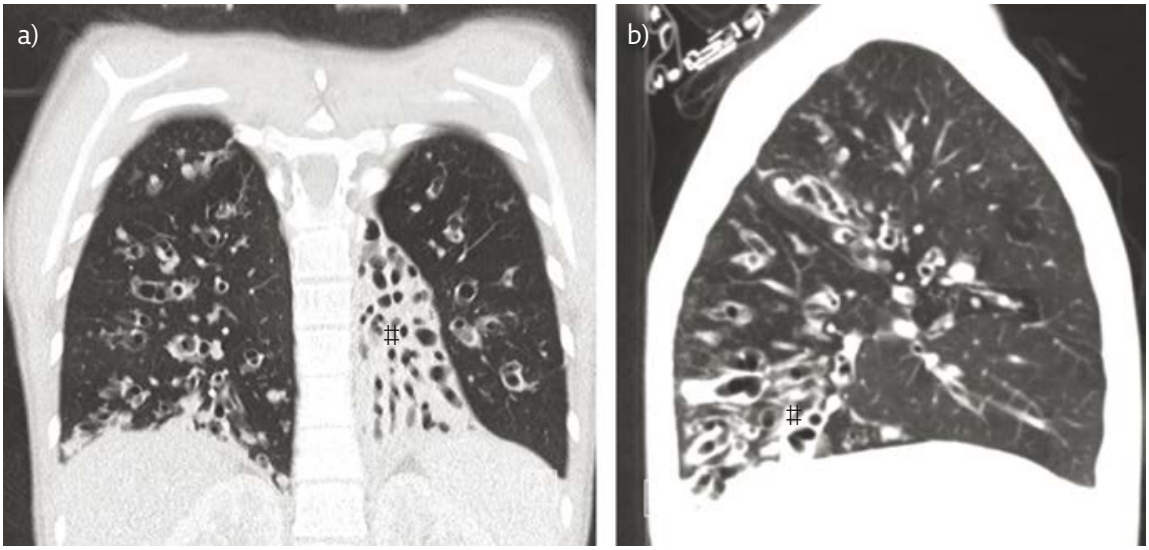

Figure 3. CT scan of a 15-year-old female CF patient (the same patient as in figure 2): a) coronal plane view and b) sagittal plane view of the left lung. Bilateral mucus plugging and bronchiectasis, as well as atelectasis of the left lower lobe (#) is clearly visible. Courtesy of E. Stranzinger.

complication seen in CF patients with long-standing, advanced pulmonary disease, especially in those with severe hypoxaemia.

For most patients, lung disease is the major health problem in terms of symptoms and treatment required and because it is the most likely cause of morbidity and death.

Management of lung disease

Nowadays, most CF patients in Europe receive care on a regular basis every 1–3 months, coordinated by a team of trained and experienced health professionals in a tertiary centre. CF centre care is essential for optimal patient management and outcome. A CF team is usually led by a respiratory physician and includes many other specialists (specialised CF nurse, gastroenterologist, microbiologist, respiratory therapist, dietician, social worker, psychologist). For patients living a long distance from a CF centre, formalised "assisted" care with local clinics can be considered, but only when the quality of the assisting team is up to standard.

During follow-up outpatient visits, an interval history should always be taken, and a physical examination performed. A sputum sample should be obtained for microbiological analysis. If the child is unable to expectorate spontaneously, sputum induction should be performed with inhalation of hypertonic saline. If sputum cannot be obtained, a lower pharyngeal swab should be taken during or after a forced cough. Pulmonary function tests including indices of ventilation inhomogeneity should be performed at regular intervals to monitor lung disease progression. Chest radiographs, thoracic CT scans or lung MRI are usually included as part of the annual review. Apart from the annual review, imaging of the lung should be considered when atelectasis or a pneumothorax is considered. In some centres, yearly bronchoscopy with BAL is performed for microbiological surveillance in young children unable to expectorate; however, to date, it is unclear whether this approach results in better outcomes.

Current management of CF is predominantly symptomatic. The cornerstones of CF respiratory care are clearance of lower-airway secretions and treatment of pulmonary infections. Annual influenza vaccination is recommended. The goal of therapy is to maintain a stable condition and to prevent any irreversible structural lung changes. Much of the clinical practice has evolved over decades without being subjected to high quality randomised controlled trials, especially in children <6 years of age.

Knowledge of the basic CF defect has led to the development of new therapeutics aimed at potentiating or even correcting defective CFTR channel function, which also improves lung function. The first such CFTR modulators (Ivacaftor, Lumacaftor/Ivacaftor, Tezacaftor/Ivacaftor) have been licensed in the USA and Europe in the past decade, but due to their high costs they are not available in every country. Recently, triple modulator therapy was shown to improve clinical outcomes in patients carrying the most frequent CFTR mutation Phe508del. Personalised therapy for CF reached an important milestone with the discovery and development of these compounds, which have the potential to dramatically improve health and survival of individuals with CF and to revolutionise CF care.

Treatment modalities

Treatment aims and modalities for CF lung disease vary according to the disease stage (table 1).

Early disease stages

To date, there have been very few controlled trials on chronic pulmonary therapies in young children with CF. This is, in part, because appropriate end-points are difficult to identify, but also because federal regulations make inclusion of young children in research studies complicated. Therefore, current recommendations for therapies in preschool age children are mainly based on studies in older children. Studies including very young patients must be designed and undertaken, because it is likely that early therapy, before lung disease is established, will provide the most significant and long-term benefits for children with CF.

Preventive therapy with chest physical therapy is recommended. The goal of physiotherapy is to clear secretions from the airways. There are many techniques available to augment clearance of tenacious airway secretions. These include postural drainage, vibration and percussion, airway-oscillating devices, positive expiratory pressure (PEP) devices, active cycles of breathing techniques and autogenic drainage (a series of respiratory huffs and coughs designed to move mucus from distal to proximal airways so it can be coughed out). Close supervision by an experienced physiotherapist and continuity of care is essential. There is a divergence of opinion about specific aspects of therapy, but the consensus is that this form of therapy is highly effective in older subjects, as it favours clearance of secretions that accumulate in the small airways, even before the onset of symptoms. Its role is far less clear in younger children diagnosed through newborn screening, and some forms of physical therapy might even be detrimental (*e.g.* by inducing GOR).

Hypertonic saline acts as a hyperosmolar agent and presumably rehydrates the airway surface liquid layer, thus improving mucociliary clearance. It is delivered using a small compressor that drives a hand-held nebuliser. It has been shown to be effective children as well as in infants. Saline at a concentration of 6–7% is usually applied. Whether lower strength saline (3% or even 0.9%) is also efficacious has not yet been systematically studied. In general, hypertonic saline is well tolerated. In patients with reactive airways, salbutamol or other bronchodilators can be added. In the light of the current knowledge about the pathophysiology of the disease, starting inhalation with hypertonic saline early seems reasonable. Mannitol is another hydrator therapy, which is available as a dry powder formulation thereby reducing treatment time, and can be used in older children.

The only efficacious mucus degrading agent in CF is rhDNase (recombinant human deoxyribonuclease, dornase alfa). Studies have demonstrated improvements in lung function and a reduction in pulmonary exacerbations regardless of disease severity. Other mucolytics, such as guaifenesin or *N*-acetylcysteine, have not been proven to be effective.

Early antibiotic treatment of typical CF pathogens is recommended. Antibiotics are the mainstay of therapy against pulmonary infection. Their goal is to control progression of lung infection and to delay progressive lung damage. Antibiotic treatment varies from intermittent short courses of oral antibiotics to continuous treatment with one or more oral or inhaled antibiotics. Dosages of oral antibiotics for CF patients are often two to three times the amount recommended for minor infections in order to achieve effective drug levels in sticky respiratory tract secretions, and because CF patients have proportionately more lean body mass and higher clearance rates for many antibiotics than do other individuals. Whenever possible, *in vitro* sensitivity testing should be performed to guide the choice of antibiotics, although it does not always reflect bacterial susceptibility to antimicrobial agents *in vivo*.

Infection with *S. aureus* and *H. influenzae* is usually treated with oral antibiotics, but despite this, chronic infection persists in many patients. Anti-staphylococcal prophylaxis with oral antibiotics is performed in some countries, but this approach is subject to debate.

P. aeruginosa initially grows in a non-mucoid form that can be eradicated by aggressive antibiotic treatment. Over time, it builds colonies that synthesise an alginate coat and forms biofilms, which are difficult, if not impossible, to clear with antibiotic treatment. Patients infected with *P. aeruginosa* have more rapid lung function decline and diminished survival compared with non-infected subjects. Therefore, heightened surveillance and aggressive treatment of *P. aeruginosa* is warranted.

First infection with *P. aeruginosa* is always treated with antibiotics with the goal of eradication. Treatment with 1 month of tobramycin nebulisation is currently the first line of treatment, and eradication can be achieved in most cases. Other treatment protocols have been shown to be of similar effectiveness and include oral, inhaled and intravenous antibiotics. In cases of eradication failure, repeating antibiotic eradication treatment is recommended.

Intermediate disease stages

In school-aged children, treatment with inhaled hypertonic saline, rhDNase and intensive airway clearance is recommended. Exercise is beneficial for CF patients, as it improves sense of wellbeing and quality of life and might stabilise lung function to some degree. However, exercise alone should not be used as an alternative to airway clearance.

Continuous oral azithromycin treatment, which has both antibacterial and anti-inflammatory effects, is often added to improve lung function and to reduce exacerbations. Oral high-dose ibuprofen has been shown to slow disease progression, but its use is hampered by the necessity of monitoring serum concentrations and unfavourable side-effects. Systemic corticosteroids are useful for the treatment of ABPA, but side-effects (growth retardation, cataracts, abnormalities of glucose tolerance) have limited their use as a standard therapy. Inhaled corticosteroids show no significant benefits in CF lung disease, unless the patient has concomitant asthma.

For CF patients with chronic *P. aeruginosa* infection, long-term treatment with inhaled antibiotics (*e.g.* tobramycin, colistin or aztreonam) is recommended, with the goal of reducing the frequency of pulmonary exacerbations and slowing the disease progression.

Intravenous antibiotics are indicated for patients who have progressive or unrelenting symptoms (pulmonary exacerbation) or a decline in lung function despite intensive home therapy. Intravenous antibiotic therapy is usually initiated in the hospital but is often completed on an ambulatory basis. The usual duration of intravenous antibiotic therapy is 14 days, but this can be extended to several weeks. In general, a combination therapy is applied. Since most patients with pulmonary exacerbations have *P. aeruginosa* in their airways, the usual in-hospital treatment is a combination of a β-lactam/cephalosporin and an aminoglycoside. *In vitro* antibiotic sensitivity tests unfortunately do not predict clinical outcome in patients with chronic infection and routine testing of the susceptibility of bacteria to combinations of antibiotics (synergy testing) is not recommended. In some centres, intravenous antibiotics are given on a routine basis independent of pulmonary exacerbations.

Late disease stages

Low-flow oxygen therapy and noninvasive ventilatory assistance at home, especially with sleep, physiotherapy and exercise, is applied in cases of chronic respiratory failure. Lung transplantation is the final therapeutic option for patients with end-stage lung disease. Transplantation has the potential to extend and substantially improve quality of life in properly selected patients. How to select patients (especially children) in an optimal way for this high-risk procedure is still the subject to debate (see chapter "Lung transplantation and management after transplantation").

Respiratory treatments represent the greatest challenge to patients and their families; proper physiotherapy and inhaling hypertonic saline, rhDNase and/or antibiotics is very time consuming and takes 1–2 h per day during periods of good health and much longer during a respiratory exacerbation.

Further reading

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Extrapulmonary manifestations of CF

Vanessa Stadlbauer

Nutritional approach in patients with CF

Malnutrition is both a frequent feature and a comorbidity of CF. Maintaining adequate nutritional status in terms of lung health and survival is a cornerstone of the CF multidisciplinary approach. A normal nutritional status needs to be achieved. Consensus-based nutritional guidelines provide a valuable tool in daily care management. Neonatal screening programmes enabling very early care, prior to clinical pulmonary involvement, offer a unique opportunity for nutritional assessment at a crucial period of rapid growth.

Nutrition

Nutrition education and behavioural counselling for patients with CF and their families to achieve and maintain healthy feeding and eating behaviours and achieve and maintain adequate growth and weight is necessary.

Energy requirements vary depending on degree of malabsorption, lung function and degree of inflammation, and are between 100% and 200% of the healthy age-matched population. Therefore, energy intake must be individually adjusted to

Key points

- Nutritional status is strongly associated with pulmonary function and survival in CF. Thus, nutritional management should be started as soon as possible after diagnosis. Exocrine pancreatic insufficiency should be confirmed and pancreatic enzyme replacement therapy should be started as soon as possible, together with fat-soluble vitamins.
- The gastrointestinal tract is a major source of comorbidity in CF patients. Entities such as fibrosing colonopathy, appendiceal mucocoele, meconium ileus or distal intestinal obstruction syndrome are specific to CF. CF-related liver disease can lead to cirrhosis and portal hypertension.
- CF-related diabetes is common and treatment differs in some aspects from standard diabetes treatment. Hypoglycaemia needs to be avoided.
- Fertility issues need to be considered in male and female patients. Pregnancies are possible but carry a high risk of complications.

achieve normal growth and nutritional status while avoiding obesity. Breastfeeding is recommended since breastfed babies with CF have better lung function and fewer infections. Additional calories can be added to expressed breast milk and/or infant formula can be concentrated (1.2–1.5 cal·mL^{-1}) if weight gain is poor, rather than increasing milk volumes, due to the enhanced risk of GOR. There is no evidence to support the use of protein hydrolysate formulas apart from in infants undergoing small bowel resection for meconium ileus, with severe failure to thrive or with coexisting cows' milk protein intolerance. Solid food can gradually be introduced as in non-CF infants; parents should seek the dietician's advice on the most suitable foods and pancreatic enzyme dosage. Young children should later eat three regular meals and two snacks of high nutrient and calorie density.

Current consensus guidelines recommend that children with CF consume 35–40% of their caloric intake from fat, 20% from protein and 40–45% from carbohydrates. Sodium supplementation is recommended for all infants in hot climates, and in the case of fever or sporting activities. The need for sodium supplementation can be assessed by the urinary sodium:creatinine ratio and should be in the range of 17–52 mmol·mmol^{-1}. Sodium can be supplemented by sodium chloride capsules or vials, or by salty foods.

Adolescence is another crucial period with increased energy requirements related to rapid physical growth. Maintaining optimal nutritional status in adulthood is a challenge, as the prevalence of malnutrition increases with age-related CF complications. Patients' height and weight should be measured at each clinical visit and BMI calculated (percentile or z-score in children, absolute BMI in adults).

Patients who develop CF-related diabetes (CFRD) are encouraged to continue eating a diet rich in energy and fat. Carbohydrate intake may be individualised depending on glycaemic control. Artificial sweeteners should be avoided.

Pregnancy is possible in women with CF, but the risk of a negative impact on survival may increase with more severe disease. Additional recommended energy requirements for pregnancy vary from 200 to 300 kcal·day^{-1}. Nutritional status before and during pregnancy influences the evolution of pregnancy and newborn outcome. Breastfeeding increases nutritional demands on the lactating mother and may need to be discontinued in women with a marginal nutritional status or malnutrition.

Bone mineral density should be assessed starting at 8 years of age. A dietary review should be performed every 3–6 months. The use of oral nutritional supplements together with pancreatic enzyme replacement therapy (PERT) is recommended for treating children and adults who fail to achieve optimal growth rates and nutritional status with oral dietary intake and sufficient PERT. In children, behavioural interventions have been shown to improve nutritional outcome.

Nocturnal enteral feeding through a nasogastric tube or gastrostomy, according to the patient's preference, must be considered to provide long-term nutritional support in patients not gaining (children) or keeping (adults) weight. Enteral tube feeding should be evaluated when weight and length are <10th percentile (<2 years) or BMIp <10th percentile (2–18 years) or BMI <18.5 kg·m^{-2} in adults. Nocturnal enteral tube feeding should be considered also to optimise nutritional status to meet lung transplantation criteria since outcome after lung transplantation clearly correlates with BMI before transplantation. The majority of patients tolerate high-energy polymeric feed, but a semi-elemental feed may be beneficial in selected cases. All feeds need PERT. Patients may need up to 70% of their recommended dietary allowance by enteral feeding to

improve their weight and are encouraged to continue with a high-energy diet during the day. It is important to monitor for glucose intolerance and GOR symptoms.

Pancreatic enzyme replacement therapy

Exocrine pancreatic insufficiency (EPI) is present in 85–90% of patients. A faecal elastase-1 of <200 $\mu g \cdot g^{-1}$ is diagnostic of EPI. Initially pancreatic sufficient patients can develop EPI later, therefore annual reviews of pancreatic function are recommended in pancreatic sufficient CF patients. Once EPI is confirmed, PERT should start immediately. Currently available preparations are derived from porcine pancreas. Enteric-coated preparations dramatically decrease enzyme degradation by stomach acidity and improve the release of enzymes in the duodenum. PERT preparations from non-animal sources (vegetable enzymes, bacterial enzymes) are currently not sufficient for exclusive therapy.

For some patients with a poor response to PERT needing high doses, reduction of gastric acid production by H_2-receptor antagonists or proton pump inhibitors may be beneficial.

A daily dose of 10 000 IU lipase per kilogram per day or 4000 IU lipase per gram of fat of "standard" or "high–strength" enzyme preparations should not be exceeded due to the possibility of fibrosing colonopathy (a rare occurrence). Enzymes should be given with all fat-containing foods at the beginning and middle of the meal, with the dose gradually increased, starting with 2000 IU per gram of fat.

In infants, micro- or mini-microspheres can be mixed with a small amount of breast milk, formula or fruit puree. Microspheres should not be crushed, chewed or mixed with the meal.

There is insufficient evidence to establish a dose–response association between PERT and weight gain. Usually, adequacy of PERT is evaluated clinically by growth, weight, stool pattern and abdominal pain. In some cases, it may be helpful to assess the coefficient of fat absorption (3-day stool collection and diet intake). The first case reports suggest that early CFTR corrector/potentiator therapy may reverse EPI or stop progression.

Fat-soluble vitamin supplementation

Patients with EPI should be supplemented with fat-soluble vitamins (table 1) from the time of diagnosis and serum levels should be measured annually, with doses adjusted accordingly. Pancreatic-sufficient patients should also have their serum fat-soluble vitamin levels checked annually. To ensure satisfactory oral bioavailability, all fat-soluble vitamin (A, E, D and K) formulations need to be ingested concomitantly with pancreatic enzymes during the meal.

Vitamin A is stored in the liver. Plasma retinol measurements should be taken during clinical stability. β-carotene, a pro-vitamin A antioxidant, is subject to regulation in its conversion to vitamin A, potentially decreasing the risk of hypervitaminosis A.

Vitamin E represents an important, powerful antioxidant; however, high doses have been associated with higher cancer risk in healthy people. Vitamin E status can be evaluated by serum level concentration or serum concentration/lipid ratio.

Vitamin K deficiency is common in pancreatic-insufficient patients with additional risk factors: first year of life, frequent antibiotic use (reduced production of menaquinones by the modified gut microbiome), and cholestasis. Prothrombin time is monitored annually. Routine supplementation for all patients might be beneficial.

Table 1. Fat-soluble vitamin guidelines for CF patients with EPI

Vitamin	Supplementation	Serum reference values and monitoring frequency
Vitamin A	Amounts dependent on serum values, and supplement form Retinol (preformed): Start low Adapt rapidly to target normal serum reference range β-carotene (provitamin A): 1 mg·kg^{-1} per day (maximum 50 mg per day) for 12 weeks Follow with maintenance dose (maximum 10 mg per day)	Normal reference range provided by the laboratory processing the sample Monitor annually and 3–6 months after a dosage change; also test when pregnancy is considered
Vitamin D	Dependent on serum values, which vary with dietary intake and sun exposure Starting dose of D3 (cholecalciferol): Infants 400 IU per day (advance to upper limit of 1000 IU per day) All others 800 IU per day (advance to upper limit of 2000 for children age 1–10 years, and 4000 IU per day for older) Maintenance dose: adapt to annual serum values, preferably measured at the end of dark months	Serum 25-hydroxyvitamin D minimum 20 ng·mL^{-1} (50 nmol·L^{-1}) Monitor annually, and check 3–6 months after a dosage change
Vitamin E (tocopherols)	α-tocopherol dosing: 100–400 IU per day 50 IU per day for infants <12 months (1 mg=1.49 IU)	Plasma α-tocopherol: cholesterol ratio >5.4 mg·g^{-1} Monitor annually, and check 3–6 months after a dosage change
Vitamin K	Vitamin K_1: Infants: 0.3–1.0 mg per day Older children and adults: 1–10 mg per day	Routine biochemical measurement not widely available, serum prothrombin time

Reproduced and modified from Turck *et al*. (2016) with permission. To convert between weight and international units, online calculators can be used.

Low plasma 25-hydroxyvitamin D levels have often been reported and suboptimal status after adjusting for season remains common. Cholecalciferol (vitamin D_3) supplementation is more effective than ergocalciferol (vitamin D_2).

Recent improvement in our knowledge of the different roles of fat-soluble vitamins emphasises the need for optimal supplementation. Water-miscible multivitamin formulations with satisfactory bioavailability profiles have been developed. Quality of evidence for the dosing of vitamin substitution is still low, as shown by several Cochrane reviews.

Other micronutrients

Daily calcium intake should meet normal dietary reference values for healthy people of the same age. In cases of iron deficiency, the first measure is to resolve underlying inflammation; then only if deficiency persists, iron should be supplemented. Zinc supplementation is suggested in CF patients at risk of zinc insufficiency (*e.g.* growth retardation, increased susceptibility to infections, delayed sexual maturation, eye problems and anorexia). Supplementing glutathione or selenium is not recommended due to lack of sufficient data.

Gastrointestinal complications in CF

Digestion, absorption and motility

In CF, digestion, absorption and motility are impaired. Maldigestion and malabsorption are secondary, and the main cause is abnormal pancreatic function with reduced bicarbonate secretion (thus impairing pancreatic enzyme lipase activity and precipitating bile acids, inhibiting lipid emulsification) and a dramatic decrease in enzyme secretion. Other luminal factors are excessive mucus production with abnormal composition, impaired gut motility, small intestine bacterial overgrowth, dysbiosis of the colonic microbiome, chronic gut inflammation (as evidenced by elevated calprotectin levels) and gut lumen dehydration closely related to a CFTR basic ion transport defect (*i.e.* decreased chloride secretion, and enhanced sodium and water absorption from the lumen).

Pancreatic exocrine and extrahepatic biliary complications

Pancreatitis occurs in up to 20% of pancreatic-sufficient patients carrying at least one mild *CFTR* mutation (class IV or V). It is more common in adolescents and adults. Patients are at risk of recurrent acute or chronic pancreatitis. Progression to EPI with acinar destruction, which may take years, contributes to the resolution of the pancreatitis. Possible triggering factors include alcohol, gallstones, abnormalities of the pancreaticobiliary junction, dehydration, modifier genes and specific non-*CFTR* mutations. The typical presentation includes recurrent acute abdominal pain, vomiting, increased lipase levels, and pancreatic ultrasonography or CT abnormalities. Lipase levels may also be normal or only slightly elevated. Management consists of pain relief, a short period of fasting (only when food is not tolerated), intravascular hydration, and progressive diet reintroduction (initially of a low-fat diet) as in non-CF pancreatitis. Because pancreatitis may be a presenting feature of CF or CFTR-related disorder, sweat testing and *CFTR* genetic testing are recommended in pancreatitis of unknown cause.

Extrahepatic biliary manifestation with undetectable gallbladder in CF fetuses is common. Later, gallstones with cholesterol or calcium bilirubinate are frequent and are a consequence of chronic bile salt loss and enhanced unconjugated bilirubin in the colon impairing colonic reabsorption. Medical treatment of gallstones with ursodeoxycholic acid (UDCA) is ineffective. In the case of complications (pain and jaundice), which occur in 4–10% of patients, surgery is required.

Gut manifestations

Gastro-oesophageal reflux

GOR is very frequent in CF, even in infants. Several factors have been suggested to play a role in the pathophysiology including altered gastric emptying, low basal lower oesophageal sphincter pressure, hiatal hernia, altered peristalsis, diet and lifestyle

factors. Symptoms are heartburn (pyrosis), nocturnal cough, vomiting, abdominal epigastric pain, dysphagia and unexplained pulmonary deterioration, but GOR may also remain asymptomatic. GOR may negatively affect both respiratory function and nutritional status. Diagnostic work-up includes upper endoscopy, a 24-h ambulatory oesophageal pH probe, oesophageal manometry and imaging studies. Standard management combines thickening food in infants, raising the head of the bed and acid suppression with H_2-blockers or proton pump inhibitors. Prokinetic drugs are no longer available in many countries. For patients who fail to respond, a surgical fundoplication can be discussed and may slow pulmonary decline, reduce the number of exacerbations and improve weight gain. Potential negative effects of long-term proton pump inhibitor use need to be weighed against the surgical risk.

Meconium ileus, meconium plug syndrome and DIOS

Meconium ileus is the earliest CF clinical manifestation occurring in up to 20% of newborn babies with CF. Diagnosis can be made through ultrasonography *in utero* during the second trimester revealing polyhydramnios with a dilated, hyperechogenic fetal bowel. Meconium ileus is not exclusive to CF patients (although the majority have CF) and thus diagnostic tests should be performed as soon as possible to confirm or refute CF diagnosis. Diagnostic prenatal work-up includes ultrasound follow-up, genetic testing of the carrier state of the parents, genetic counselling and delivery in a tertiary care centre. The clinical presentation of meconium ileus consists of distension, bilious vomiting and failure to pass the meconium within 48 h of birth. Radiography identifies abdominal distension and dilated loops. Barium enema shows a microcolon with a "soap bubble" aspect in the right iliac fossa corresponding to meconium pellets in the distal ileum. Uncomplicated meconium ileus is managed with intravenous hydration and enema with diluted Gastrografin, a hyperosmolar, water-soluble, radio-opaque meglumine diatrizoate solution containing 0.1% polysorbate 80 (Tween 80), slowly infused at low pressure under fluoroscopy control to relieve obstruction (use around 10 $mL \cdot kg^{-1}$). Enema can be repeated and the success rate is ~40%. In case of failure, surgery is required. Complicated meconium ileus (40% of cases) with peritonitis, volvulus and intestinal atresia requires immediate surgery. Depending on the severity of the newborn's clinical condition, different surgical approaches can be considered: enterostomy irrigating the distal bowel through the stoma, resection of the compromised bowel with complete proximal and distal meconium evacuation, and either a primary anastomosis or a temporary enterostomy. Post-operative care and nutritional support by a gastroenterology team is part of meconium ileus management. With early detection, appropriate therapy and nutritional support, death is now uncommon, and long-term nutritional and pulmonary outcomes are equivalent to those of other CF patients.

Meconium plug syndrome consists of abnormal meconium accumulation located in the colon that produces mild abdominal distension and failure to pass meconium. Management relies on contrast enema. ~25% of patients present underlying CF.

Distal intestinal obstruction syndrome (DIOS) is specific to CF and is a common complication that affects ~20% of CF patients and has a recurrence rate of 50%. It is characterised by the accumulation of viscid faecal material in the terminal ileum and/or the right colon. Risk factors include a severe CF genotype, pancreatic insufficiency (but it may also occur in pancreatic-sufficient CF patients), dehydration, poorly controlled fat malabsorption and intestinal dysmotility. It is proposed that high faecal fat increases stool viscosity and activates the ileal brake leading to inspissation

of luminal contents. DIOS typically has an acute onset of colicky abdominal pain and vomiting.

Complete DIOS is defined as the combination of:

- Complete intestinal obstruction with bilious vomiting or fluid levels on radiography
- A faecal mass in the right iliac fossa
- Abdominal pain and/or distension

Incomplete DIOS gathers the latter two symptoms. Other causes of abdominal pain (appendicitis, intussusception, volvulus adhesions, *etc.*) have to be ruled out by imaging.

Complete DIOS with moderate obstruction can be treated with polyethylene glycol (PEG) lavage; in the case of more severe presentation with bilious vomiting, hospitalisation with fasting, intravascular hydration and diluted sodium meglumine diatrizoate (Gastrografin) enema under direct vision until the terminal ileum is reached may achieve resolution of obstruction. Close monitoring of the patient is recommended because Gastrografin enema may cause major ion and water shifts. In the case of failure, because surgery is a high-risk intervention, a colonoscopy with local instillation of Gastrografin in the caecum and ileum lavage may be an alternative. If it fails an attempt of washout, enterostomy may be tried before considering resection of the ileocaecum. Patients presenting with incomplete DIOS usually respond to oral rehydration combined with osmotic laxative lavage containing PEG or oral intake of Gastrografin. Maintenance therapy with oral PEG and close monitoring of frequency and completeness of bowel movements can decrease the risk of recurrence of DIOS episodes in up to 50%. Bowel preparation before surgery (transplantation) has been suggested to prevent DIOS post-operatively.

Other gut manifestations

Fibrosing colonopathy with submucosal fibrosis in the colon, but an intact epithelium border was associated with excessive PERT supplementation (>50 000 IU lipase per kg per day). Thus, guidelines agreed to recommend restrictions on PERT doses to ≤10 000 IU·kg^{-1} per day; since then, cases have virtually disappeared. However, cases of fibrosing colonopathy without PERT have been described, therefore the causal relationship is still under question.

Acute appendicitis is less common in CF patients (1.5–5% compared with 7% in healthy peers), but if present, it is associated with a high rate of perforation and abscesses related to subacute presentation and delayed diagnosis probably as a consequence of frequent antibiotic prescriptions for pulmonary exacerbations. Appendiceal mucocoele is a mucoid distension of the appendix that can remain asymptomatic or cause chronic pain or mimic appendicitis. It can occur at all ages. Clinical examination of the right iliac fossa identifies a small ovoid mass. Ultrasonography focusing in the right iliac fossa shows a multilayer mass with an enlarged appendix (>6 mm) filled with echogenic material. To rule out other aetiologies, CT is indicated. In the case of symptoms, appendectomy with resection of the appendix edges and resection of the caecal tip will avoid the risk of recurrence. At histology the appendix is distended with inspissated mucus.

Intestinal intussusception occurs in 1%, mainly in children and adolescents. It is usually ileocolic, but can also be ileoileal; it may resolve spontaneously. It is a consequence of dehydrated mucus and impaired intestinal motility, but frequently

a trigger can be identified, such as inspissated secretions, lymphoid follicles, the appendix or polyps (with a malignancy risk in adults). Clinical presentation combines severe colicky abdominal pain, vomiting, bloody stools and a palpable mass in the right iliac fossa. Abdominal radiography may show obstruction, ultrasonography may reveal the characteristic "bull's eye" and abdominal CT can confirm the diagnosis if there is a doubt concerning the differential diagnosis. Treatment with enemas is the first choice unless complicated (perforation). If it fails or is complicated, immediate surgery is required.

Rectal prolapse occurs mainly at preschool age and usually resolves after adjustment of PERT, an adequate-fibre diet, stool softeners and advice concerning voiding. Rectal prolapse may be also be a presenting feature of CF.

The risk of intestinal malignancies at sites where CFTR is expressed is higher in CF. Although malignancy risk peaks after the third decade of life, CF patients age 20–29 years have a 23-fold increased risk of digestive tract malignancy. Additionally, those with CF who have undergone lung transplant have a markedly higher risk of colon cancer than other pulmonary transplant recipients. Surveillance colonoscopy should be performed, starting at age 40 years.

Comorbid gastrointestinal conditions

Milk protein intolerance occurs more often in CF than in the general population. Infants present nonspecific symptoms such as diarrhoea, constipation, vomiting, failure to thrive and eczema. Abnormal biological tests, including IgE levels, specific antibodies and prick tests, are helpful for indicating a semi-elemental diet.

Coeliac disease has a prevalence of 1.2% in CF, which is higher than in the general population. It should be considered in any CF patient presenting with chronic diarrhoea or abdominal pain despite adequate PERT replacement. The presence of anti-endomysium and anti-transglutaminase antibodies has good sensitivity, but a duodenal biopsy is required to confirm diagnosis and start the patient on a lifelong, strict gluten-free diet.

Crohn's disease has been reported in CF. Symptoms are difficult to differentiate from symptoms of CF, including diarrhoea, abdominal pain, weight loss and inflammatory parameters. A colonoscopy with multiple biopsies is essential to confirm diagnosis.

CF-related liver disease

CF-related liver disease (CFLD) accounts for ~2.5% of overall mortality in CF. 27–35% of patients will develop some sort of liver involvement, while ~5–10% will develop liver cirrhosis with portal hypertension. In patients developing severe liver disease, liver involvement commonly starts during the first decade of life and develops to cirrhosis with portal hypertension during the second decade of life. Therapy of portal hypertension is similar to non-CF portal hypertension, *i.e.* with nonselective β-blockers, endoscopic treatment of varices, transjugular portosystemic intrahepatic shunt or ultimately liver transplantation.

Pathophysiology

CFTR is expressed on the apical surface of the cholangiocytes, and the current belief is that missing CFTR results in obstruction of the small intrahepatic bile ducts and retention of toxic substances, leading to the most common histological feature in CFLD, focal biliary cirrhosis. The reason for its focality is unknown. The focal biliary

cirrhosis slowly develops into multilobular cirrhosis without any symptoms. Patients with two severe mutations (class I–III) and pancreatic insufficiency and the presence of modifying non-CFTR gene mutations, such as SERPINA1 Z allele, are at highest risk to develop cirrhosis.

Other liver involvement

Neonatal hyperbilirubinaemia can be associated with CF, but normally resolves spontaneously. Liver enzymes are often raised during the first year after diagnosis and not related to later severe liver disease. Up to 75% of patients with CF have steatosis of differing degrees, most probably related to nutritional deficiencies. Massive steatosis in the early years has become less common, probably due to improved care and nutrition. Currently, steatosis in CF is considered a benign condition not related to the development of cirrhosis.

Screening for liver disease

Since the development of cirrhosis with or without portal hypertension is usually asymptomatic, screening for CFLD is necessary. At the annual review, alanine transaminase (ALT), aspartate transaminase (AST), serum alkaline phosphatase, γ-glutamyl transpeptidase (GGT), albumin, bilirubin and prothrombin time should be measured, and a thorough physical examination must be included. Yearly ultrasound of the liver and the biliary tract are recommended. The presence of CFLD should be suspected when the liver enzymes (ALT, AST and GGT) are raised more than twice over a 12-month period after excluding other causes of liver disease, and ultrasonography shows hepatomegaly/splenomegaly, increased/irregular echogenicity or irregular margins. Transient elastography measurement may be useful in the detection of CFLD; however, optimal cut-offs need to be established and validated. When leukopenia, thrombocytopenia or splenomegaly develops, portal hypertension is suspected and a gastroscopy has to be performed to detect or exclude oesophageal varices. It is important to emphasise that not all patients developing CFLD display pathologically increased liver enzymes and ultrasonography may be more sensitive than clinical or biochemical abnormalities. In some situations, liver biopsy can be indicated.

Treatment

Liver disease in CF develops slowly, and may remain stable for years and possibly decades. In many cases, liver transplantation is not needed. Based on the hypothesis that the starting event in CFLD is bile duct obstruction, UDCA, a bile acid that has hydrophilic and choleretic properties and may act as a cytoprotective agent, is used for treatment of CFLD, mostly in Europe. Although evidence of an effect on the level of liver enzymes, biliary drainage, ultrasound changes and possibly liver histology exists, data on halting the progression of CFLD are scarce. It has been suggested that patients would gain from early treatment when there are less severe pathological changes, although there is no evidence to support this. The recommended starting dose is 15–20 $mg \cdot kg^{-1}$ per day. Common recommendations include avoidance of hepatotoxic drugs, vaccination against hepatitis A and B, and special attention to nutritional status to ensure adequate caloric intake (increase energy intake, and enteral nasogastric feeding when awaiting a liver transplant). CFTR modulators may lead to elevation of liver enzymes, therefore liver enzymes need to be monitored during therapy and treatment should be interrupted when values rise >5 times the upper limit of normal.

All patients with signs of CFLD should be evaluated by a paediatric gastroenterologist with knowledge of liver disease in CF.

CF-related diabetes

CFRD is the most frequent comorbidity in CF. Starting with a prevalence of <3% at the age of 10 years, the prevalence increases and peaks at 25–30% at age 35–40 years. CFRD mimics some aspects of type 1 and other aspects of type 2 diabetes: it is an insulin-deficient status but with some (often unpredictable) remaining insulin secretion. CFRD is associated with a faster decrease in lung function, weight loss and reduced survival compared with age- and sex-matched nondiabetic CF patients. It is difficult to diagnose CFRD at an early stage because typical clinical symptoms are often absent. There is no simple laboratory test to screen for CFRD. Glycated haemoglobin (HbA1c), as a single laboratory marker, will miss ~30% of all CF patients with CFRD. The oral glucose tolerance test (OGTT) is the "gold standard" for diagnosing CFRD. Some specialised centres use continuous glucose monitoring, a more sophisticated method for early identification of CF patients with CFRD. Annual OGTTs starting at the age of 10 years are a recommended screening procedure for CFRD. Screening for CFRD is especially important for patients who are on nocturnal feeding, pregnant, experiencing a severe acute exacerbation or on systemic steroids.

It is well accepted to start treatment of CFRD independent of fasting hyperglycaemia. Insulin treatment has positive clinical effects with an increase in lung function and nutrition and decreasing risk of exacerbation. The recommendation is initially single short-acting insulin doses with main meals and adding long-acting insulin as soon as fasting hyperglycaemia is observed. In general, nutritional advice differs significantly between diabetes treatment in general and in the case of CFRD. CF patients have to maintain a high caloric intake to prevent weight loss and management of CFRD must be individualised. Oral antidiabetic drugs have been used in the treatment of CFRD, and in 2018 a prospective randomised trial showed they were as effective as insulin in initial treatment (Ballmann *et al.*, 2018). The use of oral antidiabetic drugs is therefore not recommended outside clinical trials. CFTR correctors/potentiators may improve CFRD and glycaemic control. Late complications of CFRD are well described for microvascular (retinopathy, neuropathy and nephropathy) but not for macrovascular diseases. CF patients on insulin should participate in CFRD education programmes and follow their treatment like other diabetic patients, including self-managed glucose measurements, blood pressure control and 3-monthly HbA1c measurements. The aim is HbA1c <7% and no hyper- or hypoglycaemic situations. The risk of hypoglycaemia is real and must be addressed with education of the patient and monitoring of blood glucose levels. Since ketoacidosis is untypical in CFRD, in these rare cases, type 1 diabetes must be excluded. In CF centres, treatment of CFRD is by a team approach including pulmonologists, diabetologists, dieticians and psychologists.

Sinus disease in CF

Sinus abnormalities are prevalent in CF and chronic rhinosinusitis has been shown in up to 74–100% of the patients, increasing with age, but is not always symptomatic. The pathophysiology is unclear, but is believed to be a combination of increased viscosity of mucus, decreased clearance and chronic infection. Problems from the upper airways should be handled in close cooperation with an otolaryngologist with experience of CF sinus disease.

Common radiological findings are frontal sinus agenesis/hypoplasia and opacification of the maxilla ethmoid sinus. There is no or only low correlation of CT findings with symptoms. Nasal polyps are common from childhood, increasing with age. Symptoms of the upper airways, like nasal obstruction, chronic or recurrent headache due to

sinusitis and anosmia/hyposmia, are frequently found when the patient is asked, and it is important to include these symptoms in the annual assessment.

Medical management includes nasal steroids, saline irrigation and antibiotics (adapted to local sampling). The type of bacterial colonisation of the upper airways may differ from the colonisation of the lower airways. Up to 25% of CF patients have to undergo sinus surgery, where endoscopic sinus surgery has been more successful than polypectomy alone or Caldwell Luc procedures (Haworth, 2010).

CF-associated osteoporosis

Osteoporosis is a common medical problem in adults with CF. Although osteoporosis is seldom symptomatic in the paediatric age group, osteopenia/osteoporosis starts during childhood/adolescence. It is therefore of vital importance that this problem is addressed during these age periods, with special attention to the risk factors mentioned below, to be able to decrease the prevalence of osteopenia/osteoporosis in adults.

The pathogenesis is a combination of factors: malnutrition/malabsorption, delayed puberty and hypogonadism, vitamin D and K deficiency, systemic inflammation due to pulmonary infections, use of oral corticosteroids, low activity levels, and possibly a direct effect of CFTR dysfunction on bone cells.

Assessment of bone mineral density using dual-energy X-ray absorptiometry (DXA) should be performed in all patients, starting at age 8–10 years, every 1–5 years depending on the age of the patient, result of the previous scan and presence of risk factors. Preventive measures rely on normal nutritional status, weight-bearing exercise, supplementation with cholecalciferol to achieve optimal plasma 25-hydroxyvitamin D levels, high dietary intake of calcium depending on age and possibly supplementation with vitamin K_1.

Fertility in CF

As the life expectancy of CF patients continues to increase, and more patients become adults with a chronic disease, the impact of male and female fertility gains importance. Most men with CF have significant anatomical abnormalities of the reproductive tract causing infertility. However, most women with CF have anatomically normal reproductive tracts and many of them may be able to conceive spontaneously, although infertility and subfertility rates are higher than in the non-CF population. Male infertility in CF is, in most cases, caused by obstructive azoospermia because of a congenital bilateral absence of the vas deferens. In addition, sperm motility and capacitation can be impaired and other genital abnormalities have been described. Fertility problems in female CF patients are multifactorial: impaired transport of sperm through the female reproductive tract due to thick secretions has been thought to play a major role, but the underlying disease severity, especially impaired lung function, malnutrition leading to hypothalamic suppression and poorly controlled CFRD seem to have a larger impact on fertility. Assisted reproductive technologies are important to help both infertile male and female patients with CF to achieve successful parenthood; therefore, counselling by a reproduction medicine specialist should be offered. Physiological changes during pregnancy can increase the risk for pulmonary exacerbations, therefore, close multidisciplinary monitoring is necessary. The risk for congenital anomalies of the fetus is not increased and breastfeeding is possible without complications.

Regarding contraception, progestin-only methods, as well as non-hormonal methods carry no additional risks in the setting of CF. Oestrogen-containing contraception is not

recommended due to potential side-effects, such as higher risk for venous thrombosis. Drug interactions need to be considered, especially with immunosuppression. CFTR modulator therapy decreases contraceptive effectiveness and increases the incidence of menstrual adverse reactions. Data on benefits and risks of CFTR modulator therapy during pregnancy and lactation are still scarce and should be assessed with each woman individually.

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Microbiology, cross-infection and hygiene in CF

Michael Hogardt and Silke Besier

Although CF is a multisystem disease, most of the morbidity and mortality among people with CF is due to lung disease resulting from chronic respiratory infections. The underlying defect of CFTR and resulting dysregulation of epithelial electrolyte transport leads to depletion of airway surface liquid (ASL), the formation of a thick and highly viscous mucus, impaired mucociliary clearance and bronchial mucus plugging. This environment creates an ideal niche for bacterial colonisation, growth and persistence. The airways of people with CF usually become infected during infancy, often by *Staphylococcus aureus* and/or *Haemophilus influenzae*. Advancing CF airway disease involves a complex polymicrobial spectrum with *Pseudomonas aeruginosa* being the leading pathogen. Finally, recurrent episodes of acute and chronic pulmonary infection with a broad spectrum of respiratory pathogens involving bacteria, viruses and fungi result in inflammation, repeated pulmonary exacerbations, progressive airway damage, lung function decline, and premature death.

Microbial pathogens of CF lung infection

In general, there is an age-dependent bacterial infection pattern of the CF airways. *S. aureus* and *H. influenzae* are the most frequently isolated bacterial pathogens in

Key points

- People with CF die prematurely primarily as a result of chronic lung infection. Key pathogens are (mucoid) *P. aeruginosa*, *S. aureus* and *B. cepacia* complex.
- Chronic CF lung infection is polymicrobial and comprises various micro-organisms (*e.g. Achromobacter* spp., *S. maltophilia*, nontuberculous mycobacteria) and fungi as well as typical commensals of the upper respiratory tract such as anaerobes.
- *B. cenocepacia*, a species within the *B. cepacia* complex, is associated with higher mortality and is a contraindication for lung transplantation. Chronic methicillin-resistant *S. aureus* lung infection and infection with *M. abscessus* are associated with worse outcomes.
- Hygiene measures are an integral part of CF care, since several CF-specific pathogens may be acquired from environmental sources and/or by interperson transmission.

infancy. Colonisation with *H. influenzae* (typically unencapsulated strains) is found in ~20% of children with CF. Although this micro-organism can cause acute respiratory infections, there is still no evidence that *H. influenzae* influences the prognosis of CF lung disease. In contrast, the prevalence of *P. aeruginosa* infection in CF increases as individuals age. Once established, *P. aeruginosa* persists in the CF airways and causes chronic infection that results in progressive deterioration of lung function. Thus, *P. aeruginosa* is the leading pathogen in CF. Early eradication strategies for initial infections have effectively postponed the onset of chronic *P. aeruginosa* infection. In European countries, chronic respiratory infection with *P. aeruginosa* in children is found on average in about 20% (range 7–49%). In addition, several other Gram-negative and typically environmental bacteria, most often *Achromobacter* spp., *Burkholderia cepacia* complex (BCC), *Stenotrophomonas maltophilia*, and occasionally *Inquilinus limosus* (always mucoid) and *Pandoraea* spp. (related to *Burkholderia* spp.), as well as nontuberculous mycobacteria (NTM), and fungi may be recovered from CF respiratory secretions. Many of these micro-organisms are difficult to eliminate and may cause chronic lung persistence. Respiratory viruses are frequently detected in cases of acute exacerbations.

Of note, in children with CF, *S. aureus* and *H. influenzae*, and with increasing age also *P. aeruginosa*, can be detected from paranasal sinuses. Sinus colonisation/infection is thought to be a potential (protected) reservoir for intermittent colonisation and/or recurrent lung infection, *e.g.* with *P. aeruginosa*.

In the past decade, non-culture-based molecular technologies have increasingly pointed to the polymicrobial nature of CF lung disease and identified thus far unrecognised micro-organisms as potential pathogens (*e.g.* the *Streptococcus anginosus* group and anaerobic bacteria). However, the role of these organisms in the progression of CF airway disease is still unclear. Microbiome analysis showed that microbial diversity within CF airways secretions declines with disease progression. Commensal and possibly protective microbes (*e.g.* some anaerobes) are increasingly displaced, until during end-stage disease *P. aeruginosa* dominates. Despite significant therapeutic advances and a remarkable increase in life expectancy, chronic lung infection remains the major cause of premature death of people with CF. Beside the typical epidemiological trends mentioned, data from CF registries (*e.g.* the European Cystic Fibrosis Society Patient Registry) show that prevalences of CF pathogens are variable from centre to centre and with country of origin.

Pseudomonas aeruginosa

P. aeruginosa is still the major bacterial pathogen of chronic infection and the major predictor of morbidity and mortality in CF. The majority of people with CF become chronically colonised with *P. aeruginosa* in early adulthood. During acute infection, *P. aeruginosa* can produce an array of tissue-damaging virulence factors including type III secretion toxins, haemolysins, proteases (*e.g.* elastase) and pyocyanin. It is suggested that chronic infection may be established when *P. aeruginosa* develops into mucoid (alginate-overproducing) and/or biofilm-growing phenotypes. Biofilms are microbial communities that show an increased tolerance to antibiotics and resist phagocytosis and other mechanisms of the innate and the adaptive immune system. During chronic infection, *P. aeruginosa* thrives within the heterogenous and microaerophilic CF lung environment and diversifies due to genomic mutations and rearrangements into phenotypically and genetically distinct variants that can coexist for years. Hallmarks of this pathoadaptive process of *P. aeruginosa* include reduced motility, increased biofilm formation, loss of virulence factors, occurrence

of hypermutable variants and the selection of small colony variants (SCVs). Repeated courses of antibiotic therapy result in the selection of multidrug-resistant *P. aeruginosa*.

People with CF with chronic *P. aeruginosa* infections have worse lung function and higher rates of lung function decline. Initial *P. aeruginosa* infection is thought to be transient and associated with non-mucoid and highly susceptible isolates (wildtype) that may be eradicated (window of opportunity). Early eradication antibiotic therapy may delay the onset of chronic infection and conversion to mucoid *P. aeruginosa*. Infection with mucoid strains has been associated with more severe lung disease. Once chronic infection has been established the anti-infective strategy shifts from eradication to long-term suppressive therapy, which aims to reduce bacterial burden, inflammatory lung tissue, damage and frequency of exacerbations. Currently, inhalation of anti-pseudomonal antibiotics (colistin, tobramycin, aztreonam or levofloxacin) is the cornerstone of suppressive therapy. Intravenous antibiotics courses of at least 2 weeks are typically administered for exacerbations.

Staphylococcus aureus

S. aureus is a frequent coloniser of the upper respiratory tract and a common cause of chronic CF lung infection that can result in increased lower airway inflammation, worsening of lung function and poor overall clinical outcome. In most countries, the peak prevalence of *S. aureus* (specifically methicillin-sensitive *S. aureus* (MSSA)) occurs during adolescence and declines in adults. Children under 6 years of age and with co-infection of *S. aureus* and *P. aeruginosa* show increased endobronchial inflammation and poorer clinical status. Especially in young children it is, therefore, widely accepted to treat early infection with *S. aureus*. By contrast, continuous anti-staphylococcal prophylaxis in children with intermittent colonisation is not endorsed by most countries (although colonisation rates are reduced), as a prognostic benefit is not proven and some studies reported an increased incidence of *P. aeruginosa*. However, in the UK, anti-staphylococcal antibiotic prophylaxis is recommended until the age of 3 years, whereas in the USA it is recommended against. Similarly, in cases of chronic *S. aureus* infection there is no definite agreement about the best treatment regime, except that *S. aureus*-positive respiratory tract cultures are treated in case of exacerbations.

European countries report prevalences for methicillin-resistant *S. aureus* (MRSA) between 3% and 13%. Chronic infection with MRSA is associated with an accelerated lung function decline, failure to recover to baseline after pulmonary exacerbation, and higher mortality. Eradication, although possible, is demanding, as is treatment of transient and chronic MRSA infection; to date, no standardised protocols for antibiotic therapy exist.

It is relevant to note that chronic infection and long-term antibiotic selection pressure lead to adaptation of *S. aureus*, including the emergence of *S. aureus* SCVs that are typically characterised by their slow growth and underlying auxotrophism (*e.g.* thymidine, menadione, haemin). Aminoglycoside therapy is associated with the emergence of menadione- or haemin-dependent SCVs, whereas sulfamethoxazole therapy selects for the emergence of thymidine-dependent SCVs, which occur most often in CF. All thymidine-dependent SCVs are resistant to co-trimoxazole. It has been hypothesised that SCVs persist intracellularly in eukaryotic cells, escape host defence and may be responsible for recurrent infections. *S. aureus* SCVs are independently associated with worse CF respiratory outcomes in children with CF.

Burkholderia cepacia complex

BCC infections present a significant challenge for people with CF. BCC lung infection is associated with increased inflammatory tissue damage, lower FEV_1 % predicted and a poor outcome. The BCC comprises over 20 *Burkholderia* spp.: *B. cepacia* (the type species), *B. multivorans*, *B. cenocepacia*, *B. stabilis*, *B. vietnamiensis*, *B. dolosa*, *B. ambifaria*, *B. anthina*, *B. pyrrocinia*, *B. ubonensis*, *B. arboris*, *B. seminalis*, *B. metallica*, *B. lata*, *B. diffusa*, *B. latens*, *B. contaminans*, *B. pseudomultivorans*, *B. stagnalis*, *B. territorii*, *B. catarinensis*, and *B. puraquae*. *Burkholderia* spp. are ubiquitously distributed in the environment, including in soil and the rhizosphere.

The relative frequency of *Burkholderia* spp. may vary considerably from centre to centre, but *B. multivorans* and *B. cenocepacia* are the predominant BCC species among people with CF. *B. cenocepacia* is associated with higher mortality and is historically linked to cases of overwhelming necrotising pneumonia known as "cepacia syndrome" and is a strong contraindication for lung transplantation. The incidence of BCC lung infection increases with the age and poorer lung function of people with CF. *B. dolosa* is found more rarely, but may also cause deterioration of lung function. There is no evidence of an effective eradication protocol for BCC or for the best treatment of chronic infection.

B. gladioli, a species that does not belong to the BCC, accounts for a significant proportion of *Burkholderia* infections in CF and may lead to poor outcomes after lung transplantation. Due to species-specific characteristics and for epidemiological purposes, accurate species identification of *Burkholderia* spp. is absolutely mandatory in CF.

Stenotrophomonas maltophilia

S. maltophilia is a ubiquitous environmental organism with several intrinsic antimicrobial resistances, particularly to aminoglycosides and carbapenems. It has been shown that recovery of *S. maltophilia* from CF sputum is not an independent risk factor for accelerated deterioration of lung function. However, some reports describe that: 1) chronic colonisation with *S. maltophilia* is associated with respiratory exacerbations; 2) some people with CF show elevated serum antibodies against *S. maltophilia* antigens; and 3) individual people with CF with *S. maltophilia* as the only cultured pathogen respond to targeted treatment. In summary, it remains uncertain whether *S. maltophilia* is solely a marker of more severe lung disease or a causative agent of infection, at least in a subset of people with CF.

Achromobacter spp.

Achromobacter spp. are ubiquitous environmental organisms that may also become opportunistic pathogens, for example in CF. *Achromobacter* spp. can be found in diverse, mainly aquatic environments, including hospitals. The prevalence of *Achromobacter* spp. is variable among different CF centres (range 3–30%) and increases with age and progressive lung disease. However, the clinical relevance of *Achromobacter* spp. in CF (represented by *A. xylosoxidans*, *A. denitrificans*, *A. ruhlandii* and others) remains unclear. *Achromobacter* spp. are often associated with pulmonary exacerbation and advanced lung disease, but frequently concomitantly isolated with *P. aeruginosa*, making interpretation of their pathogenicity difficult. A subset of people with CF may be infected with *A. xylosoxidans* without any lung function decline. Shared genotypes of *A. xylosoxidans* isolates among people with CF, epidemic strains and nosocomial

spread have been described, underlining the risk of person-to-person transmission. *Achromobacter* spp. are resistant against several commonly used antibiotics, resulting in restricted antibiotic treatment options.

Nontuberculous mycobacteria

NTM are ubiquitous environmental organisms. NTM have emerged as clinically important pathogens in individuals with CF. NTM can be isolated from the sputum of 10–20% of people with CF, with varying prevalences by age, CF centre and country. Recommendations for the screening, diagnosis and management of NTM were recently published. The clinical relevance of NTM detection from people with CF is variable. Some people with CF show progressive deterioration of lung function, known as NTM pulmonary disease (according to American Thoracic Society criteria), others are clinically stable. The NTM species most often found in people with CF are the slow growing *Mycobacterium avium* complex (MAC), including *M. avium*, *M. intracellulare* and *M. chimaera* and the rapid grower *M. abscessus* (comprising the subspecies *M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *bolletii* and *M. abscessus* subsp. *massiliense*). In many CF centres in Europe, *M. abscessus* has become the most common NTM species isolated from CF respiratory secretions. *M. abscessus* is intrinsically multidrug-resistant, can lead to an accelerated decline in lung function, needs prolonged antibiotic combination therapy (3–5 substances for a minimum of 12 months) and is a relative contraindication to lung transplantation in several centres. Early detection and effective treatment of NTM is crucial and probably may preserve lung function. Subspecies specification is of prognostic interest as treatment success is reached less often in case of *M. abscessus* subsp. *abscessus.* This presumably is related to a functional *erm41* gene (encoding methyltransferase) that results in inducible macrolide resistance, whereas *M. abscessus* subsp. *massiliense* is generally susceptible to macrolides.

Fungi

Progression of CF respiratory disease is also influenced by infection with fungal pathogens. Prevalence of fungi (yeasts and filamentous fungi) isolated from CF respiratory secretions has significantly increased in recent years. *Candida* spp. are the most prevalent fungi isolated from CF respiratory secretions (in about 48%) but are thought to be non-pathogenic. Increasing detection rates of *Candida* spp. are associated with lower FEV_1. In addition, *Aspergillus fumigatus*, the species of the *Scedosporium apiospermum* species complex, *Lomentospora prolificans*, *Rasamsonia* spp., *Trichosporon mycotoxinivorans* and *Exophialia dermatitidis* are of special relevance in case of CF (table 1). Except for *A. fumigatus*, the clinical significance of these species remains to be defined. Although these species are often associated with lung function decline, their detection may be only a marker of disease severity. Prevalences may be highly variable from centre to centre. Microbiological diagnosis is not standardised and depends on prolonged incubation periods. As minimal inhibitory concentration (MIC) values for antifungals may vary significantly within a species, testing of individual isolates is meaningful.

Aspergillus spp.

A. fumigatus is the most common filamentous fungal species cultured from CF sputum and can be responsible for colonisation, *Aspergillus* bronchitis and allergic bronchopulmonary aspergillosis (ABPA). Colonisation rates range between 10% and 30% of cases, and increase with age and progression of lung disease. Therefore,

Table 1. Characteristics of rare fungi that are typically recovered from CF airway secretions

Species	Characteristics	Clinical relevance	Antifungal options
E. dermatitidis	"Black yeast" (black pigment) Slow growing Thermotolerant (up to 45ºC) Environmental source	Unknown Prevalence of ~2% Opportunistic pathogen Colonisation Association with lower FEV_1/ exacerbation	Voriconazole Posaconazole Amphotericin B[§]
T. mycotoxinivorans	Yeast-like fungus	Unknown Prevalence of ~2% Opportunistic pathogen Severe (exacerbations)	Voriconazole Posaconazole
***S. apiospermum* species complex[#] and *L. prolificans*[¶]**	Filamentous fungus Greyish/black pigmentation Slow growing Environmental source *L. prolificans:* highly resistant	Unknown Prevalence of ~3% Opportunistic pathogens Colonisation Increasing respiratory signs Association with exacerbation/ severe deterioration after LTX *L. prolificans*: relative contraindication to LTX	Voriconazole Posaconazole *L. prolificans*: voriconazole/ terbinafine
***Rasamsonia argillacea* complex[+]**	Filamentous fungus Slow growing Highly thermotolerant Environmental source	Only occasionally detected Opportunistic pathogens	Caspofungin Amphotericin B[§]

[#]: *S. apiospermum*, *S. boydii* (formerly *Pseudoallescheria boydii)*, *S. aurantiacum*, *S. minutispora*; [¶]: formerly *Scedosporium prolificans*; [+]: formerly *Geosmithia* spp.; [§]: inhaled amphotericin B may be an alternative option for chronic infections. LTX: lung transplantation.

it is often not clear if the detection of *A. fumigatus* is of clinical relevance or only a marker of more severe lung disease. Treatment is recommended when criteria for ABPA (including elevated fungal specific IgG/IgE) are met. *Aspergillus* bronchitis is often associated with a high burden of *Aspergillus* in sputum. Affected individuals benefit clinically from antifungal therapy. Invasive fungal disease among people with CF, who are typically immunocompetent, is rare and may occur mainly after lung transplantation. Pre-transplantation, suppression of *Aspergillus* spp. with an azole is thus recommended by several centres. There is no evidence that treating *Aspergillus* colonisation in individuals without allergic symptoms is beneficial. Azole resistance of *A. fumigatus* is increasingly recognised, but is generally very low (below 1%).

Respiratory viruses

In children, respiratory viruses are recovered in about 60% of airway secretions during episodes of pulmonary exacerbation. Exacerbations due to respiratory viruses are linked to lung function decline, increased antibiotic use and higher risk of hospitalisations. The most commonly identified viral pathogens in people with CF are respiratory syncytial virus (RSV), human rhinovirus, influenza types A and B, parainfluenza, and adenovirus. RSV and influenza infections are associated with the greatest decreases in lung function. Viral infections may indirectly promote bacterial infection and persistence. Acquisition of *P. aeruginosa* in people with CF correlates with seasonal respiratory virus infections, and *P. aeruginosa*/viral co-infection is linked with more severe exacerbations and declines in lung function. People with CF with acute exacerbations due to respiratory viruses are less likely to recover to baseline FEV_1 and are more often hospitalised.

Microbiological diagnosis of CF respiratory samples

For the optimal clinical management of CF lung infections, regular microbiological diagnosis is essential. Children with CF often do not produce sputum; thus, oropharyngeal swabs are commonly used as a surrogate for lower airway infection. It is important to provoke children to cough to improve the recovery of lower respiratory organisms (cough swab). Several studies have compared the diagnostic accuracy of oropharyngeal swabs with the "gold standard" of BAL with variable performance data. A recent Cochrane review concluded that there is no clear benefit of routine BAL for the diagnosis of pulmonary infections in young children. Thus, the current practice is to primarily investigate oropharyngeal swabs that display the presence of lower airway pathogens with reliable sensitivity and specificity. Alternatively, induced sputum samples can be used, but specimens are not easily available in (young) children. No consensus statement exists for how to best implement sinonasal samples into the clinical care of children with CF.

Surveillance cultures (oropharyngeal swabs, induced sputum), intended to detect initial *P. aeruginosa* acquisition, should be performed regularly, at least four to six times per year. In clinically stable individuals with chronic *P. aeruginosa* infection respiratory tract cultures are recommended at least every 3 months during routine clinic visits. Chronic *P. aeruginosa* infection is defined by positivity of more than 50% of respiratory samples collected during the past 12 months (at least four samples are requested) and/or significantly raised anti-pseudomonal antibodies (modified Leeds criteria). The diagnostic value of serology as a predictor of early *P. aeruginosa* infection is still under debate and is probably best in young non-expectorating children. At several CF centres the current practice is to determine *P. aeruginosa* antibodies at least once a year (in *P. aeruginosa*-negative individuals).

The microbiological processing of CF samples requires special laboratory protocols as well as experienced microbiologists. Diagnostic microbiology needs to be focused on the typical and highly complex spectrum of CF pathogens. Plating on a standardised set of selective and chromogenic media along with prolonged incubation times is generally recommended, at least for *S. aureus*, *P. aeruginosa* (also other Gram-negative bacteria), BCC, *H. influenzae* and fungi. NTM culture should routinely be performed at least once per year. Initial homogenisation of sputum samples improves bacterial and fungal recovery rate.

Correct species identification is crucial and should be performed primarily by matrix-assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI-TOF MS).

MALDI-TOF MS is highly specific and has increasingly replaced biochemical tests that, especially in CF, are associated with high rates of misidentifications. As a result of niche adaptation bacterial isolates from CF secretions can exhibit altered morphological and metabolic phenotypes. It is recommended to individually test phenotypic variants. Mucoid and SCVs of *P. aeruginosa* and *S. aureus* are indicators of chronic infection and bacterial adaptation and should be reported. For direct identification of CF-specific pathogens from clinical samples, molecular technologies, such as single or multiplex PCR as well as next-generation sequencing, will be increasingly available in the future (*e.g.* for re-examination of samples that are negative for traditional CF pathogens).

Conventional antibiotic susceptibility testing (AST) is still part of CF microbiology (table 2). For chronic *P. aeruginosa* airway infection, especially in older people with CF, it has been shown that conventional AST does not reliably predict treatment success. It is recommended that AST can be performed less frequently in this age group. AST is anticipated to correlate better with the clinical outcome in children with CF, but this needs to be demonstrated by clinical studies. For the selection of antibiotics for treatment, CF clinicians should assess each person individually and consider both AST results and also previous clinical responses and drug tolerability. It is important to recognise that routine AST and applied interpretive criteria (clinical breakpoints) are intended for systemic but not for inhaled administration.

CF lung microbiome and new sequencing technologies

A decade ago, culture-independent molecular methods (not relying on microbial growth), such as 16S ribosomal DNA sequencing, showed that microbial complexity of CF secretions is much greater (polymicrobial) than previously appreciated from conventional culture. Microbiome studies (of all micro-organisms in a niche) have detected a broad array of bacterial species in CF respiratory samples and identified previously unrecognised micro-organisms from CF lung secretions that may play a role in chronic CF lung infections, for example anaerobic bacteria and the *Streptococcus anginosus* group. Of particular interest is the high number of anaerobes in CF sputum (*e.g. Prevotella* spp. and *Veillonella* spp.). However, the pathogenic significance of many of these micro-organisms is still unknown. Microbiome studies also have shown that as the diversity of organisms decline, *P. aeruginosa* emerges and reaches high densities. Expanding the use of molecular technologies (*e.g.* microbiome and metagenome studies) in the field of CF research will allow the investigation of microbial population dynamics, host–pathogen interactions and the microbial resistome, and thus enable better understanding of the complexity of CF lung infection and underlying pathophysiology. Increased knowledge of the CF lung microbiome offers new perspectives to improve clinical outcomes and assess the impact of new therapies (*e.g.* CFTR modulators), and opens a door to personalised medicine.

Hygiene aspects and transmissibility of CF pathogens

Chronic lung infection negatively affects life expectancy and quality of life of people with CF. Thus, prevention of colonisation and infection is an integral part of CF care. Transmission routes of CF pathogens are not completely understood, as many CF pathogens are ubiquitously distributed in the environment. Potential reservoirs include the natural environment (*e.g.* soil, water, plants), the healthcare setting (*e.g.* sinks, medical equipment such as nebulisers, contaminated surfaces) and other people with CF (cross-transmission). CF pathogens can be transmitted by direct or indirect contact with contaminated secretions and objects or by infectious aerosols.

Table 2. Typical antibiotic susceptibilities of common CF pathogens

Species	Antibiotic														
	PIP/T	CAZ	CEF/T	IMP	MER	ATM	LEV	CIP	TEM	TOB	COL	SXT	MIN	VA	CLA
P. aeruginosa	+	+	+	+	+	+	+	+	–	+	+	–	–	–	–
BCC	+/–	+	+/–	+/–	+	–	+	–	+	–	–	+	+	–	–
***Achromobacter* spp.**	+	+/–	n/a	+	+/–	–	+	+	–	–	+/–	+	+	–	–
S. maltophilia	–	+/–	–	–	–	–	+	+/–	–	–	+/–	+	+	–	–
I. limosus	–	+/–	n/a	+	+	–	+	+	–	–	–	+	+/–	–	–
***Pandoraea* spp.**	+/–	–	n/a	+	–	–	+/–	+/–	–	–	–	+	+/–	–	–
H. influenzae	+	+	+	+	+	+	+	+	–	+/–	+/–	+/–	+/–	–	+/–
MSSA	+	+/–	–	+	+	–	+	+	–	+	–	+	+	+	+
MRSA	–	–	–	–	–	–	+	+	–	+	–	+	+	+	+
M. abscessus	–	–	–	+	+/–	–	MOX[#]		–	AN[#]	–	+	TIG[#]	–	+
Available dosage forms	*i.v.*	*i.v.*	*i.v.*	*i.v.*	*i.v.*	*i.v.*/ih	*i.v.*/oral/ih		*i.v.*	*i.v.*/ih	*i.v.*/ih	*i.v.*/oral		*i.v.*/ih	*i.v.*/ih

+: *in vitro* susceptibility; +/–: borderline susceptibility; –: (intrinsic) resistance; n/a: resistance type unknown; PIP/T: piperacillin-tazobactam; CAZ: ceftazidime; CEF/T: ceftolozane/tazobactam; IMP: imipenem; MER: meropenem; ATM: aztreonam; LEV: levofloxacin; CIP: ciprofloxacin; MOX: moxifloxacin; TEM: temocillin; TOB: tobramycin; AN: amikacin; COL: colistimethate sodium; SXT: co-trimoxazole; MIN: minocycline; TIG: tigecycline; VA: vancomycin; CLA: clarithromycin; ih: inhaled. [#]: substance of choice for *M. abscessus*, belongs to the same antibiotic class as the substances given in the header, but these substances (*e.g.* MIN) are not useful/active against *M. abscessus*.

Colonisation with *P. aeruginosa* that is primarily recovered from aquatic sources may be both community-acquired and healthcare-associated. Hygiene measures have proved to be successful in preventing the acquisition of epidemic strains of *B. cenocepacia* and *P. aeruginosa* (mainly by cohort segregation). As a consequence, in many countries the peak prevalence of *Burkholderia* spp. has changed from *B. cenoce*pacia to *B. multivorans*, and today acquisition of *B. multivorans* is thought to be mainly sporadic. Highly transmissible strains of *P. aeruginosa* have been reported in Europe, Canada and Australia. Moreover, cross-transmission of MRSA and *M. abscessus* has been described in individual CF centres. A major risk factor for MRSA acquisition is hospitalisation, as MRSA is transmissible between individuals with and without CF. In the case of *M. abscessus*, data regarding person-to-person transmission are conflicting as shared *M. abscessus* clones in CF may either derive from direct cross-transmission events or result from the presence of dominant clones that are distributed worldwide in the environment. Moreover, strains of *S. maltophilia*, *Achromobacter* spp., *Pandoraea* spp. and other Gram-negative pathogens may be shared by individuals with CF.

To limit the risk of pathogen acquisition and spread between people with CF, specific hygiene measures must be implemented by CF centres, generally with regard to local epidemiology. Consensus guidelines for infection control in CF have been released by several CF organisations. Pathogen-dependent segregation of people with CF with positive sputum cultures into different cohorts (*P. aeruginosa*-negative, *P. aeruginosa*-positive, *P. aeruginosa*-positive for epidemic strains, BCC-positive, MRSA-positive) is a mainstay in CF.

Aerosol transmission by droplets (>5 µm in diameter, travel up to 2 m) and droplet nuclei (lower size, travel over longer distances and remain in the air for longer, no face-to-face contact necessary) has been suggested as a major route for the transmission of CF pathogens. Surgical masks significantly reduce the amount of air contamination by aerosolised *P. aeruginosa* (*e.g.* due to (uncontrolled) coughing). Thus, people with CF are increasingly asked to routinely wear surgical masks when in a healthcare setting.

Infection control guidelines recommended for people with CF regardless of their microbiological status include the following:

- Contact precautions: gowns and gloves for healthcare providers and surgical masks for people with CF
- Spacing of people with CF: a distance of at least 2 m between individuals in all settings
- Segregation of people with CF according to microbiological status (see earlier)
- Hand hygiene: after potential contamination and generally in the healthcare setting
- Measures related to diagnostic/therapeutic procedures (*e.g.* physiotherapy, pulmonary function testing)

For further details and specific measures, the published guidelines need to be consulted. As for many hygiene recommendations the effectiveness has yet to be determined, future surveillance of incident cases is pivotal to monitor the spread of CF pathogens (*e.g.* by multilocus sequence typing (MLST) or whole genome sequencing). Whether universal segregation of all individual people with CF, regardless of the financial and personnel costs, may be more effective in reducing the incidence of new cases needs to be demonstrated.

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Airway malformations

Ernst Eber and Andreas Pfleger

This chapter cannot cover the complete spectrum of congenital airway malformations, but rather gives an overview of important anomalies (table 1). Furthermore, laryngeal cleft and tracheo-oesophageal fistula are dealt with in the section of this *Handbook* on "Aerodigestive disorders".

Most children with airway malformations are already symptomatic in the neonatal period or in infancy; only rarely are airway malformations discovered incidentally. Early and accurate diagnosis as well as appropriate management is particularly important in children with severe central airway stenoses. Airway endoscopy is the most important diagnostic procedure. In many instances, essential diagnostic techniques are MRI and CT, frequently including angiography (especially pre-operatively and in children with associated cardiovascular anomalies).

Depending on the type and severity of the malformation, conservative or surgical management options may be chosen. With airway growth, mild to moderate airway stenoses frequently become less prominent in the first years of life. However, patients with tracheal stenoses due to cartilaginous rings may become more symptomatic with growth, as the rings may grow less than the other parts of the trachea. Conservative symptomatic treatment and support often is the preferred approach. In most patients the long-term prognosis is favourable.

Key points

- Airway anomalies may be part of complex syndromes and, in many cases, are associated with other congenital anomalies.
- With airway growth, mild-to-moderate stenoses in the first years of life frequently become less prominent.
- Depending on the type and extent of the malformation, conservative or surgical management options are chosen on an individual basis.
- With adequate management, in most patients the long-term prognosis is favourable.

Table 1. Important congenital airway malformations

Nasopharyngeal airway
Choanal stenosis and atresia
Pierre Robin sequence
Craniofacial malformations
Larynx
Laryngeal atresia
Laryngeal web
Subglottic stenosis
Laryngomalacia (infantile larynx)
Laryngeal cyst
Laryngeal (laryngo-tracheo-oesophageal) cleft
Trachea and bronchial tree
Tracheal agenesis and atresia
Tracheo-oesophageal fistula and oesophageal atresia
Isolated tracheo-oesophageal fistula (H-type fistula)
Tracheomalacia
Tracheal stenosis
Tracheal bronchus and other topographic anomalies
Bronchial atresia
Bronchomalacia
Bronchial stenosis

Nasopharyngeal airway

Choanal stenosis and atresia

This is one of the most common congenital upper airway anomalies (~1 in 8000 births). Most cases are due to bony occlusion of the airway; some children show membranous obstruction. Approximately two-thirds of patients with choanal atresia show associated congenital anomalies (*e.g.* CHARGE association, characterised by coloboma of the eye, heart defects, atresia of the nasal choanae, retardation of growth and/or development, genital and/or urinary abnormalities, and ear abnormalities and deafness). Unilateral lesions are twice as common as bilateral ones.

Bilateral choanal atresia causes immediate respiratory distress at birth; unilateral lesions are often not detected until later in childhood. Some children present with feeding difficulties and persistent rhinorrhoea, especially if the patent nostril is occluded during respiratory infections.

Flexible airway endoscopy and CT can confirm the diagnosis and delineate the exact site of obstruction as well as whether it is bony or membranous.

A nasal airway should be established as soon as possible. This can be achieved by a transnasal approach with a dilating instrument and passing airway stents through the nasal passage to ensure continued patency for several weeks. Alternatively, repeated choanal dilation may be performed at weekly intervals. In severe cases, transpalatal surgery may be required.

(Pierre) Robin sequence

This anomaly is characterised by micrognathia, glossoptosis and (pharyngeal) airway obstruction of variable severity. More than half of affected infants have an associated syndrome, most commonly Stickler syndrome or 22q11.2 deletion syndrome, and

frequently a cleft palate or other airway pathologies. As the mandible grows forward with age, airway and feeding problems may gradually resolve during the first year of life.

In severe cases, the anomaly can necessitate intubation, especially when associated airway pathologies (*e.g.* laryngomalacia, tracheomalacia) exist. Prone positional therapy has proved to be efficient in mild cases. Airway obstruction may be relieved by a nasopharyngeal airway. Noninvasive respiratory support can relieve upper airway obstruction, with CPAP application in mild and moderate cases, or with noninvasive positive-pressure ventilation in severe cases. Surgical procedures include tongue–lip adhesion, mandibular distraction osteogenesis and tracheostomy. Feeding difficulties can be alleviated by upright feeding techniques, modification of the nipple for bottle feeding, temporary use of feeding tubes and the placement of a gastrostomy. Palatal plates such as the pre-epiglottic baton plate with a velar extension pull the base of the tongue forward. This can be helpful in the relief of airway obstruction, facilitates the swallowing mechanism during feeds and accelerates mandibular growth. Patients with Robin sequence should be cared for by a multidisciplinary team.

Other craniofacial anomalies

Many syndromic craniofacial anomalies can affect upper airway patency. These dysmorphic syndromes are typically characterised by mandibular or maxillary hypoplasia and include Crouzon, Treacher Collins, Apert, Pfeiffer, and Goldenhar syndromes. 36 syndromes with craniofacial anomalies have been found to be associated with one or more of 14 laryngotracheal malformations. Several anomalies, such as a narrowed nasopharynx with associated adenotonsillar hypertrophy, midface hypoplasia and hypertrophy of the tongue can cause airway compromise in children with Down syndrome.

Larynx

Laryngeal atresia

This is a life-threatening malformation, and in the past virtually all affected newborns died. Today, antenatal ultrasound scans may allow diagnosis of congenital high airway obstruction syndrome (CHAOS), which may be related to intrinsic causes such as atresia of the larynx or upper trachea or extrinsic laryngotracheal obstruction caused by large masses (*e.g.* cervical teratoma). Identification of the condition by sonography and MRI helps facilitate management, including *ex utero* intrapartum treatment (EXIT).

Without antenatal diagnosis, newborns with isolated laryngeal atresia may only survive when emergency tracheostomy is performed immediately after birth. Bag-mask ventilation may save the lives of children with incomplete laryngeal atresia. Laryngeal function in survivors is usually abnormal, and surgical reconstruction is required later in life. The prognosis also depends on the presence of associated malformations (*e.g.* VACTERL association, characterised by vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities) or syndromic anomalies (*e.g.* Fraser syndrome). Data on long-term follow-up after successful EXIT procedure are not yet available.

Laryngeal web

Laryngeal webs are usually located at the level of the glottis; supraglottic and subglottic webs may also occur. The webs may be complete or incomplete, and vary in thickness (figure 1).

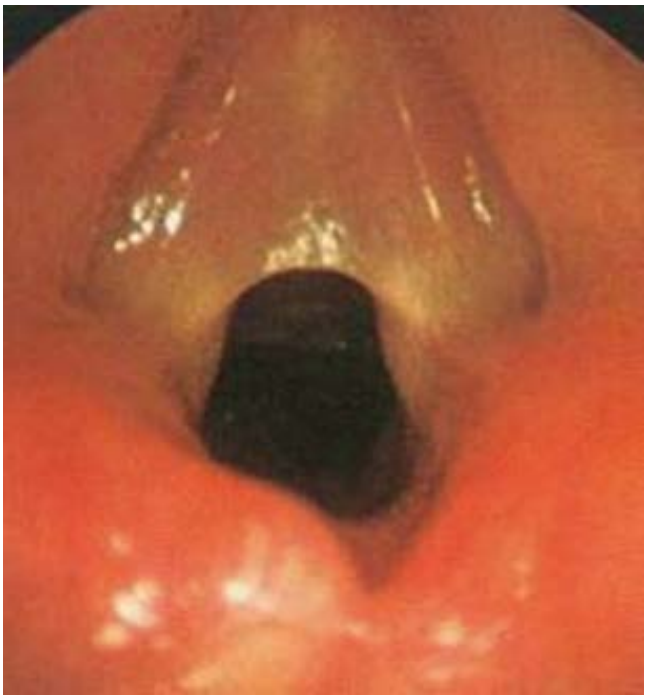

Figure 1. Incomplete glottic web.

Incomplete laryngeal webs, typically located anteriorly with posterior openings, are strongly associated with the velocardiofacial syndrome. Complete laryngeal webs present like a laryngeal atresia; symptoms with incomplete webs range from (biphasic) stridor and hoarseness to aphonia and varying degrees of respiratory distress. The diagnosis is established by airway endoscopy. Treatment options include (laser) excision and dilation. Sometimes endotracheal intubation solves the problem, but re-stenoses are relatively common. The prognosis mainly depends on the extent of the lesion.

Subglottic stenosis

Congenital subglottic stenosis is the second most common laryngeal malformation. The more common membranous form is characterised by symmetrical thickening of the soft tissues in the subglottic area. Cartilaginous subglottic stenosis is due to a malformation of the cricoid cartilage, resulting in circumferential stenosis of variable appearance. Myer *et al.* (1994) proposed a grading system for subglottic stenoses based on endotracheal tube sizes (table 2).

The clinical presentation depends on the grade of stenosis and ranges from severe respiratory distress at birth to the development of inspiratory or biphasic stridor within the first months of life (recurrent or atypical croup). Children with congenital subglottic stenosis are at risk of developing additional acquired subglottic stenosis

Table 2. Grading system for subglottic stenoses

	Degree of obstruction of the lumen
I	≤50%
II	51–70%
III	>70% (any detectable lumen)
IV	No detectable lumen

Adapted from Myer *et al.* (1994).

due to airway trauma (mostly iatrogenic, such as prolonged endotracheal intubation or tracheostomy).

Airway endoscopy is the procedure of choice to establish the diagnosis and to differentiate subglottic stenosis from subglottic haemangioma. Sonography and MRI may be helpful.

As congenital subglottic stenosis generally improves with airway growth, a conservative supportive approach is recommended whenever possible. Surgery should be reserved for severe forms; treatment options include cricoid split, laryngotracheoplasty and long-term tracheostomy.

Laryngomalacia (infantile larynx)

This is the most common congenital laryngeal anomaly (50–75%) and the most common cause of persistent stridor in children (~60%). The term laryngomalacia suggests that laryngeal cartilage is abnormally soft. However, whether laryngomalacia is primarily an anatomic anomaly or is due to delayed neuromuscular development is controversial. According to Holinger *et al.* (1997), five types of laryngomalacia can be distinguished (two or more may occur simultaneously) (table 3). Laryngomalacia is frequently associated with other airway lesions and with gastro-oesophageal reflux.

The natural history is characterised by onset of inspiratory stridor usually within the first 4–6 weeks of life; cry and cough are normal. Stridor varies considerably with posture and airflow, is loudest with increased ventilation (*e.g.* crying, agitation, feeding) and worsens during respiratory tract infections. Some patients will have increasing symptoms during the first few months of life; thereafter, stridor tends to resolve with time. In (very rare) severe cases with significant airway obstruction, serious complications such as failure to thrive, obstructive apnoeas, pulmonary hypertension and cor pulmonale may develop.

The diagnosis is suspected based on history and physical examination, and confirmed by flexible airway endoscopy. Laryngoscopy demonstrates supraglottic collapse during inspiration (figure 2). Topical anaesthesia can potentially exaggerate the findings; thus, the larynx should be examined before applying topical anaesthesia.

In the majority of cases, apart from parental reassurance and support, no specific therapeutic measures are needed. In severe cases (failure to thrive and/or obstructive apnoeas) surgical treatment (various forms of supraglottoplasty; rarely, tracheostomy) is needed. In isolated forms, prognosis is excellent; with associated malformations, prognosis usually depends on the latter.

Table 3. Types of laryngomalacia

1	Inward collapse of the aryepiglottic folds, primarily the cuneiform cartilages, which are often enlarged
2	Long, tubular epiglottis (pathological exaggeration of the normal omega shape)
3	Anterior, medial collapse of the arytenoid cartilages
4	Posterior inspiratory displacement of the epiglottis against the posterior pharyngeal wall or inferior collapse to the vocal cords
5	Short aryepiglottic folds

Adapted from Holinger *et al*. (1997).

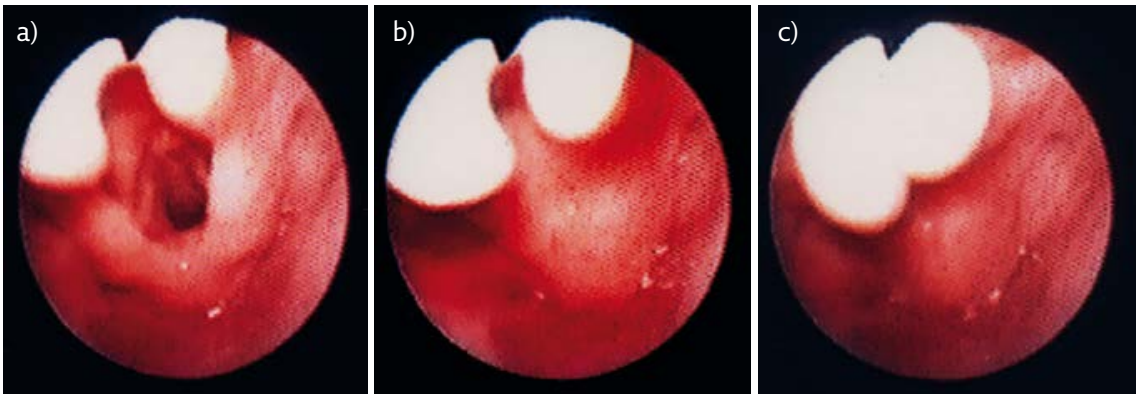

Figure 2. Laryngomalacia (infantile larynx). a) Patent airway during expiration; b) prolapse of arytenoids and aryepiglottic folds into the glottis during mid-inspiration; c) prolapse of arytenoids and aryepiglottic folds and folding of epiglottis along its long axis ("floppy epiglottis") at end-inspiration, resulting in complete obstruction of the larynx. Reproduced from Eber (2010) with permission.

Laryngeal cyst

Supraglottic cysts, commonly located at the aryepiglottic folds or at the epiglottis, are usually congenital. In contrast, subglottic cysts are usually acquired as a result of airway trauma (*e.g.* endotracheal intubation). The appearance of cysts varies widely; while some are covered by thin mucosa and are easy to recognise, others appear as a submucosal mass. A laryngocele is a rare form of a laryngeal cyst, which originates from the laryngeal ventricle, consists of an air-filled saccule and may be difficult to diagnose. Infants commonly present with stridor, hoarseness, weak cry or aphonia, and sometimes feeding difficulties. Airway endoscopy confirms the diagnosis. The treatment of choice is resection of the cyst.

Trachea and bronchial tree

Tracheal agenesis and atresia

These are rare malformations ranging from complete tracheal agenesis to short-segmental atresia, commonly associated with a broncho- or tracheo-oesophageal fistula or other anomalies in various organ systems (*e.g.* VACTERL association). Similarly to laryngeal atresia, these malformations are usually lethal. Without antenatal diagnosis, affected newborns with short-segmental atresia of the proximal trachea may only survive when emergency tracheostomy is performed immediately after birth; in the presence of a fistula or a cleft, intubation of the oesophagus may allow temporary ventilation. After antenatal diagnosis an EXIT procedure may save the life of the affected baby. In those who survive, the short-term prognosis mainly depends on the presence of associated anomalies. Long-term data on follow-up after successful EXIT procedure are not yet available.

Tracheomalacia

This common anomaly (~1 in 2000) is characterised by weakness of the tracheal wall, due to reduction and/or atrophy of the longitudinal elastic fibres of the pars membranacea, a widened pars membranacea or impaired cartilage integrity ("immaturity"). Congenital tracheomalacia has to be distinguished from acquired forms; the latter may develop as a result of prolonged intubation and mechanical ventilation, tracheostomy or severe tracheobronchitis. Tracheomalacia can be primary or secondary, and may be localised or generalised. Primary tracheomalacia is found

in association with oesophageal atresia, Down syndrome, Ehlers–Danlos syndrome, and with laryngomalacia or bronchomalacia. Localised secondary tracheomalacia may occur as a consequence of compression from a vascular malformation (*e.g.* double aortic arch, right aortic arch variants, left pulmonary artery sling, "anomalous" innominate artery) or a mediastinal tumour. After surgical repair (*e.g.* division of a vascular ring), the tracheomalacia very often continues to cause symptoms. The prognosis of these anomalies is determined by the respiratory tract.

Intrathoracic tracheomalacia is associated with dynamic airway compression on expiration, in particular during increased respiratory effort (*e.g.* crying) and coughing, or during respiratory infections (figure 3).

Tracheal collapse may result in retention of secretions from the lower airways, which in turn may cause bronchopulmonary infections. In contrast, malacia of the extrathoracic part of the trachea may result in partial or complete airway collapse on inspiration. Signs and symptoms of tracheomalacia include a "barking" or "brassy" cough, tachypnoea and dyspnoea, retractions, cyanosis, localised monophonic (expiratory) wheezing, and possibly (inspiratory) stridor. Feeding may cause "blue spells" or "dying spells", as food in the oesophagus may compress the malacic trachea. Tracheomalacia is frequently misdiagnosed as bronchial asthma or other respiratory conditions. Thus, patients may be treated unnecessarily with inhaled corticosteroids for long periods of time, and may be undertreated for recurrent or chronic lower airway infections.

With intrathoracic tracheomalacia, a chest radiography typically reveals bilateral hyperinflation; lateral inspiratory and expiratory radiographs may show marked changes in airway calibre of the malacic part of the trachea. The registration of (tidal and) maximal flow–volume curves allows distinction between extra- and intrathoracic airway obstruction and between variable (tracheomalacia) and fixed (tracheal stenosis) obstruction. Flexible airway endoscopy is the diagnostic procedure of choice; it can be done with only minimal mechanical distortion of the airway anatomy and dynamics, while rigid instruments inevitably distort the airways. It is mandatory that evaluation of airway dynamics is performed during spontaneous breathing. CT and MRI (with angiography) are complementary techniques, in particular when extrinsic compression is suspected in patients with localised tracheomalacia.

Generally, in patients with isolated tracheomalacia, airway function improves with age, as the airway grows and the airway wall stiffens. Thus, most patients can be managed conservatively, with chest physiotherapy and antibiotics for secondary infections. In particular, infants with generalised tracheo- and/or bronchomalacia

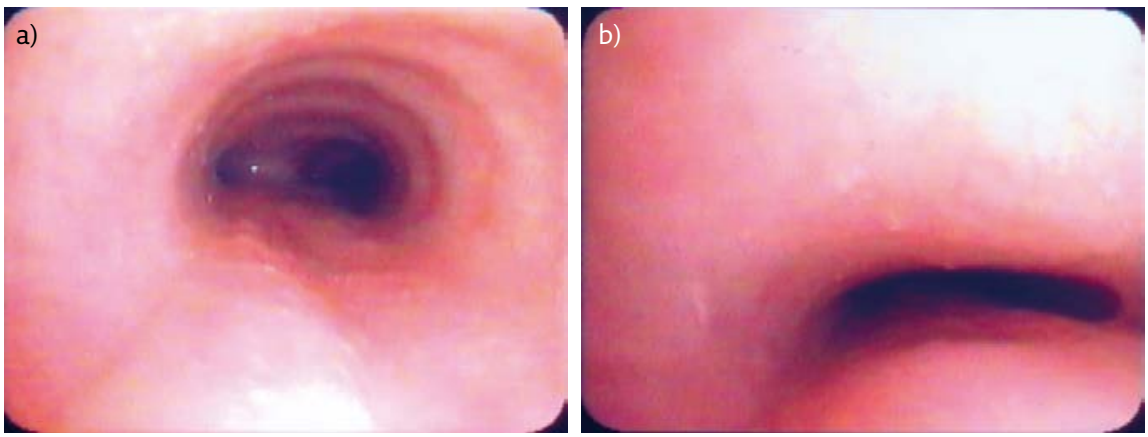

Figure 3. Intrathoracic tracheomalacia during a) inspiration and b) expiration. Reproduced from Eber (2014) with permission.

and significant airway obstruction may benefit from long-term application of CPAP or ventilation with PEEP *via* tracheal cannula to splint the airway. In most of these patients, gradual reduction of positive airway pressures and eventual decannulation is possible. Clinical and radiological parameters, as well as flexible airway endoscopy and pulmonary function testing enable determination of the individual optimal airway pressure. One advantage of this approach is the avoidance of major surgery; disadvantages include long-term tracheostomy and technology dependency. Surgical treatment is indicated in children with life-threatening tracheomalacia. Aortopexy is usually effective in localised tracheomalacia, but is of limited value in generalised forms. Stents may be effective in patients with diffuse tracheomalacia, but severe complications, including death, have been reported. Thus, stents should only be employed as a last resort when all other conservative and surgical options have failed to wean patients off the ventilator over a long period of time or have failed to relieve life-threatening obstructive episodes. Treatment and prognosis depend on the type and severity of the malacia and on associated anomalies.

Tracheal stenosis

This anomaly is less common than tracheomalacia. Membraneous stenoses (webs) are less common than anomalies of the tracheal cartilages. Complete cartilaginous tracheal rings ("napkin-ring cartilages") mainly occur in the intrathoracic trachea along a variable length; sometimes the whole trachea is affected. The shape of the stenosis can be hourglass- or funnel-like (carrot-shape, "rat-tail" trachea). Tracheal stenoses are frequently associated with other anomalies such as a left pulmonary artery sling, abnormal bronchial arborisation (*e.g.* tracheal bronchus), or a single right or left lung. Various classifications have been proposed, based on the length of stenosis, the severity of symptoms and according to bronchial involvement.

Congenital tracheal stenosis may be life-threatening or may only be detected incidentally. Signs and symptoms depend on the severity and the site of the stenosis, and include localised monophonic (expiratory or biphasic) wheezing or (inspiratory or biphasic) stridor, tachypnoea and dyspnoea, retractions, cyanosis and respiratory distress.

Unless a severe stenosis precludes a complete endoscopic examination, flexible airway endoscopy with an ultrathin instrument is helpful in defining airway anatomy including bronchial arborisation, in detecting possibly associated tracheo- and/or bronchomalacia, and in planning treatment. Usually, CT or MRI (with three-dimensional reconstruction) is necessary to define the extent of the lesion, and to confirm or rule out compression by an extrinsic lesion (figure 4).

Pulmonary function testing shows evidence of fixed airway obstruction with plateaus in both the inspiratory and expiratory limb of the flow–volume loop.

As tracheal stenosis may improve with airway growth, conservative and symptomatic treatment (including chest physiotherapy and antibiotics) should be recommended whenever possible. Surgical options for more severe stenoses include tracheostomy to bypass stenosis of the cervical trachea, resection and primary anastomosis for short-segment stenosis, and slide tracheoplasty (including repeated balloon dilation to prevent subsequent recurrence of the stenosis) for long-segment stenosis. Tracheal surgery should only be exercised in specialised referral centres. In the future, tissue-engineered tracheal replacement is expected to play an increasingly important role. Treatment and prognosis depend on the type and severity of the stenosis and on associated anomalies.

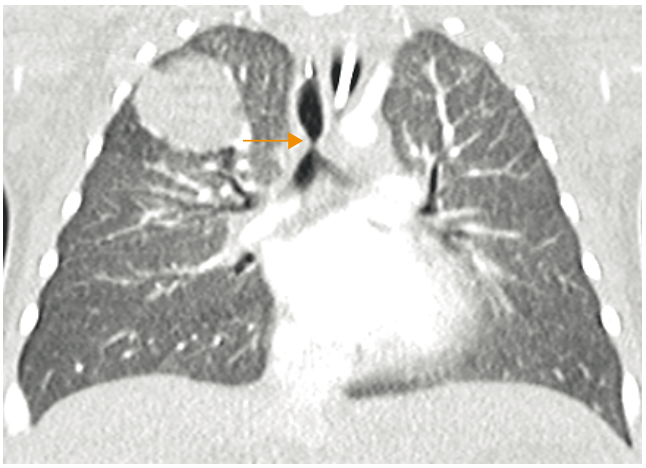

Figure 4. Severe, short segment tracheal stenosis (arrow), and parenchymal lung malformation in the right upper lobe.

Tracheal bronchus and other topographic anomalies

Topographic anomalies are the most common anomalies of the tracheobronchial tree and are mostly observed on the right side. A tracheal bronchus ("pig bronchus") may be associated with other anomalies in the tracheobronchial tree or in other organ systems. It originates from the right tracheal wall and supplies either an accessory segment within or separated from the right upper lobe, the apical segment of the right upper lobe (in this case a normal right upper lobe bronchus supplies the other two segments), or the whole right upper lobe (in this case the normal right upper lobe bronchus is absent). The tracheal bronchus may also originate from the trachea at the level of the carina ("trifurcation"). A detailed description of the so-called "bridging bronchus" in patients with a tracheal bronchus and a left pulmonary artery sling is given in the chapter "Vascular malformations".

These anomalies are often asymptomatic and thus only detected incidentally. However, if structural anomalies (stenosis, malacia) are present the malformation may result in recurrent or persistent pneumonia or atelectasis, and later bronchiectasis in the respective segment or lobe. Diagnosis is established by bronchoscopy and CT or MRI. Chest physiotherapy and antibiotics are the treatment of choice in symptomatic patients. When problems persist despite conservative measures, resection of the affected segment or lobe may be necessary.

Topographic anomalies of the whole lung (*e.g.* situs inversus or bronchial isomerism (bilateral right or bilateral left lung)) are usually associated with topographic anomalies of the heart and/or abdominal organs (*e.g.* Ivemark syndrome with asplenia).

Bronchial atresia

This rare anomaly is frequently associated with congenital lung malformations and is seen by many authors as the underlying cause of the latter. A lobar or (sub)segmental bronchus ends blindly, separated by a short gap from the distally located bronchial tree supplying the lobe or (sub)segment. The clinical picture varies widely, from the neonate with respiratory distress to the asymptomatic adult. CT or MRI is used to confirm the diagnosis. Resection of the affected segment or lobe is usually recommended.

Bronchomalacia

Bronchomalacia is characterised by abnormal weakness of the bronchial wall. Localised forms are distinguished from generalised forms (*e.g.* Williams–Campbell

syndrome), and primary from secondary forms; the latter are usually caused by vascular compression. Bronchomalacia is frequently associated with tracheomalacia, and the left main bronchus is predominantly affected.

Signs and symptoms depend on severity and include cough, localised monophonic wheezing and decreased breath sounds. Some children only develop symptoms during respiratory infections. Flexible bronchoscopy is the diagnostic procedure of choice; echocardiography, CT and MRI are complementary techniques, in particular for localised bronchomalacia.

Gradual improvement may be expected with age and airway growth. Only a minority of patients with significant respiratory problems requires treatment apart from the usual conservative measures (chest physiotherapy, antibiotics). Prognosis mainly depends on associated anomalies.

Bronchial stenosis

This anomaly is rare and predominantly occurs in mainstem (left>right) and lobar bronchi. Retention of secretions may lead to bronchopulmonary infections and the development of bronchiectasis. Signs and symptoms are the same as with bronchomalacia. Diagnosis is confirmed by flexible bronchoscopy, CT or MRI. As patients tend to show improvement with age and airway growth, conservative management is recommended. Resection and primary anastomosis may be necessary for severe short-segment stenosis; localised bronchiectasis may necessitate resection of the affected segment or lobe.

Summary

As respiratory and gastrointestinal morbidity may be significant, children with airway malformations should be regularly evaluated by a multidisciplinary team. Transition of young adults from paediatric care to an adult physician with expertise in airway malformations is recommended.

Further reading

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Lung malformations

Ashok Daya Ram, Katherine Burke, Jennifer Calvert and Sailesh Kotecha

Congenital thoracic malformations (CTMs) are a heterogeneous group of rare congenital developmental anomalies and disorders of the lung parenchyma and airways with an incidence of ~3.5 per 10 000 live births. Characterisation and identification of these lesions has been vastly improved by antenatal and post-natal imaging, including the routine use of antenatal ultrasound scanning and targeted MRI, but at the same time imaging has introduced complexities, especially in the management of asymptomatic lesions. Many excellent recent reviews and textbooks of paediatric respiratory medicine cover all CTMs in detail (table 1); thus, we focus in this chapter on congenital pulmonary airway malformations (CPAMs) and their relative bronchopulmonary sequestrations (BPS). Close multidisciplinary cooperation between fetal medicine experts, neonatologists, paediatric surgeons, geneticists, paediatricians and/or paediatric pulmonologists is crucial to the overall management and outcome of children with CTMs.

Congenital pulmonary airway malformations

CPAMs are the most common developmental anomaly of the airways and pulmonary tissues, in which abnormal development appears to occur in part of the lung, usually

Key points

- Congenital pulmonary airway malformations (CPAMs) can act as space-occupying lesions with pressure effects, which can result in lung hypoplasia, polyhydramnios, pulmonary effusions or hydrops fetalis.
- Antenatal "resolution" of CPAMs is reported in up to 20% cases, but in most cases there is evidence of their persistence on post-natal CT images.
- Management of asymptomatic CPAMs is controversial, with some physicians opting for regular follow-up and imaging to gauge progress, while others opt for surgical removal.
- Long-term follow-up studies are required to assess the natural history, including respiratory and neurodevelopmental outcomes, especially after fetal intervention.

Table 1. Differential diagnosis of CTMs

Tracheobronchial malformations
Tracheal agenesis/atresia/stenosis
Tracheal bronchus
Oesophageal bronchus/lung
Tracheomalacia/bronchomalacia
Enteric duplication cyst
Neuroenteric cyst
Bronchogenic cyst
Bronchial cyst
Bronchiolar cyst
Pulmonary parenchymal malformations
Agenesis/aplasia/hypoplasia of the lungs
Congenital lobar emphysema
CPAMs
BPS
Vascular malformations
Haemangioma
Arteriovenous malformations
Scimitar syndrome (congenital venolobar syndrome)
Congenital pulmonary lymphangiectasia
Lymphangioma
Congenital chylothorax

at the lower lobe of either lung. CPAMs act as space-occupying lesions with pressure effects on the following:

- Lungs, which can lead to lung hypoplasia
- Oesophagus, resulting in polyhydramnios
- Heart, vessels and mediastinum, resulting in pleural effusions or hydrops fetalis

Epidemiology

CPAMs are uncommon, with reported incidence ranging from one per 8300 to one per 35 000 live births. Although rare, they are the most common developmental anomaly of the airways and pulmonary tissues. Occurrence is sporadic and unrelated to maternal factors such as age, race or exposures. Some, but not all studies report a slight male preponderance with no known genetic or familial association (although these are increasingly described for specific lesions). Incidence has increased over the past two to three decades, predominantly due to early identification of these lesions by the introduction of routine antenatal ultrasound.

Embryology

The lungs develop as an outpouching from the developing foregut at 3 weeks of gestation. The respiratory diverticulum begins to grow caudally and divides at 4 weeks and further subdivides in a dichotomous fashion. Further lung growth occurs in tightly regulated stages of lung development, namely the embryonic, pseudoglandular, canalicular, saccular and alveolar phases. By the end of the sixth month of gestation, 17 generations of subdivisions have formed. Lung growth and development continues post-natally until at least 2 years of age. The exact aetiology of most CTMs remains unknown, but, for CPAMs, the embryological insults are speculated to occur during the pseudoglandular stages of lung development for type I–III CPAMs and during the

late saccular phase of lung development for type IV lesions. Although transcription and growth factors such as homeobox-B5, thyroid-transcription factor-1 and platelet-derived growth factor-BB have been shown to be increased in resected or autopsy-acquired CPAM tissues, their exact role in the pathogenesis of CPAMs remains uncertain.

Pathology

CPAMs are congenital lung anomalies in which abnormal development appears to occur in part of the lung, usually at the lower lobe of either lung. The lesion grows fastest between 20 and 26 weeks of gestation, and then plateaus before decreasing in volume relative to fetal size towards term. The abnormal lung consists of terminal bronchiolar or acinar structures that can act as space-occupying lesions, although it is connected to the tracheobronchial tree, making them susceptible to airborne infections. The lesions usually draw their blood supply from the pulmonary circulation, but in hybrid lesions, *i.e.* lesions showing elements of both CPAM and BPS, they may also have a systemic blood supply. CPAMs can vary in size and consistency, and their continued growth can cause pressure effects on the remainder of the lungs, oesophagus, the mediastinum or the great vessels. CPAMs are usually isolated, but type 2 CPAMs are often associated with other systemic abnormalities.

Classification

There have been many classifications for CPAMs, but those by Stocker (2002) and Langston (2003) are most commonly used, with significant overlap between the two. The Langston classification includes lesions other than CPAMs, including bronchial atresia and pulmonary hyperplasia. The Stocker classification, which focuses on CPAMs, is based on histology and the size of the lesions, as follows:

- Type 1: individual cysts are >2 cm in diameter and are lined by pseudostratified epithelium
- Type 2: individual cysts are <2 cm in diameter with the cysts resembling dilated bronchioles; they are lined by ciliated cuboidal or columnar epithelial cells
- Type 3: solid lesions without cystic components with an excess of acinar structures

Other types have subsequently been added to this classification, including type 0, which is best viewed as describing congenital acinar dysplasia, and type 4, which overlaps with type 1 pleuropulmonary blastoma. Type 1 is the most common lesion, forming ~50–70% of all CPAMs, and has the best prognosis. Type 2 CPAMs are often associated with other malformations, which should be looked for at antenatal ultrasound screening.

Stocker's classification is based on histological observation, but Adzick *et al*. (1998) suggested a more clinical classification based on antenatal ultrasound measurements of the cysts to classify CPAMs into two types:

- Macrocystic, where the cyst or cysts are >5 mm in diameter and constitute 75% of all lesions
- Microcystic, where the cyst or cysts are <5 mm in diameter and constitute 25% of all lesions

While many classifications are based on histology, the best approach is for the antenatal ultrasonographer to accurately report the findings including the characteristics of the lesion, whether solid or cystic, describing the cysts in detail including size,

position, vasculature, effect on surrounding tissue and organs including presence of fetal hydrops, polyhydramnios and associated abnormalities, and change over time. Accurate description of the findings is most likely to be helpful in managing the lesion.

Antenatal diagnosis

The routine introduction of antenatal ultrasound scanning has not only increased our knowledge of CTMs, but has also resulted in improved antenatal counselling and management of conditions (figure 1a). While antenatal scanning has improved detection, it has also led to some unique challenges, namely the management of lesions with a presumed diagnosis and of lesions that may resolve. Often an attempt is made to make a pathological diagnosis based on ultrasound observations, but a pathological diagnosis would clearly require tissue for examination. Thus, it is important to describe the lesion in detail and formulate a differential diagnosis (table 1). Important differential diagnoses include congenital diaphragmatic hernia and bronchogenic cysts; the latter are an important differential diagnosis. These are congenital cysts derived from the primitive foregut containing viscid, milky mucus and which occasionally communicate with the airway. They can present on routine antenatal ultrasound scan, as respiratory distress in infancy, as recurrent/persistent pneumonia or as an incidental finding of a smooth mediastinal mass on chest radiography. Treatment is by surgical excision.

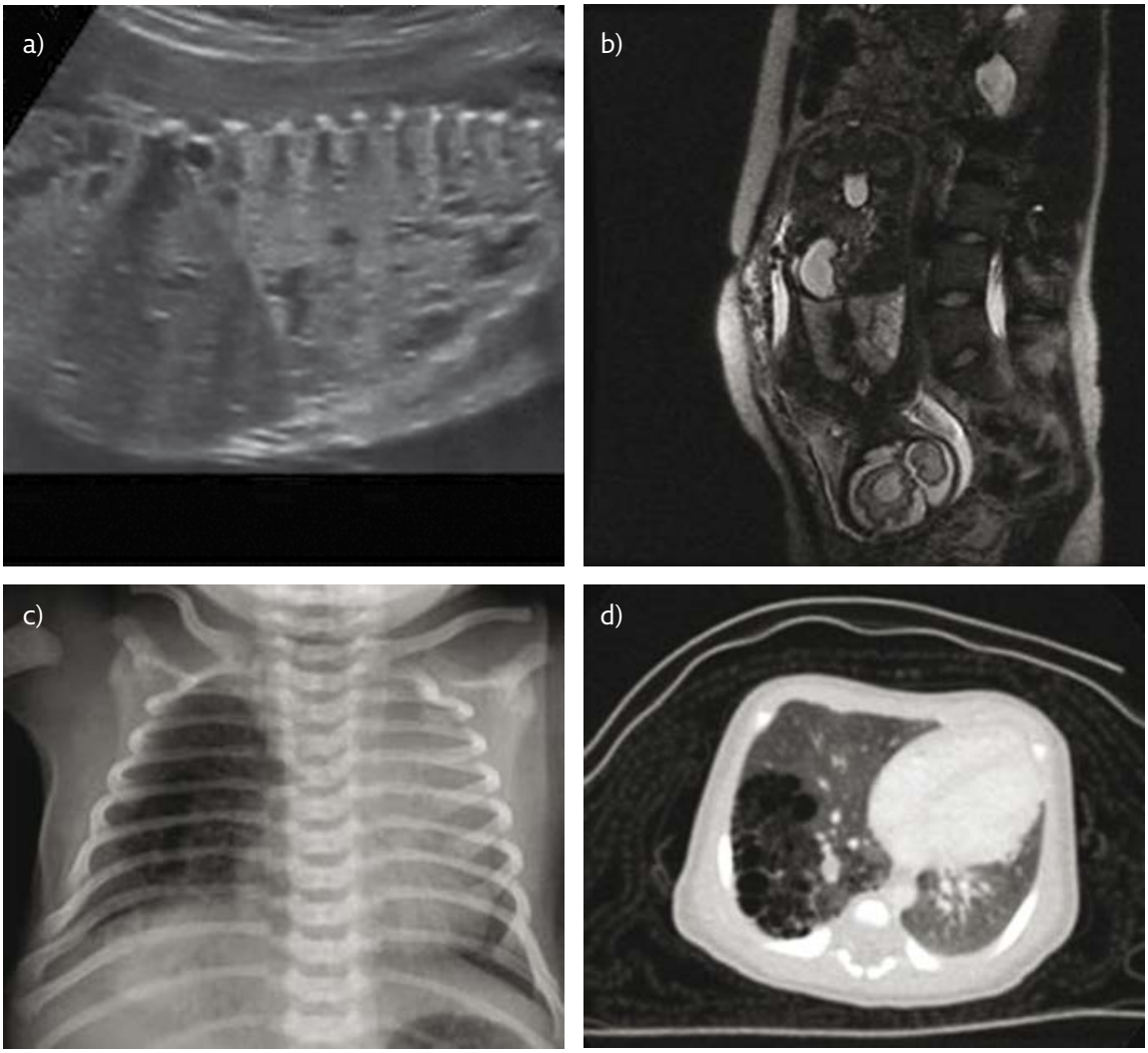

Figure 1. a) Antenatal ultrasound and b) MRI scan of an extensive right-sided CPAM, which was symptomatic at birth, with respiratory distress and mediastinal shift as confirmed by c) chest radiograph and d) CT scan. It was surgically removed successfully at 3 days of age.

Modalities such as antenatal MRI (figure 1b) are increasingly used to more accurately delineate and quantify the CTMs and other associated abnormalities. MRI provides an excellent method for morphological and volumetric evaluation of the fetal lung, but should be used as an adjunct to routine antenatal ultrasound rather than as a primary investigation. Although it is used increasingly, MRI is best performed when the diagnosis is uncertain, important features such as the vasculature or effect of the lesion on surrounding organs need further evaluation or when antenatal intervention is considered as an option.

Ultrasound findings

As described, accurate reporting of the findings including position, size, characteristics, vascular abnormalities, change of lesion over time, associated abnormalities and effect on surrounding tissue and organs are most likely to be helpful in managing the lesion. Antenatal ultrasound scanning can detect these lesions as hyperechoic pulmonary masses (figure 1a), as well as features of associated complications (*e.g.* polyhydramnios or hydrops) in >80% of cases. With BPS, an aberrant feeding arterial supply will be present arising directly from the abdominal or thoracic aorta. Systemic abnormalities including the cardiovascular, abdominal and mediastinal structures should also be searched for. Antenatal "resolution" of CPAMs is reported to occur in up to 20% cases, but in most cases, there is evidence of their persistence on post-natal CT images. 5–10% of these lesions can lead to the development of hydrops fetalis, which is associated with markedly increased fetal demise; thus, this association has received great attention for antenatal fetal surgical intervention.

Currently the best available indicator of prognosis for CPAM is the CPAM volume ratio (CVR), usually measured and compared on the antenatal ultrasound using the following formula (all measured in centimetres):

$$\text{CVR} = \frac{\text{length} \times \text{width} \times \text{height of the lesion} \times 0.52}{\text{head circumference}}$$

CVR values >1.6 are associated with increased risk of between 15% and 75% for developing fetal hydrops, *i.e.* poor prognosis. Due to the increased risk of developing a complicated course, the CVR is often used to guide antenatal fetal surgical intervention, but has limited sensitivity and specificity. Several other measurements have been used, including fetal lung volumes estimated by MRI, mass–thorax ratio, lung–head ratio and mediastinal shift angle, but these need further prospective evaluation to determine their accuracy in estimating prognosis.

Antenatal management

Antenatal interventions, with variable results, include steroid administration, thoracocentesis, thoracoamniotic shunt, laser ablation, fetal surgery or injection of a sclerosing agent into any feeding vessel. Hedrick *et al*. (2005) reported an 89% overall survival in nine patients who underwent the *ex utero* intrapartum treatment procedure for fetal hydrops, extensive mediastinal shift or persistently elevated CVR. Ultrasound-guided intrauterine thoracoamniotic shunting for a macrocystic CPAM with a large cyst has the best outcome with the lowest fetal and maternal risk. Out of 23 such patients treated with this approach in one series, the volume reduction of the CPAM was 70% and survival throughout the neonatal period was 74%. Open maternal–fetal surgery with pulmonary resection of a large CPAM yields a 50% probability of survival to discharge from the neonatal intensive care unit, but given

the technical complexity this should only be performed at a centre with experience. However, most studies report a small number of patients and report success, although publication bias suggests that those that resulted in failure are unlikely to reach the wider literature. Furthermore, most of these interventions have not been formally assessed, thus, results need to be interpreted with caution. Longer-term outcomes after fetal intervention have not been reported in any detail, but will clearly need careful follow-up, especially for neurodevelopmental outcomes.

Clearly, it is important to counsel the parents, with a multidisciplinary team offering all available options.

Post-natal management

Most CPAMs will have been identified antenatally on routine sonography and infants with large lesions may need supportive therapy for stabilisation prior to surgical intervention. Planning to deliver in appropriate centres with the required expertise is a must for these babies. However, the majority of CPAMs are asymptomatic (and indeed may appear normal on chest radiography, although CT imaging may show residual lesions), but some may present with acute (figure 1c and d) or chronic respiratory distress, recurrent pulmonary infections, bronchiectasis, lung abscesses, haemoptysis, pneumothorax, air embolism, haemothorax, pyopneumothorax, steroid-resistant asthma or high-output cardiac failure (if there is a large systemic arterial blood supply). They may present incidentally on chest radiographs obtained for other reasons.

There is little controversy that surgical resection of symptomatic lesions is appropriate in most cases and is relatively straightforward, with minimal morbidity and mortality in experienced paediatric/neonatal surgical centres.

Management of asymptomatic lesions is more controversial. Possible reasons for elective surgical removal of asymptomatic lesions include prevention of chest infections and other rarer complications, as follows:

- To decrease post-operative complications
- Prevention of bleeding and pneumothorax
- To encourage potential compensatory lung growth if performed <2 years of age
- Prevention of future malignancy risk

In most cases, surgery is performed between 2 and 12 months. With advances in video-assisted thoracoscopic surgical skills and increasing use and safety of single-lung anaesthesia, elective surgery is considered relatively safe in expert surgical hands, involving a short hospital stay with few complications, but may be associated with poorly delineated longer-term outcomes such as scoliosis. Complete excision of the lesion is usually achieved by lobectomy, but segmentectomy may be used to preserve parenchyma for small lesions or if there is multiple lobe involvement. If elective surgery is performed during infancy, there may be potential for compensatory lung growth, but definitive evidence is lacking. Thoracoscopic surgery may decrease the risks of traditional open thoracotomy, such as scoliosis, rib crowding, injury to nerves and vessels, *etc.*, and thus may be preferable, but needs further evaluation and may not be available in all parts of the world.

In contrast, there are proponents of a "wait and see" approach, favouring a conservative approach citing many counterarguments to surgical intervention. For asymptomatic lesions, a recent meta-analysis of 41 series with 1070 patients suggests that the rate of infection among asymptomatic infants beyond the neonatal period is 3.2%, occurring at a median age of 7 months; thus it is claimed that the risks of post-natal

infection for asymptomatic lesions are exaggerated. Furthermore, these advocates suggest that the risks of future malignancy are small, there is no evidence for lung physiological improvement after early surgery, and the post-operative risks for surgery after respiratory infection in a few children do not justify exposing those children who may never develop symptoms to unnecessary surgery.

Whichever route is taken for management of asymptomatic CPAMs, it is important to ensure appropriate counselling of the parents by a multidisciplinary team and for full risk assessment of any surgical interventions to be balanced against the need for repeated CT scans and risk of loss to follow-up of patients. For an asymptomatic child who develops infection, the surgical risks and complications are marginally higher than those who undergo elective surgery, but the absolute risk of development of infection in an asymptomatic child has been poorly reported. Newer interventions, such as thoracoscopic surgery, are being introduced, but need to be fully assessed before they become routine, especially for asymptomatic CPAMs.

The natural history of CPAMs is not well defined. It is unclear what proportion of children with asymptomatic CPAM will develop symptoms in the future. Many reports of limited numbers of children suggest symptoms occur in up to 10%, but the duration of follow-up is often short. Criss *et al*. (2018) reported follow-up data, up to 19.8 years, of 39 infants (out of 140 CTMs identified between 2006 and 2016) with asymptomatic CTMs; 28 had CPAM and five had BPS. 13 (33%), all from the CPAM/BPS group, developed symptoms requiring surgery, especially pneumonia, at a median age of 6.8 years (range 0.7–19.8 years); thus, greater numbers may develop symptoms in the longer term, especially if the lesions are large. Although tumours such as pleuropulmonary blastoma, rhabdomyosarcoma and bronchoalveolar carcinoma are reported to occur with CPAMs, the true risk is unclear, as is whether the risk is decreased after surgery, especially in view of one report suggesting that it may not be (Papagiannopoulos *et al*., 2001).

Studies reporting physiological lung function in surgical survivors of symptomatic CPAMs were reviewed by Hall *et al.* (2017), reporting conflicting lung function data. From the limited data reported, TLC may be decreased equivalent to lung lesion volume reduction, normal, or even increased, but whether any increase represents compensatory lung growth or simple increased volume is uncertain. Newer methods such as hyperpolarised 3-helium or 129-xenon MRI scanning may help identify new compensatory lung growth. Other findings include decreased FEV_1 and increased RV. Clearly, further longitudinal studies are required to guide clinical management, including whether any existing inhaler treatment has a role to play.

Bronchopulmonary sequestrations

BPS can be intralobar (~80%) or extralobar (~20%), with the lesion comprising lung tissue with its own blood supply *via* an aberrant blood vessel and lacking continuity with the rest of the respiratory tract. Intralobar BPS predominantly occur in the posterior basal lateral segment of the left lower lobe in otherwise normal lung tissue. It has single or multiple systemic arterial supplies directly arising from the thoracic or abdominal aorta in 75% of the cases and venous drainage is usually into the pulmonary veins. Extralobar sequestrations are completely separated from the normal lung, invested by an individual pleura. The most common site is the left lower lobe, but they can occur anywhere in the lungs and even in subdiaphragmatic areas. In as many as 50% of cases, there are other associated abnormalities, including CPAMs, congenital cardiac anomalies, pericardial defects, pectus excavatum, bronchogenic cysts and vertebral anomalies. The blood supply is usually from the systemic circulation. BPS are the

most common differential diagnoses of CPAM; they each have distinct radiological, pathological and clinical characteristics. The main distinct characteristics are lack of communication to the tracheobronchial tree and the aberrant blood supply from systemic circulation. In some cases, features of both CPAM and BPS coexist in the same lesion, often termed hybrid lesions.

The treatment for both intralobar and extralobar BPS is surgical resection because of risks of haemorrhage, infection, arteriovenous shunting and late malignancy, but smaller lesions may be left alone or selectively embolised. The most essential step in surgery of these lesions is identification and control of systemic blood vessels. Unrecognised or uncontrolled bleeding from these vessels can be associated with serious morbidity or even mortality.

Summary

Although CTMs are rare, they are an important cause of respiratory distress in newborns and children. They are increasingly diagnosed antenatally, which allows for planning of intervention, delivery, *etc*., but which also introduces newer problems, particularly the management of asymptomatic lesions. While symptomatic lesions are amenable to surgical excision, the management of asymptomatic lesions remains controversial and both medical and surgical management needs to be balanced against the risks for each approach. New interventions are being introduced increasingly, but need careful evaluation not only in the short term, but also for long-term outcomes. However CTMs are dealt with, appropriate counselling of the parents with a multidisciplinary team is essential.

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Vascular malformations

Oliviero Sacco and Laura Petrarca

A wide spectrum of congenital anomalies can occur during the formation of the aortic arch, brachiocephalic arteries, pulmonary arteries and ductus arteriosus, due to the failure of embryonic structures to fuse and regress regularly. Knowledge of the normal embryonic development of the aortic arch and related structures is important in order to understand and classify the various form of vascular malformation.

During fetal development, six pairs of primitive aortic arches are formed sequentially and, as successive arches develop, the previous arches regress. The major persistent arches in humans are the fourth and sixth. The fourth arches contribute to a portion of the left aortic arch and of the right subclavian artery; the proximal portions of the sixth arches become the mediastinal segment of the pulmonary arteries, while their distal portions form the ductus arteriosus. Abnormal development of the aortic arch complex may represent an uncommon but potentially serious cause of variable degrees of compression of the trachea, bronchi and/or oesophagus, due to the formation of a vascular "ring" or "sling". Some of these anomalies, such as the double aortic arch and the right arch/left ligament, are anatomically complete rings,

Key points

- The clinical incidence of vascular malformations is ~1%, but the true incidence is difficult to assess if less severe abnormalities/compression are included.
- The most severe forms of vascular rings can be detected during the neonatal diagnostic work-up, cause serious symptoms in the newborn period and require surgery within the first year of life.
- The less severe abnormalities are detected in later life, when unexplained recurrent respiratory symptoms or occasional mild dysphagia lead to radiographic or endoscopic evaluation. Symptoms such as dyspnoea, wheezing and cough are often misdiagnosed as asthma, particularly if they occur in older children.
- The vascular malformations that most frequently cause symptoms are double aortic arch, right aortic arch with a left ligament arising from the descending aorta, aberrant subclavian artery, pulmonary sling, and aberrant innominate artery.

while others, *i.e.* anatomically incomplete or partial rings, are called slings, such as the pulmonary sling.

Clinical presentation and classification

In children with vascular abnormalities, the severity of the resulting respiratory disorder does not appear to correlate tightly with the degree of anatomical obstruction of the airways. Signs and symptoms at presentation are variable, including apnoeic spells, recurrent apnoeas, stridor/noisy breathing, chronic or recurrent cough, a brassy cough similar to a seal's bark, recurrent respiratory infections and dysphagia for solid foods.

The most severe forms of vascular rings can be detected during the neonatal diagnostic work-up by performing fetal echocardiography with colour Doppler imaging. The presence of any vessels coursing around and behind the trachea forming a U-, 6- or 9-shaped structure is a telling sign for the presence of a vascular ring. A vascular ring, particularly if associated with congenital cardiac malformations, can cause serious symptoms in the newborn period and require surgery within the first year of life. Less severe abnormalities are detected in later life, when unexplained recurrent respiratory symptoms or occasional mild dysphagia requires radiographic or endoscopic evaluation. Symptoms such as dyspnoea, wheezing and cough are often misdiagnosed as asthma, particularly if they occur in older children.

The true incidence is difficult to assess if we include less severe abnormalities/compression. Autopsy studies suggest that 3% of people have a congenital malformation of the aortic arch, but approximately two-thirds of cases remain undiagnosed. Here, we focus on the vascular malformations that most frequently cause symptoms (figure 1):

- Double aortic arch
- Right aortic arch with a left ligament arising from the descending aorta
- Aberrant subclavian artery
- Pulmonary sling
- Aberrant innominate artery

Double aortic arch

The most common and serious complete type of vascular ring is usually an isolated anomaly without associated cardiac malformation, but in ~20% of the cases is associated with congenital cardiac malformations, such as ventricular septal defect or tetralogy of Fallot, anomalies of the aortic arch, aortic branches, ductus arteriosus and pulmonary arteries. The distal chromosome 22q11.2 deletion syndrome or CATCH 22, associated with DiGeorge syndrome, is frequently found in these patients. It is due to the persistence of both fourth aortic arches encircling the trachea and oesophagus in a tight ring. In 75% of affected infants, the right-sided arch is dominant (larger and positioned higher than the left arch); in 20% the left arch is dominant; and in 5% the arches are equal in size (figure 2a and b). A portion of the left aortic arch can be atretic and persists only as a fibrous band. Each aortic arch passes over the ipsilateral principal bronchus and fuses behind into a common descending aorta, which is more commonly located on the left side of the spine. The ligamentum arteriosum is usually located between the distal part of the left arch and the left pulmonary artery, but may be present on both sides when the aortic arches are both patent. A plain/standard chest radiograph can give a suspicion of this anomaly, showing a right-sided aortic arch indenting the trachea

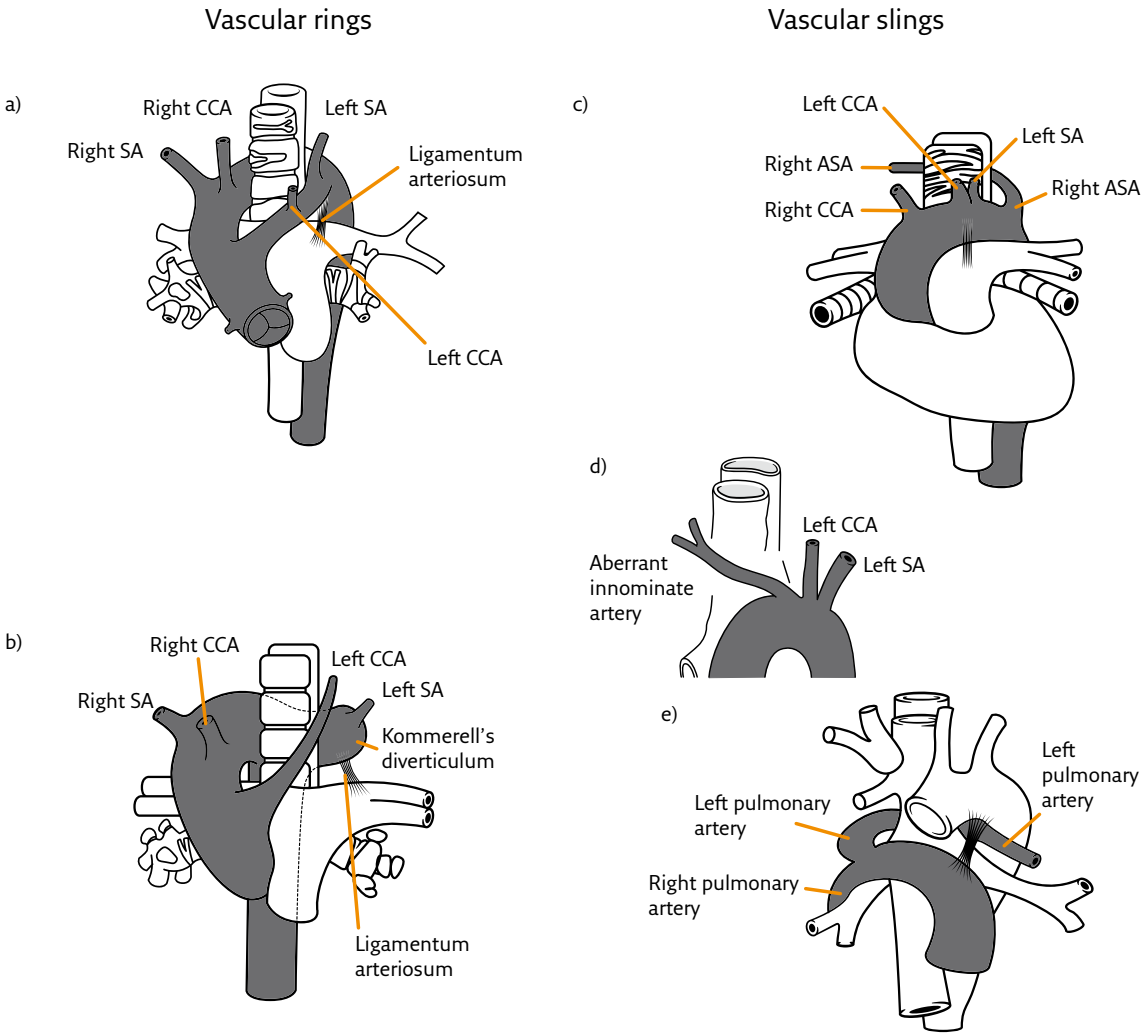

Figure 1. The vascular malformations that most frequently cause symptoms. Vascular rings: a) double aortic arch, b) right aortic arch. Vascular slings: c) aberrant subclavian artery (ASA), d) aberrant innominate artery, e) pulmonary sling. SA: subclavian artery; CCA: common carotid artery.

and an increased right paratracheal soft tissue thickness, or two aortic arches. A lack of air column in the thoracic portion of the trachea at the level of the vascular ring, or for a longer portion in case of segmental stenosis, is a sign more difficult to visualise. In any case, a "suspicious" standard chest radiograph must indicate a CT scan examination with contrast medium.

Children with this anomaly usually present with severe respiratory symptoms and some swallowing difficulty early in life. Surgical interruption of the smaller or atretic aortic arch and of the ligament is usually required. The most severe case of tight vascular ring can interfere with normal tracheal development; the tracheal lumen can show segmental stenosis with complete cartilaginous rings (figure 2e).

Right aortic arch

Comprising 12–25% of cases of vascular rings, a right aortic arch is usually associated with congenital cardiac malformations such as persistent truncus arteriosus, pulmonary atresia with ventricular septal defect, and tetralogy of Fallot. In this group of abnormalities, the regression of the embryonic structures involves the left aortic arch, resulting in the right arch lying to the right side of the trachea, passing over the right principal bronchus and generally continuing as the right descending aorta,

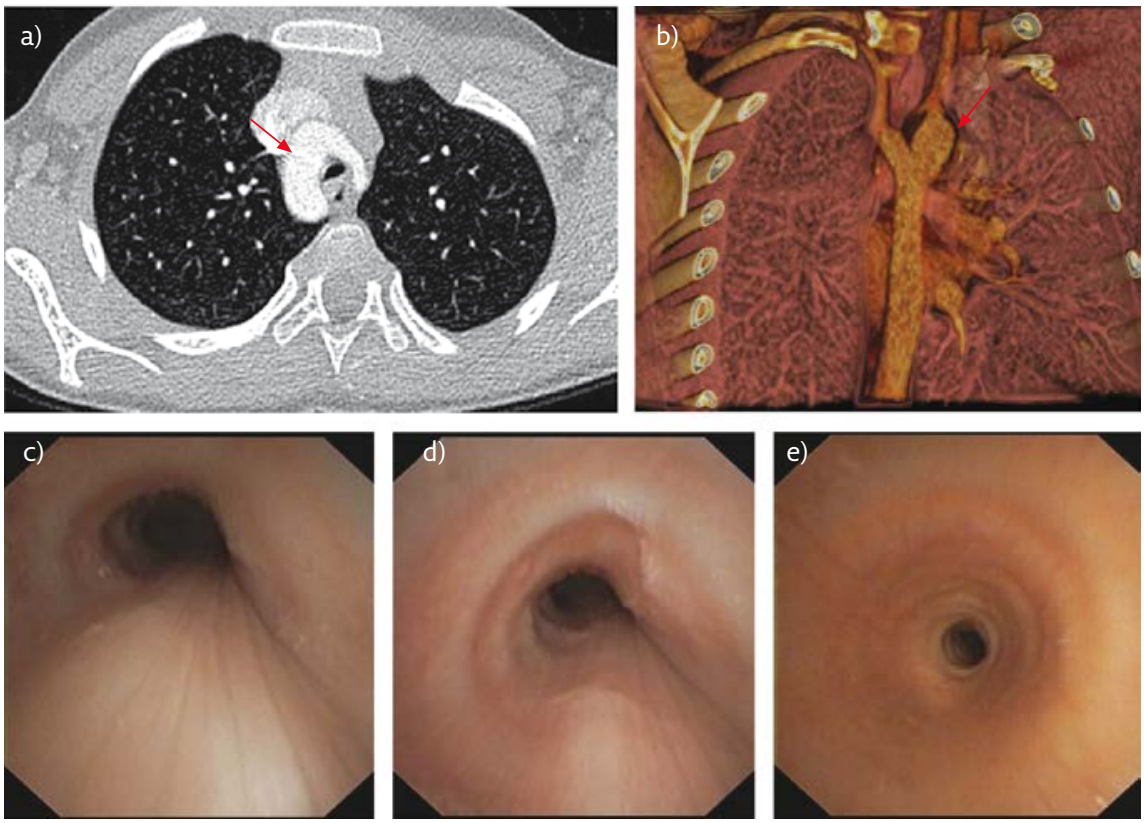

Figure 2. Multidetector CT a) axial view and b) three-dimensional imaging posterior view of right-sided dominant double aortic arch (arrows). c–e) Endoscopic images of double-arch compression of trachea, increasing severity; in e) the tracheal rings are complete or circumferential.

located to the right of the spine (figure 3a and c). A combination of a right aortic arch and a persisting left descending aorta results in a circumflex right aortic arch with a horizontal retro-oesophageal portion of the dorsal aortic arch, which contributes to the compression of trachea and oesophagus from behind (figure 4). The brachiocephalic vessels may originate as a mirror image of a normal left aortic arch, but many variants are possible. The association of a right aortic arch with a left ligament that passes from the left pulmonary artery to the descending aorta or to the left subclavian artery, coursing to the left of the trachea and oesophagus, describes a complete vascular ring around these structures. If the left fourth aortic arch regresses proximal to the left subclavian artery, a right aortic arch with an aberrant left subclavian artery as the last branch results. The artery passes behind the oesophagus and forms a complete vascular ring together with the left-sided ligamentum arteriosum.

The origin of the left subclavian artery from the descending aorta is frequently dilated, forming the so-called Kommerell diverticulum (figure 3a and c). In patients with a right aortic arch, the airway compression can be due to different mechanisms: vascular ring due to a left ligamentum arteriosum (figure 3b), enlargement of the Kommerell diverticulum and/or a midline/left descending aorta.

Aberrant subclavian artery

The most common among the aortic arch anomalies, aberrant subclavian artery occurs in nearly 1% of the population and in 25% of Down syndrome patients. Originally described by Bayford in the 18th century as “dysphagia lusus naturae” (dysphagia “freak of nature”), this anomaly most commonly involves the right subclavian artery or, rarely, the left subclavian artery when there is a right-sided aortic arch, as previously described. The aberrant subclavian artery originates as

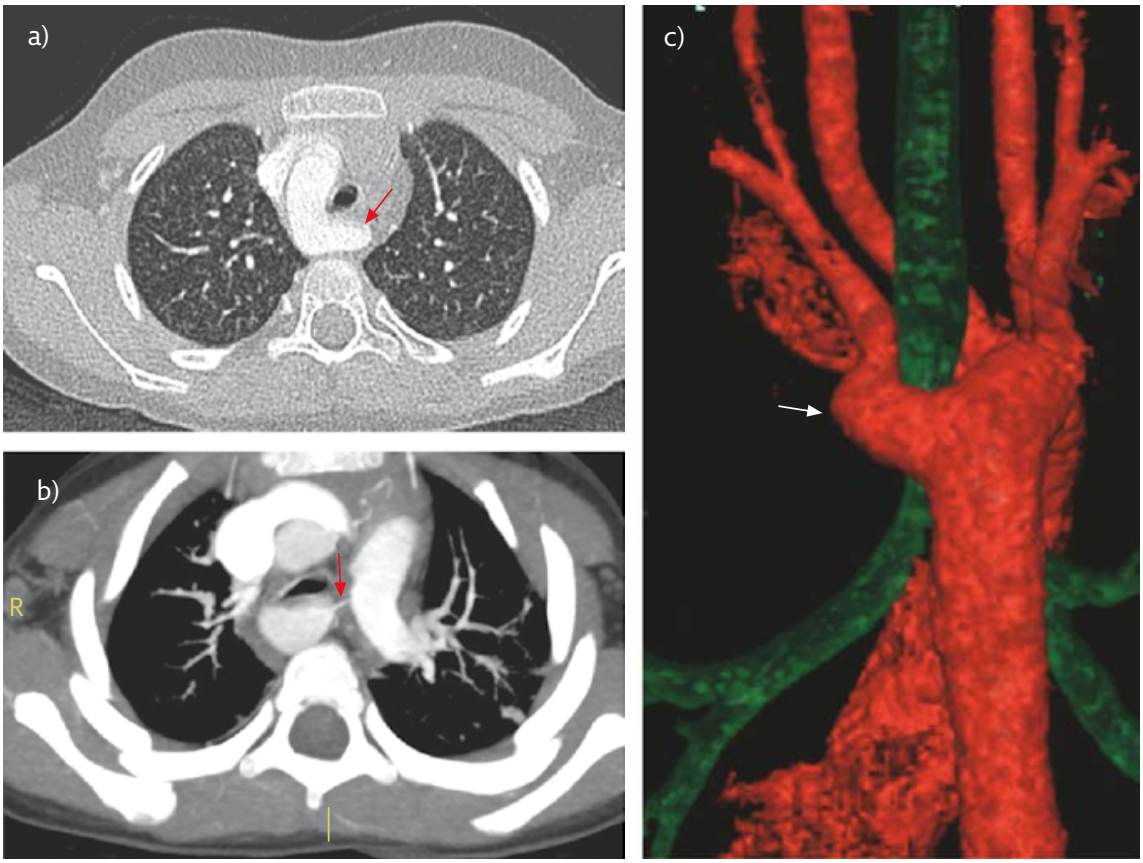

Figure 3. Multidetector CT imaging of right aortic arch. a) Kommerell diverticulum, axial view (arrow); b) rare image of ligamentum arteriosum, axial view (arrow); c) three-dimensional imaging of Kommerell diverticulum and aberrant left subclavian artery, posterior view (arrow).

the last vessel of the aortic arch and has an oblique course towards the other side, across the superior mediastinum, passing behind the oesophagus on its way to the upper extremity. An aberrant right subclavian artery as single malformation is rarely symptomatic, although in older children and in adults, mild dysphagia may be present due to compression of the oesophagus. However, an aberrant left subclavian artery, crossing behind the oesophagus as the last branch of a right aortic arch, forms a complete vascular ring together with a left-sided ligamentum arteriosum, and commonly causes symptoms due to compression of both the trachea and oesophagus.

Pulmonary sling

The embryonic origin of pulmonary artery sling occurs when the developing left lung captures its arterial supply from the right sixth arch through capillaries caudal, rather than cephalad, to the developing tracheobronchial tree. As consequence, the anomalous left pulmonary artery arises from an elongated right pulmonary artery, turns dorsally encircling the right main bronchus, and passes to the left between the trachea and oesophagus before entering the hilum of the left lung (figure 5a).

The airway may also be compromised by associated complete cartilage rings, the so called ring–sling complex present in 40–50% of cases, where the membranous portion of the trachea is absent and the tracheal cartilages are circumferential or "O"-shaped. Associated tracheobronchial abnormalities may occur, including tracheomalacia, hypoplasia and stenosis of long tracheal segments (figure 5b and c). Both the right main bronchus and the trachea are affected and compression by

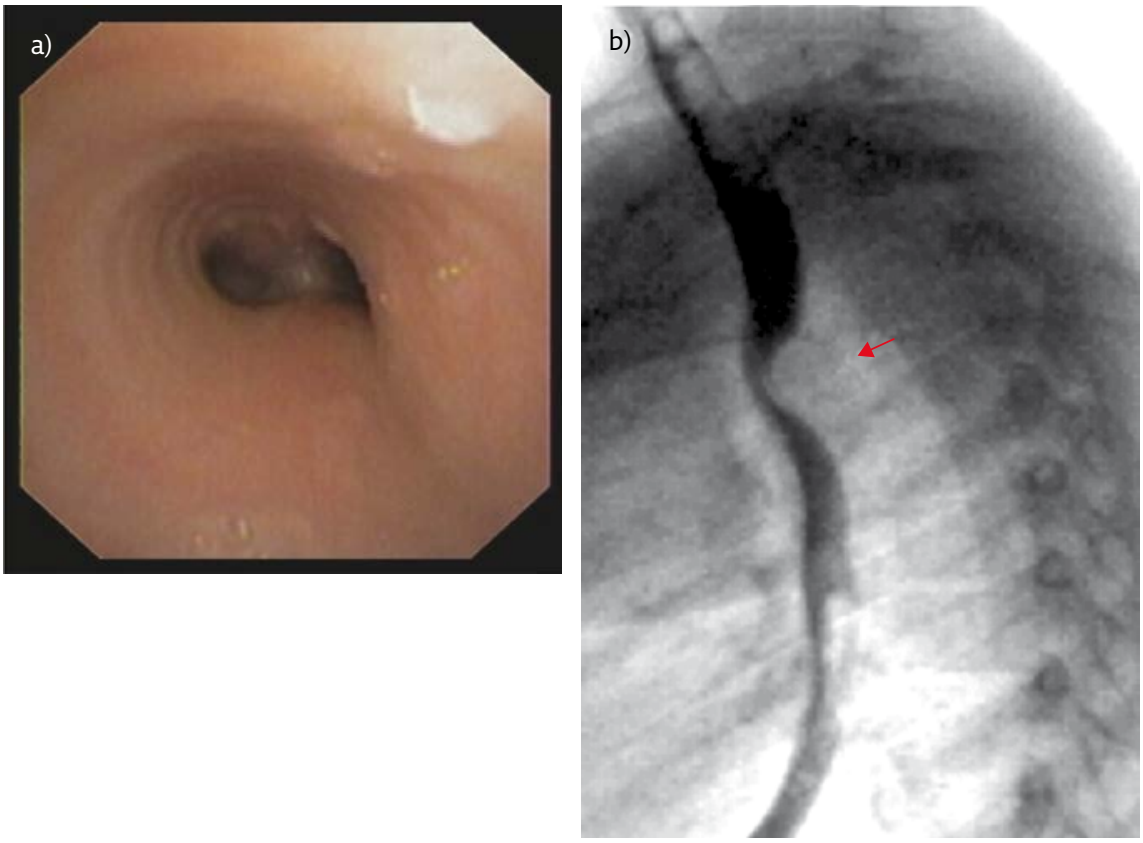

Figure 4. Vascular ring due to right aortic arch, aberrant left subclavian artery and left ligamentum arteriosum. The patient experienced mild dysphagia. a) Endoscopic image of tracheal lumen compressed on the right side; b) a persistent indentation can be seen on barium oesophagography from behind, lateral view.

the sling can result in hyperinflation or atelectasis of the right lung. Congenital heart defects are found in 50% of pulmonary artery sling cases, most commonly atrial septal defect, patent ductus arteriosus, ventricular septal defect and left superior vena cava. The left pulmonary artery sling can be associated with the presence of a bridging bronchus: a rare congenital bronchial anomaly where there is an anomalous bronchus to the right lung arising from the left main bronchus (figure 5d).

Aberrant innominate artery

Abberrant innominate artery causes tracheal compression of various degrees. Why an innominate artery, which arises from the aortic arch to the left and crosses in front of the trachea to the right side, should compress the trachea in some cases and not others is not well understood. In innominate artery compression patients, the artery appears to originate somewhat more posteriorly and leftward on the aortic arch than usual. This condition is more frequently symptomatic when associated with tracheomalacia and/or oesophageal atresia (figure 6). Severe compression of the trachea results in chronic or recurrent brassy cough, stridor, tachypnoea and recurrent respiratory infection. The most severe presentations in infancy include life-threatening events.

Diagnosis

Fetal ultrasound may detect malformation of several organs during the first trimester, including heart malformation and some aortic arch anomalies. As a consequence, the prenatal diagnosis of some aortic arch anomalies has become more common in

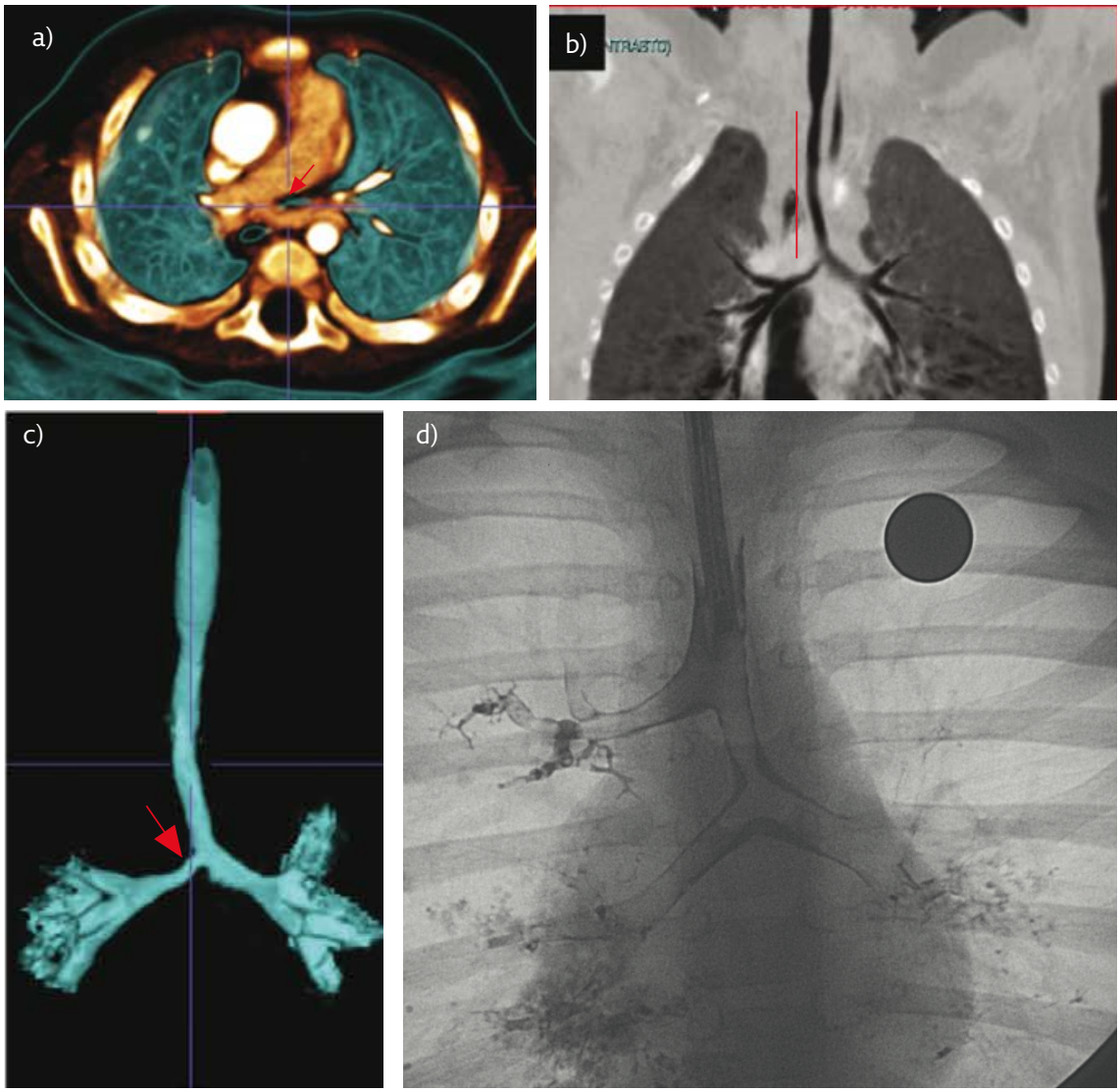

Figure 5. Multidetector CT imaging of pulmonary sling: a) anomalous left pulmonary artery (arrow) arises from an elongated right pulmonary artery, turns dorsally encircling the right main bronchus, and passes to the left between the trachea and oesophagus before entering the hilum of the left lung (axial view); b) associated long-segment tracheal stenosis: two-thirds of the trachea are stenotic and show complete cartilage rings (line) (coronal view); c) three-dimensional imaging of the trachea and bronchi: the origin of the right main bronchus is stenotic (arrow) due to compression by the anomalous left pulmonary artery. d) Tracheobronchography: an anomalous bronchus to the right lung arising from the left main bronchus: bridging bronchus. A left pulmonary artery sling was associated.

the past decade, due to the widespread use of fetal sonographic studies sufficient for delineation of the trachea, aortic arch, brachiocephalic arteries and ductus arteriosus. After birth, the presence of respiratory distress, wheezing, stridor, dysphagia and recurrent respiratory infection may require consideration of a vascular ring or sling as the underlying cause.

The historical approach was to perform chest radiography and barium swallow as the first step to evaluate children with suspected extrinsic compression of the airways, while conventional angiography was reserved for confirmation of the diagnosis. These studies have now been widely replaced by MRI and multidetector CT (MDCT). However, the recent literature demonstrates variability in the preferred diagnostic strategies for these conditions.

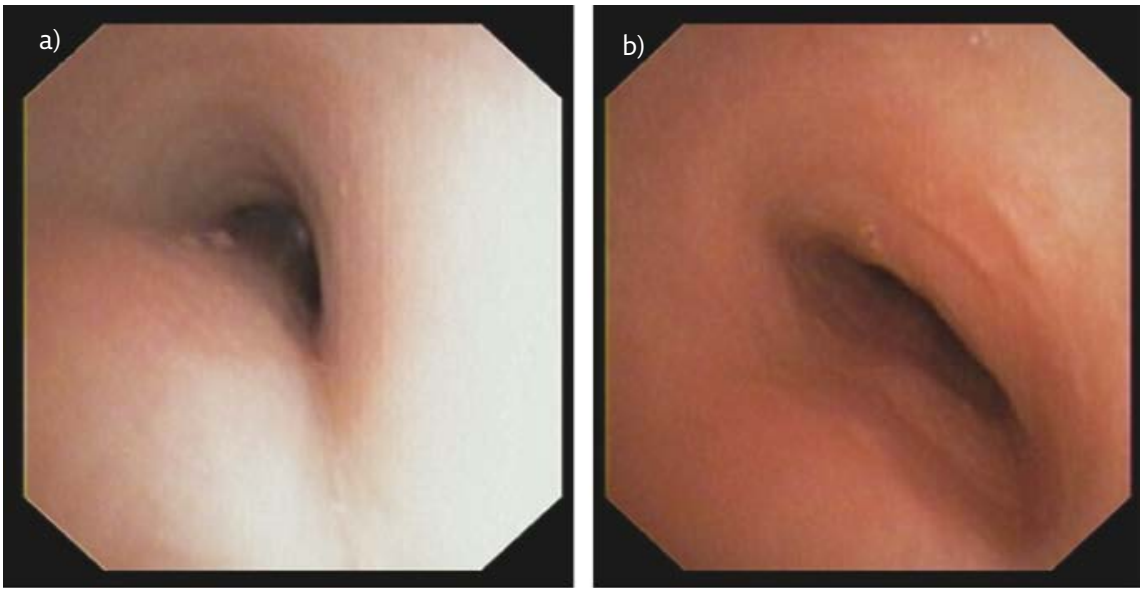

Figure 6. Tracheal compression by aberrant innominate artery in two patients aged a) 15 months and b) 20 months. a) Endoscopic image of tracheal lumen compressed on the front right side. Good vision of the tracheal rings is achieved and tracheal compression is visible without tracheomalacia. b) Patient with repaired oesophageal atresia and less well-delineated tracheal rings. The association of vascular compression and tracheomalacia caused a severe clinical picture with brassy cough, stridor and life-threatening events.

Chest radiography

In symptomatic patients, evaluation usually begins with frontal and lateral chest radiograph. On the frontal projection, the laterality of the aortic arch can be appreciated by its density and the side of the descending aorta by the presence or absence of the aortic stripe on the respective side. On the lateral projection, anterior bowing of the trachea and an increase in the retrotracheal density may also be appreciated. In pulmonary sling, chest radiographic findings include unilateral hyperinflation, tracheal narrowing and an unusual horizontal course of the left and right main bronchi, resulting in a "T-shaped" trachea. In any case, chest radiography can only arouse suspicion of the presence of a major vascular malformation.

Barium oesophagography

Upper gastrointestinal study has historically been reliable and remain an excellent technique for the diagnosis of a vascular ring, as the location of the aortic arch in relation to the oesophagus can be determined (figure 4b). Bilateral persistent indentations on the oesophagus on the anteroposterior view suggest a double aortic arch, while posterior indentation with an oblique course angled toward the left shoulder suggests an aberrant subclavian artery. Anterior pulsatile indentation of the oesophagus is virtually pathognomonic for pulmonary artery sling.

Echocardiography and angiography

Echocardiography has the advantage of a comprehensive assessment of intracardiac anatomy and function. However, it is limited by acoustic windows, a lack of depiction of airway/oesophageal involvement and high interobserver variability. Conventional angiography is invasive and is limited by high radiation dose and the need for iodinated contrast material.

Although the diagnosis of a vascular ring can be established or suspected with chest radiography and oesophagography, the exact configuration of the vascular abnormality cannot be fully defined with conventional radiology alone. The exact anatomy of an aortic arch malformation and its relationship to adjacent structures can be accurately defined only by cross-sectional imaging techniques, such as MRI and CT.

MRI and MDCT

Contrast-enhanced helical MRI or MDCT imaging allow excellent delineation of the aortic arch, its branches and their spatial arrangement. The multiplanar and three-dimensional imaging capabilities of magnetic resonance and CT noninvasive angiography have widely replaced other diagnostic techniques, such as the now obsolete catheter angiography. The direct multiplanar imaging capability of MRI allows accurate evaluation of vascular malformation and its relationships with adjacent organs and, possibly, associated intracardiac defects in a single sitting, without ionising radiation and iodinated contrast material. However, most MRI studies for vascular compression are quite prolonged (>30 min); the need for absolute immobility during image acquisition require general anaesthesia with controlled ventilation; and sedation risks are increased in children with compromised airways. Contrast-enhanced MDCT overcomes this disadvantage by allowing accurate imaging in very short scanning times, and mild sedation is sufficient in younger, uncooperative children. The disadvantage of MDCT includes ionising radiation and the need for iodinated contrast material; however, recent adjustment of specific techniques minimises the radiation dose. If assessment of the airways is important, MDCT is currently more reliable than MRI for the definition of the airway by multiplanar and three-dimensional image reconstruction (figures 2b, 3c and 5c), including virtual bronchoscopy, without appreciable respiratory artefacts. For both MRI and MDCT, the major diagnostic limit is that an obliterated vascular segment (*e.g.* the ligamentum arteriosum or an atretic aortic arch) can be visualised only rarely (figure 3b). The final decision to image with MRI *versus* MDCT should take into consideration availability of equipment and ease of scheduling, as well as the patient's ability to cooperate. In practice, the increase in speed and quality of multiplanar reconstruction provided by MDCT technology means that, increasingly, CT is used more often than MRI in most centres.

Bronchoscopy and bronchography

Despite the accuracy of both MRI and MDCT in evaluating the nature of the vascular compression of the airways, current MRI and MDCT techniques do not reliably distinguish between dynamic or static narrowing of the airways.

Such a distinction can have important clinical consequences, as many children with vascular malformation can have associated malacia of the compressed airway. Bronchoscopy and bronchography are still the best techniques to assess the presence of tracheo- or bronchomalacia (figure 6b). Bronchoscopy and bronchography are performed at the same time, injecting isotonic, nonionic contrast down the working channel of the flexible bronchoscope. Intraoperative tracheoscopy can be indicated in the aortopexy procedure, to evaluate the resolution of the tracheal collapse during the manoeuvres of suspension of the aortic arch. Bronchoscopy can be repeated 1–2 years after the surgical procedure to follow-up the airway malacia evolution.

Treatment and outcome

Vascular rings and slings inducing severe symptoms usually require prompt surgical correction. Prolonged severe vascular compression of the airways is more likely to induce severe malacia of the compressed airway and interfere with the growth of the trachea or bronchi. In most children, the problem is self-limiting and eventually the cartilage regains sufficient stiffness for the symptoms to resolve. This clinical observation suggests that the surgical procedure should be performed without delay in symptomatic patients. Children with a double aortic arch usually require surgical correction by resection of the nondominant arch and are at increased risk of remaining symptomatic later in life. It is important to assess the arch anatomy and the dominant arch before surgery because such assessment determines the operative approach. If there is an atretic portion of an arch, this is the obvious site for arch division.

A right aortic arch with a left ligamentum arteriosum and/or an aberrant left subclavian artery is reported even in asymptomatic children. Relief of symptoms such as dysphagia can be achieved by resection of the tight ligamentum arteriosum and/or excision of the Kommerell diverticulum. The intervention will be adapted to the variant of the anomaly and is aimed at decompressing the upper portion of the gastrointestinal tract or the lower respiratory tract (figure 7). In pulmonary sling, there is a strong association with long-segment congenital tracheal stenosis with complete tracheal cartilage rings. The surgical procedure is the re-implantation of the left pulmonary artery and, at the same time, a slide tracheoplasty to increase the tracheal calibre. Surgical treatment of patients with an aberrant right subclavian artery is almost never necessary; the artery has to be re-implanted only in the rare patients who have severe dysphagia.

Patients with tracheal compression by an aberrant innominate artery may have concomitant tracheomalacia rather than pure extrinsic compression; this is particularly frequent in children with oesophageal atresia. Symptoms tend to regress, at least partially, with age if tracheomalacia is not associated, and tracheoscopy can be useful to assess the malacia (figure 6b). Surgical correction, typically requiring aortopexy, is reserved for patients with severe symptoms, such as apnoeic spells in newborns or recurrent barking cough in older children; when the compression decreases the tracheal lumen significantly in resting state (quiet breathing); and/or

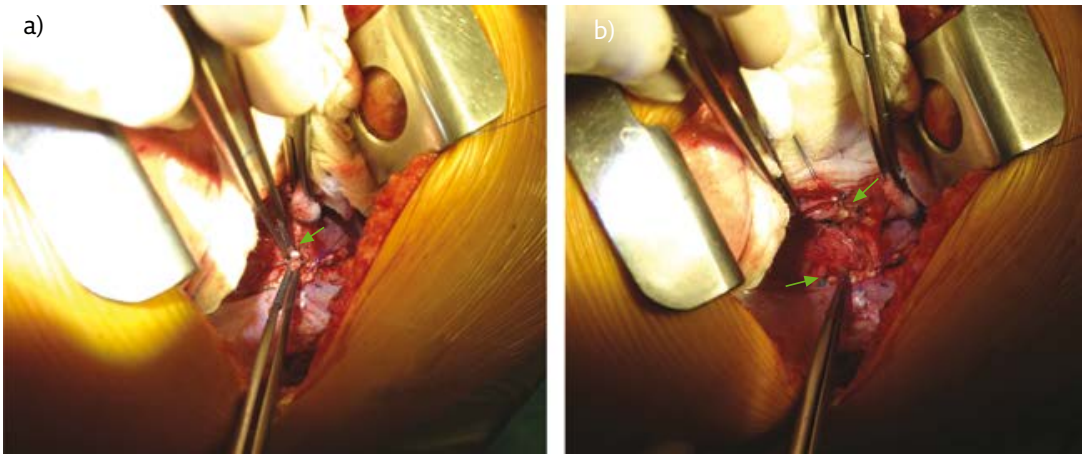

Figure 7. Vascular ring due to right aortic arch, aberrant left subclavian artery and left ligamentum arteriosum in the same patient as in figure 4. Intraoperative view: a) ligamentum arteriosum (arrow) resection; b) the two ends of the ligamentum (arrows) spontaneously move >1 cm away soon after resection.

when during cough the tracheal lumen completely collapses, impairing the ability to get rid of bronchial secretions. Intraoperative bronchoscopy is indicated to help the cardiosurgeon exert the correct traction of the aortic arch toward the sterum. The aortopexy procedure can induce significant clinical improvement in the majority of patients and is the treatment of choice. The need to proceed to tracheal stenting after aortopexy is reserved to the few cases with residual severe malacia. The new absorbable stents are preferred, particularly in paediatric patients, as a "bridge" solution until the wall malacia has improved. In patients dealing with recurrent lower respiratory tract infections even after aortopexy, particularly if a diagnosis of prolonged bacterial bronchitis has been made, courses of antibiotic therapy plus daily respiratory physiotherapy with a positive expiratory pressure device (mask) can induce a significant clinical improvement. An endoscopy to check the patency of the tracheal lumen and the disappearance of the signs of extrinsic compression by the innominate artery is generally performed 1–2 years after the aortopexy procedure.

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Epidemiology, aetiology, prevention, diagnosis, management and complications of BPD

Alice Hadchouel, Pierre-Henri Jarreau and Christophe Delacourt

Epidemiology and diagnosis

Despite considerable obstetric and neonatal advances in the care of very-low-birthweight infants, BPD remains the most common chronic respiratory disease in premature infants, and its treatment places major demands on health services. Epidemiological data greatly depend on the definitions used and the populations studied. Indeed, when collecting data from interventional studies aiming at preventing BPD, published in the past 15 years, rates varied from 25% to >60%. Data from the recent EPIPAGE 2 French cohort, including subjects born in 2011, report BPD rates of 26% for neonates born before 27 weeks post-menstrual age (wPMA) and 5% for neonates born between 27 and 31 wPMA. BPD seems to result from multiple factors that can injure the immature lung and interrupt normal alveolar and distal vascular development. Since 2001, the definition of BPD has been based on the evaluation of the need for supplemental oxygen at 28 days and 36 wPMA. The algorithm was completed in 2004 by an oxygen reduction test in order to standardise diagnosis among centres. The need for supplemental oxygen for at least 28 days but not at the evaluation at 36 wPMA defines mild BPD, whereas the need for oxygen at 36 wPMA defines moderate and severe BPD depending on the level of oxygen

Key points

- BPD is the main respiratory sequela of preterm birth and results from the conjugated effects of environmental and genetic factors that interact in an immature lung.
- Neonatal management is directed at minimising lung insults, by limiting oxygen toxicity and ventilator-induced lung trauma.
- Mid- and long-term respiratory follow-up is mandatory to detect clinical manifestations and lung function anomalies and test their reversibility, and to propose adapted treatments or simple monitoring.
- In the longer term, patients with BPD should be advised to participate in physical exercise, to abstain from passive and active smoking, and to avoid all other deleterious environmental exposures.

(<30% *versus* ≥30%, respectively) and the need for positive-pressure ventilatory support (intermittent or continuous). Moderate and severe BPD are associated with significant respiratory and neurodevelopmental morbidity. This definition may change in the coming years, since there have been substantial changes in the perinatal and neonatal management of preterm infants, particularly in respiratory support modalities available for preterm neonates. Two recent studies assessed several proposals for new definitions in order to determine the one that best predicts early childhood respiratory and neurological morbidity.

Aetiology and pathogenesis

The aetiology and pathogenesis of BPD have changed over time, owing to obstetric and neonatal advances in the care of very-low-birthweight infants. BPD was first described by Northway *et al*. in 1967 and was characterised by considerable airway lesions with extensive fibroproliferation, airway smooth muscle hyperplasia, areas of atelectasis and hyperinflation, and also reduced alveolarisation and pulmonary artery muscularisation. This disease occurred in less preterm babies with aggressive ventilatory strategies. This pattern referred to the so-called "old BPD". In the post-surfactant era, and with the resuscitation of more premature and lower birthweight babies, BPD pathological features have changed, and have moved to the "new BPD", the dominant lesion being alveolar hypoplasia, with fewer and larger alveoli, associated with an abnormal capillary vasculature, with lower than normal densities of capillaries and dysmorphic patterns of vascular organisation.

BPD is, above all, a disease of prematurity and immaturity and results from complex interactions between detrimental environmental factors and genetic susceptibility. Incidence of BPD is significantly increased when gestational age and birthweight decrease. Mechanical ventilation that induces lung trauma, high oxygen exposure, inflammatory response, post-natal infection and increased pulmonary blood flow due to persistent ductus arteriosus or high water intakes are the main risk factors for BPD. These factors have largely been studied in animal models and human epidemiological studies. The role of chorioamnionitis is still debated, with some epidemiological studies in favour of a protective role and some others in favour of a detrimental role. From the pathophysiological point of view, it might be a question of the time-frame of when the infection occurs, leading either to accelerated lung maturation or, alternatively, favouring alveolar disruption.

Besides the well-recognised detrimental effects of perinatal aggressions, genetic factors play also an important role in the occurrence of BPD. Genetic susceptibility was first suggested by the results of twin concordance studies. Following this, many candidate gene studies, genome-wide association studies and exome sequencing studies have been published, with variable but interesting results, pointing to new pathways and players in alveolar development and growth.

Prevention and care in the neonatal period

There is, to date, no curative treatment for BPD. Minimising aggressions in the neonatal intensive care unit constitutes the main approach to preventing the development of BPD. Before birth, prevention of premature delivery is of course essential. Antenatal steroids given to the mother to accelerate lung maturation, and instillation of exogenous pulmonary surfactant to the neonate have proven efficiency for the prevention and treatment, respectively, of neonatal respiratory distress syndrome. Nevertheless, these two approaches appear to have little impact on the prevalence of BPD.

Regarding oxygen exposure, a meta-analysis published in 2011 showed an overall reduction of 25% in the incidence of BPD at 36 wPMA for low-S_{pO_2} target groups, but with increased mortality and enterocolitis rates. Recently, the results of the BOOST-II trial were published and confirmed that the use of an S_{pO_2} target range of 85–89% *versus* 91–95% significantly decreased the risk of BPD at 36 wPMA but also significantly increased the risk of death or disability at 2 years of age and of death alone in *post hoc* combined analyses.

Ventilation strategies have been widely studied and no specific strategy seems to result in any significant reduction in BPD so far. Nevertheless, it may be difficult to evaluate and measure the effect of a single intervention in the setting of a multifactorial disease. The strategies studied have included NIV, volume-targeted ventilation and high-frequency oscillatory ventilation. These strategies probably at least prevent the occurrence of severe ventilation-induced lesions.

Although the risk of BPD is associated with persistent ductus arteriosus, there is no demonstrated effect of its treatment on BPD development. Similarly, the use of fluid restriction is not associated with a significant reduction in BPD.

The use of systemic steroids in the neonatal period is not recommended as routine, owing to the deleterious effects on neurological development. Their use should be restricted to exceptional clinical circumstances at minimal dosages during a limited time (~3 days). The 2019 updated European Consensus Guidelines recommended that "A short tapering course of low dose or very low dexamethasone should be considered to facilitate extubation in babies who remain on mechanical ventilation after 1–2 weeks". The recently published National Institute for Health and Care Excellence (NICE) guidelines on neonatal respiratory care for babies born preterm recommend considering "dexamethasone to reduce the risk of BPD for preterm babies who are 8 days or older and still need invasive ventilation for respiratory disease", the decision being made by taking into account the known risk factors for BPD and after having discussed the possible benefits and harms of this treatment with the parents. In 2016, Baud *et al*. published a double-blind placebo-controlled trial that studies the effect of intravenous low-dose hydrocortisone during the first 10 post-natal days in babies born at <28 weeks of gestation. The rate of survival without BPD at 36 wPMA was significantly increased by prophylactic low-dose hydrocortisone, without statistically significant difference in neurodevelopment at 2 years of age.

Regarding inhaled steroids, a meta-analysis published in 2012 did not show any effect on the prevention of BPD for late administration of inhaled steroids (after the first week of life). However, two recent trials showed a significant effect of early administration of inhaled budesonide on BPD outcome. The NEUROSIS trial showed lower rates of BPD in the treated group *versus* placebo but with an increased mortality. The second trial compared early intra-tracheal administration of budesonide and surfactant *versus* surfactant alone and showed a decreased rate of BPD in the combined treatment group. Nevertheless, the long-term effects of these treatments have not yet been evaluated. The 2019 Updated European Consensus Guidelines recommended that "Inhaled budesonide can be considered for infants at very high risk of BPD".

Vitamin A has appeared to reduce the incidence of BPD by a small amount, but the drug needs to be administrated by intramuscular injection. Consequently, its use is not widespread. Several studies demonstrated that early caffeine administration (usually before 3 days of life) can reduce the risk of BPD. Inhaled nitric oxide did not reduce the rate of BPD in a multicentre international study. Intra-tracheal instillation

of mesenchymal stem cells might be a promising treatment in BPD. Such treatment improves alveolar lesions in rats exposed to hyperoxia. A phase I dose-escalation clinical trial performed in nine preterm neonates showed that this treatment was safe and feasible, and BPD severity was lower in the transplant recipients. Further studies are expected to confirm these results and to evaluate the effect on the incidence of BPD.

Medical care after discharge

After discharge home, the main measures in infants with BPD are:

- Oxygen supplementation at home when necessary
- Avoidance of community day care, in order to avoid upper and lower airway infections
- Anti-influenza immunisation (from age 6 months)
- Palivizumab when indicated
- Avoidance of tobacco smoke exposure
- Nutritional support if needed
- Monitoring of growth and feeding, respiratory and cardiac signs, and neurocognitive factors

Systematic investigations are not necessary, but paediatric pulmonologist advice is required when there are difficulties with weaning from oxygen, or permanent respiratory symptoms.

Oxygen weaning has to be closely monitored by pulse oximetry recording after discharge home and at home if the child needs home oxygen therapy. The American Thoracic Society recently published home oxygen therapy guidelines for children and recommended home oxygen therapy for children with BPD with chronic hypoxaemia, defined as either 1) ≥5% of recording time spent with S_{pO_2} ≤93% if measurements are obtained by continuous recording, or 2) at least three separate findings of S_{pO_2} ≤93% if measurements are obtained intermittently.

Treatment with inhaled steroids should only be considered in infants with wheezy symptoms.

Mid- and long-term consequences of preterm birth and BPD

Preterm birth and BPD are associated with an increase in re-hospitalisations for respiratory causes in the first 2 years of life. Preterm birth and BPD are also associated with an increase in prevalence of school-age asthma symptoms, with a two- to 2.5-fold increase in preterm-born children with former BPD. This increase persists into adulthood, with more respiratory symptoms in preterm-born adults and a worsening effect of BPD. Exercise dyspnoea is also more frequent and is probably related to a mixed effect of respiratory and peripheral muscular limitations. Regarding lung function tests, the main finding is a decrease in FEV_1 values in children and adults with former BPD. In the largest meta-analysis published, the mean difference for % predicted FEV_1 compared with term-born controls for the preterm-born group with BPD at 36 wPMA was –18.9%. FEV_1 was also significantly reduced in the preterm-born group without BPD as compared to controls (–7.2%). Therefore, preterm birth, especially with BPD, may cause predisposition to COPD in adults. Chest CT scan anomalies exist and also persist through adulthood. The principal lesions are linear opacities, subpleural triangular retractions, air trapping and small cysts (figure 1). These lesions are associated with the severity of neonatal history (duration of oxygen supply or of mechanical ventilation) and with the subjects' current lung function variables, but not with their current symptoms.

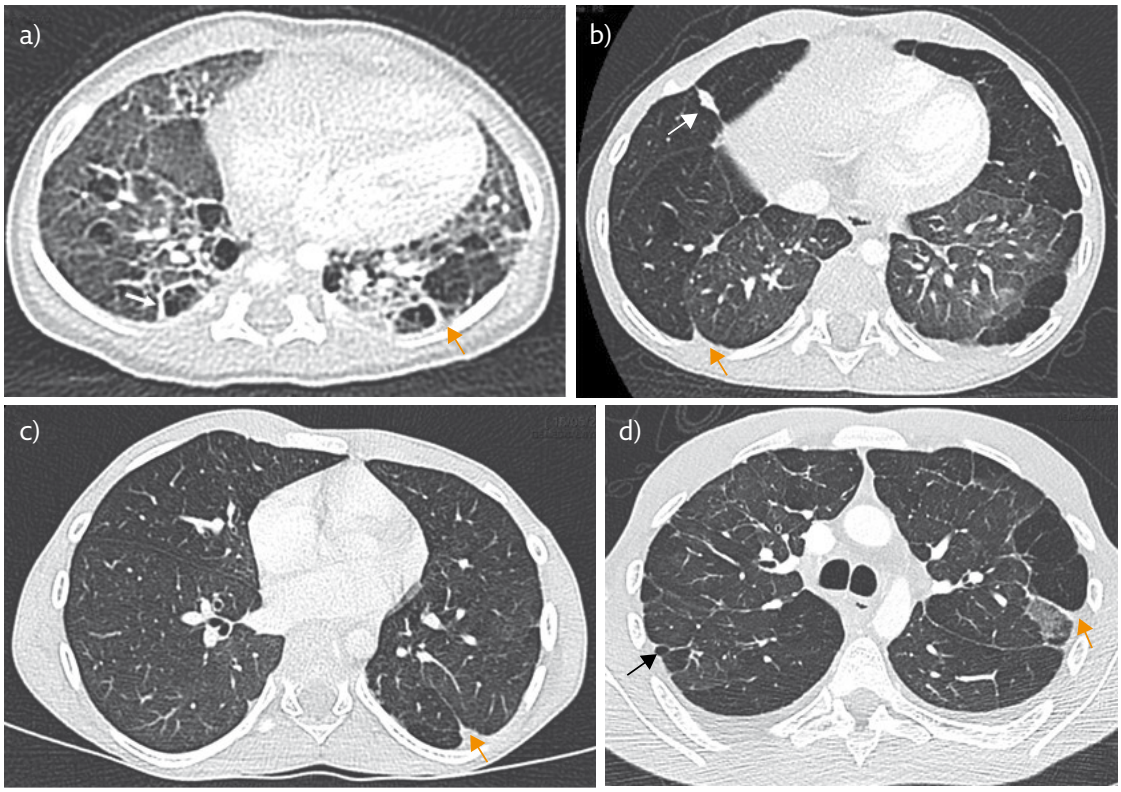

Figure 1. Characteristic imaging features of BPD on chest CT scans. Axial parenchymal views. a) 4-month-old infant. b) 3-year-old child. c) 9-year-old child. d) 19-year-old young adult. Note the mosaic pattern with hyperlucent and poorly vascularised areas. Orange arrows: subpleural triangles; white arrow: fibrotic retraction bands; black arrow: subpleural cyst.

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Long-term respiratory outcomes of BPD

Laura Moschino, Charles C. Roehr and Eugenio Baraldi

Chronic lung disease of infancy comprises a heterogeneous group of disease entities that evolve as consequences of prematurity and neonatal respiratory disorders. The most common form of chronic lung disease of infancy is BPD. Advances in obstetric and neonatal management have led to an increase in survivors of preterm birth. The widespread use of antenatal corticosteroids and exogenous surfactant administration, together with the growing use of NIV, have determined better overall outcomes of preterm infants. Nevertheless, as a result, BPD still accounts for a high rate of prematurity-related morbidity, affecting up to 40% of very preterm infants born at <28 gestational weeks. Although BPD was originally described as a consequence of prolonged oxygen exposure and mechanical ventilation, sadly this condition may now also be found in survivors of preterm birth who have never received mechanical ventilation.

The most commonly adopted definition of BPD is the one developed by Jobe and Bancalari in 2001, which classifies BPD as mild, moderate or severe according to the amount of supplemental oxygen (<30% *versus* ≥30%) and the mode of respiratory support administered at 36 weeks post-menstrual age (wPMA) to very preterm infants

Key points

- BPD is the most common chronic lung disease of infancy, accounting for about 40% of survivors of very preterm birth.
- Prematurity, especially when associated with BPD, is a cause of frequent hospitalisation over the first 2 years of life, most commonly due to respiratory infections (such as from respiratory syncytial virus).
- Typical symptoms that can be experienced in preschool and school age are cough, wheezing and, later, asthma-like symptoms with reduced exercise tolerance. The pulmonary picture may be worsened by the presence of pulmonary arterial hypertension, which, however, tends to progressively resolve with lung growth.
- Preterm infants with or without BPD present an airflow limitation from early years up to mid-adulthood, showing a tracking of lung function over time. However, those without BPD usually fare better than those affected by BPD. This characteristic is regardless of the type of BPD ("old" *versus* "new") and raises concerns for the potential development of a COPD-like phenotype in adulthood.

treated with supplemental oxygen for at least 28 days. However, these widely used criteria may not reflect contemporary neonatal respiratory care, which includes the use of the increasingly popular application of high-flow nasal cannula therapy. For this reason, in October 2016, the National Institute of Child Health and Human Development (NICHD) in the USA suggested a refined definition of BPD, as shown in table 1.

Thus, it has been recognised that commonly used criteria for diagnosing BPD may not adequately predict later childhood respiratory outcomes. A recent analysis of 18 pre-specified BPD definitions identified BPD according to treatment with respiratory support at 36 wPMA (no BPD, no support; grade 1, nasal cannula ≤2 L·min^{-1}; grade 2, nasal cannula >2 L·min^{-1} or noninvasive positive airway pressure; grade 3, invasive mechanical ventilation), irrespective of level of oxygen therapy, to be the best predictor of death or serious respiratory morbidity at 18–26 months corrected age. Given the long-standing respiratory impairment of preterm infants with BPD, future studies should assess the validity of new diagnostic criteria able to predict respiratory symptoms and lung function in later life, in order to optimise medical and ancillary support systems for those who need it most.

Morbidity associated with BPD

Oxygen requirement

About one third of infants with BPD may require oxygen supplementation on discharge from neonatal intensive care units. Lower gestational age, as well as gastrostomy tube feeds or Nissen fundoplication, may be associated with later weaning from oxygen. However, very few individuals remain oxygen dependent beyond 1 year of age, the median age of weaning usually lying between 5.5 and 8.0 months. To date, the most commonly employed safety method for weaning from supplemental oxygen remains overnight PSG.

In the most severe cases, however, when chronic respiratory insufficiency impedes growth and psychomotor development, chronic invasive ventilation *via* a tracheostomy may help facilitate neurodevelopmental progress and can lead to an improved long-term outcome.

Table 1. Refinements to the BPD definition for premature infants (<32 gestational weeks)

Grades	Nasal cannula flow <1 L·min^{-1}	Hood O_2	Nasal cannula flow 1–3 L·min^{-1}	nCPAP, NIPPV or nasal cannula ≥3 L·min^{-1}	Invasive IPPV
I	22–70	22–29	22–29	21	
II	>70	≥30	≥30	22–29	21
III				≥30	>21
III (A)	Early death (between 14 days of post-natal age and 36 wPMA) owing to persistent parenchymal lung disease and respiratory failure that cannot be attributable to other neonatal morbidities (*e.g.* necrotising enterocolitis, intraventricular haemorrhage, redirection of care, episodes of sepsis)				

Data are given as inspiratory oxygen fraction ranges or oxygen concentrations (%) required at 36 wPMA for ≥3 consecutive days to maintain in the 90–95% range, for infants with BPD as persistent parenchymal lung disease on radiographic confirmation. nCPAP: nasal CPAP; NIPPV: noninvasive positive-pressure ventilation; IPPV: intermittent positive-pressure ventilation. Reproduced and modified from Higgins *et al.* (2018) with permission.

Hospitalisation

Approximately one in three infants born preterm (<32 gestational weeks) will be hospitalised with respiratory problems in the first 2 years of life, mainly due to symptoms like cough, wheeze and food aversion, predominantly in concomitance with infections. This rate may vary between 40% and 25% in the first and second years of life, respectively. Respiratory morbidity (primarily caused by respiratory syncytial virus (RSV) infection) accounts for the majority of these hospitalisations. This is thought to be due to preterm infants' immature humoral and adaptive immunity. However, since the introduction of prophylaxis with monoclonal antibody (palivizumab), studies have shown a reduction in RSV-related hospitalisations. Prevention of RSV infection is of utmost importance for highly selected populations to avoid respiratory morbidity and mortality. RSV vaccines, as well as antivirals and new monoclonal antibodies, are currently under investigation.

Respiratory symptoms

Compared with term-born infants, infants born prematurely, and survivors of BPD in particular, experience more respiratory symptoms in childhood. In a large meta-analysis from 2014, preterm birth was associated with a 1.7-fold higher risk of childhood wheezing disorders, this risk increasing up to three times when very preterm children were considered. RSV-related lower respiratory tract infections again represented an important risk factor for childhood recurrent wheezing.

Although cough and wheeze are very common at preschool age (in up to 80% and 44%, respectively, of preterm infants born at <37 gestational weeks, in the first year of life), the clinical condition of BPD survivors generally improves with time, but respiratory symptoms may remain very common even at school age.

Asthma-like symptoms, due to a component of reactive airway disease, may be present. It has been speculated that for children born at <26 gestational weeks the incidence of asthma at 11 years of age is approximately 25%. Nevertheless, children with BPD and asthma-like symptoms are less likely to demonstrate airway hyperresponsiveness or response to bronchodilators, as they appear to suffer from fixed peripheral airway narrowing and may show an exacerbated wheezing with the use of bronchodilator therapy due to comorbid broncho- and tracheomalacia. Data on defined lung pathology are scarce, but studies on exhaled nitric oxide and HRCT have documented differences in both biomarkers and morphology in the lungs of children with asthma and of those with BPD. Thus, patients with BPD should not be diagnosed as asthmatic, and they may require different treatments.

Encouragingly, symptoms progressively subside in most survivors of BPD in adolescence, and most of these survivors will lead apparently normal lives. The relationship between clinical symptoms and lung function fades, and even patients with severe airway obstruction, detected by spirometry, may not have any clinically significant respiratory symptoms.

Exercise intolerance and response to hypoxia

Survivors of BPD may experience exacerbation of pulmonary morbidities with exercise. Indeed, these subjects may present exercise-induced bronchoconstriction and altered ventilatory response and aerobic capacity during exercise compared to healthy children. Follow-up studies in BPD survivors have demonstrated lower maximal oxygen consumption and $\dot{V}'_E$, decreased running time, and a ventilator pattern characterised by lower tidal volumes, with consequent hypoxaemia and

alveolar hypoventilation. The larger drops in FEV_1 and abnormal ventilatory reserve during exertion may lead to exercise intolerance relating to reactive airway disease and compromised gas exchange with physical activity. These, in turn, may be attributed to long-term derangements in pulmonary structure or residual right ventricular dysfunction affecting cardiac output.

Preterm-born adults with or without BPD may show an abnormal response to hypoxia exposure as well, due to a dysmature function of carotid chemoreceptors. Specifically, normal responses of increased ventilation with hypoxia or decreased ventilation with hyperoxia may be altered. Interestingly, the infants with the most severe disease seem to experience the smallest change in ventilation in response to acute hypoxia. The picture may be worsened by the coexistence of central airway disease, bronchomalacia and abnormal respiratory muscle function. Furthermore, these underappreciated abnormalities in ventilatory control may have important clinical consequences, for instance an increased risk of disordered breathing during sleep and in response to high altitude and anaesthesia.

Pulmonary arterial hypertension

The clinical course of extremely preterm infants with BPD can be worsened by concomitant pulmonary arterial hypertension (PAH). A recent systematic review and meta-analysis has shown a pooled incidence of PAH of 17% in BPD of any severity and of 24% in moderate–severe cases, with higher odds of mortality in those affected. PAH in BPD subjects arises from the combination of altered vascular development (pulmonary angiogenesis disrupted by premature birth), function (hypoxia-related increases in vascular tone and reactivity) and structure (vascular remodelling with smooth muscle cell proliferation). However, preterm infants *per se* exhibit abnormal right ventricle performance (measured by pulmonary artery acceleration time (PAAT)) at 32 wPMA, suggesting a less developed intrinsic myocardial functional response following preterm birth. While preterm infants subsequently show a progressive increase of PAAT to 1 year corrected age, reflective of the physiological post-natal drop in right ventricular afterload, BPD and PAH have a negative impact on PAAT measures.

To address the lack of consensus care guidelines and marked differences regarding optimal diagnosis, evaluation and management of BPD-PAH, in 2017 the Pediatric Pulmonary Hypertension Network (PPHNet) published a report presenting consensus recommendations for the care of children with BPD-associated PAH. Table 2 shows the report's summary of recommendations on diagnosis, management, follow-up and treatment of PAH in BPD infants.

Infants with PAH and BPD should be cared for by a multidisciplinary team (involving respiratory, cardiac and nutritional care, as well as physiotherapy) and have outpatient follow-up at intervals of 3–4 months, including echocardiography, biomarkers, haemodynamic studies and sleep studies when indicated, depending on disease severity and clinical progress. By the time BPD patients with PAH reach school age, pulmonary vascular resistance and pulmonary arterial pressure appear to return to normal in most cases, although pulmonary vascular reactivity to hypoxia may often persist into adolescence and adulthood. Currently, there is limited evidence on the appropriate duration of PAH therapies in this population. If the PAH gradually resolves with lung growth, medications can be gradually tapered. However, continued monitoring for new respiratory signs, exercise intolerance or reduced activity will be necessary. A repeat echocardiogram is recommended after stopping PAH medications, usually within 1–2 months.

Table 2. Summary of the consensus recommendations on diagnosis, management, follow-up and treatment of PAH in BPD infants by the 2017 PPHNet

Patients who should be screened for PAH by echocardiogram
Preterm infants with severe hypoxaemic respiratory failure shortly after birth attributed to PPHN physiology
Preterm infants with continued need for ventilator support at post-natal day 7
Preterm infants with sustained need for significant respiratory support at any age
Preterm infants at 36 wPMA (time of BPD diagnosis)
Echocardiogram evaluation
Complete anatomic evaluation for structural abnormalities, shunts and pulmonary veins
Right and left ventricular size, hypertrophy, systolic and diastolic function
Systolic and diastolic interventricular septal position
Tricuspid and pulmonary regurgitation jet velocities (when present)
Simultaneous systemic blood pressure documentation
Indications for cardiac catheterisation
To confirm diagnosis
To determine disease severity
To evaluate contributions of shunt lesions
To define the need for combination drug therapy
PAH definition and severity
Absent PAH: estimated sPAP <1/2 SAP
Mild–moderate PAH: estimated sPAP <1/2–2/3 SAP
Severe PAH: estimated sPAP >2/3 SAP with septal flattening or right-to-left shunt across the ductus arteriosus
Treatment options
Supplemental oxygen for target 92–95% to decrease pulmonary artery resistance
Inhaled nitric oxide for acute PAH crisis
Sildenafil (phosphodiesterase-5 inhibitor)
Bosentan (endothelin receptor antagonist)
Milrinone (phosphodiesterase-3 inhibitor)
Important: wean from oxygen and inhaled nitric oxide only gradually and after stabilisation
Follow-up
Baseline and serial BNP or NT-proBNP to monitor disease progression/regression and response to therapy, in conjunction with echo evaluation

PPHN: persistent pulmonary hypertension of the newborn; sPAP: systolic pulmonary artery pressure; SAP: systemic arterial pressure; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP. Data from Krishnan *et al.* (2017).

Lung function

Lung function measurements can be obtained from infants with evolving or established BPD up to adulthood (table 3). Early studies highlighted that lung compliance and FRC improved with increasing age, such that by 2 years of age these had reached the normal range. In contrast, airflow limitation appears to be a persisting issue in preterm subjects with and without BPD. The analysis of forced expiratory flows (obtained with infant forced expiratory manoeuvres) has revealed

Table 3. Suggested lung function tests to be performed in subjects with evolving or established BPD (in newborn period and infant age) and to follow up (in childhood, adolescence and adulthood)

Lung function test and suitable age group	Description	Advantages	Disadvantages
Newborn period and infant age			
Ventilator graphics	Real-time display of continuous measurements of pressure, flow and volume change on cot side (flow–volume and volume–pressure loops)	Pattern recognition is used to identify specific pathophysiological situations (airway obstruction or excessive inflation pressure, changes in lung compliance)	Does not yield exact numerical values
Tidal flow–volume (TFV) loops	Ratio of time to peak tidal expiratory flow to expiratory time (t_{PTEF}:t_E)	Sedation is not required	Variability
Inert gas washout (helium, sulfur hexafluoride, nitrogen) or multiple-breath washout	Measurement of FRC and gas mixing efficiency (LCI), which is a mark of ventilation inhomogeneity	Can be applied in intubated infants with or without sedation; sulfur hexafluoride less susceptible than helium to leaks	FRC may be underestimated if insufficient time is allowed for complete equilibration; nitrogen washout impractical for ventilated infants receiving high inspiratory oxygen fraction
Whole-body plethysmography	Measurement of FRC and total lung volume	If used in conjunction with a gas dilution technique, can provide an assessment of hyperinflation and gas trapping	Systems depend on electronic manipulation to close the pressure–flow loop (possible erroneous results); not suitable for cot-side measurements; possible overestimation of lung volume
Passive mechanics, single-breath occlusion	Measurements of resistance and compliance of the lung or the entire respiratory system	Can be used in both spontaneously breathing and ventilated neonates and infants	Requires airway occlusion, but the small endotracheal tubes may invalidate attempts to detect small changes in resistance

(*Continued*)

Table 3. Continued

Lung function test and suitable age group	Description	Advantages	Disadvantages
Raised volume rapid thoracoabdominal compression (RVRTC) technique	Most commonly used method to assess airway function in infants, measuring V'_{max} at FRC	Possibly a more sensitive means of discriminating changes in airway function in infants with respiratory disease	Dependent on lung volume; requires sedation
Forced oscillation technique (FOT)	Measurements of the respiratory system mechanics (impedance, resistance and reactance)	Can be applied during invasive and noninvasive ventilator support	Few data available
Preschool age (2–5 years)			
Forced oscillation technique (FOT)	Measurements of the respiratory system mechanics (impedance, resistance and reactance)	Noninvasive technique performed during tidal breathing requiring minimal cooperation; the within-breath analysis can detect airway obstruction	
Interrupter resistance (R_{int}) technique	Measurement of respiratory resistance during tidal breathing	Quick, noninvasive; can be performed in preschoolers who are not collaborative enough to perform spirometry; can assess bronchodilator response	
Children (>5 years), adolescents and adults			
Spirometry	Measurement of volumes (tidal volume, TLC) and airflow limitation (FEV_1, FVC, FEV_1/FVC, FEF_{25-75})	Bronchodilator response can be assessed	Highly dependent on patient cooperation and effort in order to obtain valuable measurements; age >5 years for reliable results

V'_{max}: maximal flow; FEF_{25-75}: forced expiratory flow at 25–75% of FVC.

substantial airflow limitation in BPD survivors during the first 3 years of life, with no significant improvements on serial measurements. Furthermore, the degree of airflow limitation in early years of life seems to predict pulmonary function later: in a small cohort of BPD survivors followed from birth, forced expiratory flow at 2 years (measured by maximal flow at FRC) correlated with pre- and post-bronchodilation z-scores of FEV_1 at 15, 20 and 24 years of age, indicating a tracking of lung function over time and a negligible "catch-up" in lung growth. In addition, no differences were found between infants treated with or without surfactant. This finding is suggestive of an irreversible early airway remodelling process, which characterises both "old" and "new" BPD survivors. However, a trend towards an obstructive spirometry pattern seems to exist even in very-low-birthweight children who do not develop BPD, raising concern that prematurity *per se* may impair lung maturation and growth with life-long detrimental effects on pulmonary function. This has been recently confirmed by two longitudinal respiratory follow-up studies after preterm birth in the surfactant era. The first, conducted in survivors born in 1991–1992, showed an increased small airway obstruction between 8 and 18 years in extremely preterm/low-birthweight survivors compared with controls, with greater increase within those who had BPD and those who were smokers at 18 years. The second study, conducted in a cohort of infants born between 1997 and 2003, similarly demonstrated that preterm children, with and without BPD, had declines in spirometry z-scores over time (from 4–8 years to 9–12 years) and compared with term controls, with FEV_1, forced expiratory flow at 25–75% of FVC (FEF_{25-75}) and FEV_1/FVC declining by at least 0.1 z-score per year in children with BPD. Interestingly, preterm children with bronchial wall thickening on chest CT (suggestive of inflammation) had bigger decreases in spirometry outcomes through childhood.

Significantly lower FEV_1/FVC ratio and FEF_{25-75} than controls are also characteristics of BPD survivors in their second and third decades. Given the results of longitudinal studies into early adulthood and the well-known physiological decline in respiratory reserves with ageing, these individuals may reach a critical threshold for significant respiratory symptoms in mid-adulthood, and it is possible that a new phenotype resembling COPD, but related to premature delivery, will emerge over the coming years.

These findings emphasise the need for novel therapies to reduce the long-term pulmonary effects of extremely premature birth, as well as for follow-up protocols to monitor these subjects and limit their exposure to risk factors associated with a faster decline of lung function, such as cigarette smoking. Emerging strategies, such as mesenchymal stem cell-based therapies, have recently come into the focus of neonatologists.

Imaging

Imaging has played an important role in the clinical assessment of BPD since its first recognition. The roles of chest radiography and CT are well documented but numerous recent advances in imaging technology have paved the way for newer imaging techniques, including structural pulmonary assessment *via* MRI, functional assessment *via* ventilation and perfusion MRI and quantitative imaging techniques using both CT and MRI. New applications for lung ultrasound have also been suggested. Ideally, noninvasive and feasible imaging techniques should be applied for the diagnosis and monitoring of BPD survivors following standardised protocols.

Traditional chest radiograph findings in survivors of BPD include reticular opacities and cystic lucencies, and late-stage findings of pulmonary interstitial emphysema, characterised by scarring and hyperinflation (figure 1). These abnormalities seem to

be milder in "new" BPD survivors compared to those with "old" BPD. The sensitivity of radiography in diagnosing minor lung abnormalities, however, is limited.

Lung ultrasound seems to be a promising tool to evaluate BPD diagnosis and severity. A prospective study has recently suggested that in BPD subjects a lung ultrasound score (defined as a semi-quantitative score representing the aeration (0–3) in three different areas of each lung) remains high until 36 wPMA. Further research is needed to assess the validity of this noninvasive technique.

Although chest CT is not routinely performed in BPD survivors, studies of CT scans reveal structural abnormalities in >85% of BPD patients, providing important information about airways and parenchymal structural changes. Several CT scoring methods have been used to evaluate chest CT scans of BPD patients, as summarised in a recent review in 2016. The most common findings being scored were patterns of hypo-attenuation on inspiratory and/or expiratory scans (representing either hypoperfusion and/or hypoventilation at inspiratory scans and possibly trapped air in expiration), linear or subpleural opacities (probably reflecting alveolar septal fibrosis), bronchial wall thickening (probably reflecting peri-bronchial fibrosis or inflammation) and collapse, consolidation or atelectasis. Lower pulmonary function and increased respiratory symptoms have both been associated with chest CT abnormalities. The most sensitive structural abnormality associated with BPD severity appeared to be low attenuation on inspiratory or tidal breathing CT scans, but these inspiratory and expiratory scans are not possible before the age of 4–5 years, unless anaesthesia is used. The presence of both hypo-attenuation and opacities can be consistent with the hypothesis that the predominant abnormality in BPD is in the peripheral lung. Furthermore, taken together, all studies included in the review indicated persistent abnormalities in the lungs of patients born preterm, irrespective of when in the evolutionary path of preterm neonatal care these patients were born ("old" *versus* "new" BPD) and regardless of age at the time of chest CT imaging.

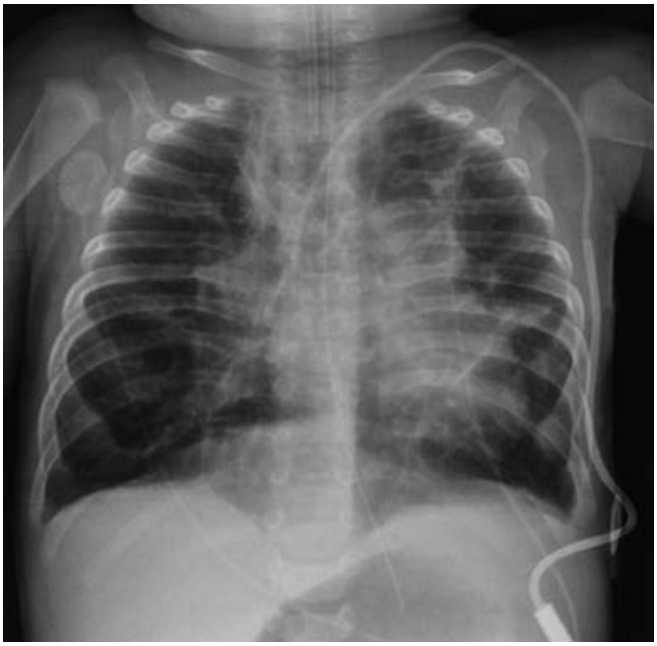

Figure 1. Typical chest radiographic changes of BPD showing cystic lucencies, pulmonary interstitial emphysema, scarring and hyperinflation.

MRI studies have been performed on quiet-breathing, non-sedated BPD survivors, allowing tomographic quantification of lung volumes and densities. These have shown that MRI can quantify hyperinflation in neonatal BPD, with lung volumes significantly increased according to disease severity. In addition, with hyperpolarised helium diffusion-weighted MRI, children with BPD have a higher apparent diffusion coefficient and similar lung volumes when compared with age-matched healthy subjects, suggesting the presence of enlarged alveoli that are reduced in number.

Treatment of BPD survivors

While several therapies and modes of ventilation have been proposed and studied for the management of early and evolving BPD, the treatment of infants and children with established BPD is still an under-investigated matter and many pharmacological treatments are routinely used with a limited evidence base. The recent European Respiratory Society guideline on long-term management of children with BPD indeed highlights the lack of research based on randomised controlled trials on the use of the most commonly prescribed drugs in infants and children with BPD. In particular, inhaled and systemic bronchodilators may improve pulmonary resistance during acute bronchospasm, although some subjects may benefit more from this therapy. There has been an increased use of inhaled steroids compared to the systemic ones, due to the possible limitation of adverse effects. Nevertheless, no studies have explored their benefits compared to placebo in BPD subjects alone. Finally, there is a wide variation in regimens, frequency, indications and duration of outpatient diuretic use, and this therapy may be more useful in infants with severe BPD or with PAH. Drugs, dosing and weaning for post-neonatal intensive care unit therapies in patients with BPD have been suggested; however, these can only be discussed on a case-by-case basis, given the paucity of evidence.

Summary

Chronic lung disease of infancy, in particular BPD, still claims a high disease burden of preterm birth, associated with increased hospitalisations in the first 2 years of life and more frequent respiratory symptoms up to adolescence. These may be worsened by the presence of PAH, for which preterm infants with evolving BPD or certain worrisome characteristics should be screened and then eventually monitored. The fact that persistent airway obstruction and correlating pulmonary structural changes can be identified in these subjects, up to their adolescence and early adulthood, highlights the importance of further research to prevent BPD development, as well as the necessity for standardised recommendations to monitor these patients through time. A European Respiratory Society guideline on long-term management of children with BPD has been recently developed by a task force of experts; it highlights the gaps in knowledge and provides guidance towards evidence-based care of these patients in the long term.

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Effects of systemic and extrapulmonary conditions on the respiratory system

Andrew Bush and Rishi Pabary

There are multiple pathways whereby the respiratory system can be affected by systemic disease. First, there may be a common aetiology for respiratory disease and another organ disease; hence, a lung presentation may be the first sign of disease in another organ, or extrapulmonary disease may be the presenting manifestation of a primary respiratory disorder. Secondly, disease in one organ may secondarily cause complications in another; thus, lung disease may affect other organs, and systemic disease may affect the lung. Thirdly, the treatment of a systemic disease may affect the respiratory system, and lung disease treatments may have extrathoracic effects. Treatments may have their effects directly or *via* secondary effects on another organ.

This chapter will give an overview of the interactions between respiratory and systemic diseases, discussing the following systemic diseases:

- Primary immunodeficiency syndromes
- Secondary immunodeficiency syndromes and immunosuppression
- Cardiac disease
- Gastrointestinal, liver and kidney disease
- Haematological disease
- Obesity
- Connective tissue diseases
- Musculoskeletal and neuromuscular diseases

Key points

- The respiratory system may be affected by systemic diseases, either because there is a common aetiology, *via* secondary complications of a systemic disease on the respiratory system or *vice versa*, or due to the effects of treatment for respiratory diseases having systemic consequences, or *vice versa*.
- Systemic diseases that may have an impact on the respiratory system include primary and secondary immunodeficiency syndromes, immunosuppression and obesity, as well as cardiac, gastrointestinal, liver, kidney, haematological, connective tissue, musculoskeletal and neuromuscular diseases.
- There is no more dangerous place to be than in a specialist clinic if there are diseases or complications outside the remit of that specialist. Look for respiratory complications in children attending other specialist clinics, and remember systemic complications in children attending your clinic.

Primary immunodeficiency syndromes

There are increasing numbers of genes implicated in causing primary immunodeficiency. They may present to the paediatric pulmonologist as recurrent infection, bronchiectasis or children's ILD (chILD), or be seen because of respiratory complications in a child with a known diagnosis. A detailed description of the pathophysiology of these conditions is given in the chapter "Immunology and defence mechanisms". It is important to make a specific diagnosis of the underlying immunodeficiency, because often management will be changed significantly.

Primary immunodeficiency presenting with recurrent infection

When considering both pulmonary and extrapulmonary infections, the acronym SPUR (severe, persistent, unusual, recurrent) is a useful prompt for when to suspect immunodeficiency. It is essential to know the range of normality for childhood infections, but also to be alert to the possibility of immunodeficiency, because diagnosis is often long delayed. A useful clue that is often ignored is a low peripheral blood lymphocyte count ($<2.8\times10^9$ cells·L^{-1}), which may precede diagnosis by many years. Other clues are from the nature of the infecting organisms: for example, recurrent pyogenic and fungal infections, especially with granuloma formation, point to neutrophil function disorders. Another clue is the age of onset: antibody deficiencies present at a few months of age, as levels of maternal antibodies wane. If primary immunodeficiency is suspected, referral to a paediatric immunologist is mandatory.

Primary immunodeficiency presenting with bronchiectasis

There are no particular features on imaging of bronchiectasis that is secondary to primary immunodeficiency. Importantly, bronchiectasis secondary to immunodeficiency may be at least partly reversible, and the possibility of primary immunodeficiency should be considered in all children presenting with bronchiectasis of unknown cause. As a minimum, a full blood count, immunoglobulins and their subclasses, mannose-binding lectin and response to vaccine antibodies should be determined in all such cases.

Primary immunodeficiency presenting with chILD

The simple minimum investigations in the previous section will be part of the work-up of most patients with suspected chILD. There are specific lung biopsy patterns that are so highly suggestive of an underlying immunodeficiency (including HIV) that immunological referral is mandated. These include follicular and cellular bronchiolitis, nonspecific interstitial pneumonitis, lymphoid interstitial pneumonia and lymphoproliferative disease. All such patients should be referred for detailed evaluation; some of these patients with chILD will respond to bone marrow transplantation. Pulmonary alveolar proteinosis is more usually caused by mutations in the genes for the α- and β-chains of the granulocyte–macrophage colony-stimulating factor (GM-CSF) receptor, or GM-CSF auto-antibodies, but it may also (rarely) be a complication of primary and secondary immunodeficiency. Further details can be found in the chapters "Interstitial lung diseases" and "Surfactant dysfunction syndromes and pulmonary alveolar proteinosis".

Pulmonary issues with specific primary immunodeficiency

Ataxia-telangiectasia is an autosomal recessive inherited disorder affecting many body systems, including the immune system. The diagnosis is frequently delayed. It

should be suspected if there is ataxia and drooling, as well as telangiectasia. Presence of a high α-fetoprotein level is a good screening test, and the diagnosis is confirmed by genetic studies. Respiratory complications include bronchiectasis related to immunodeficiency and aspiration, the latter related to an incoordinate swallow, and later-onset chILD. Children with ataxia-telangiectasia are exquisitely radiosensitive, so HRCT and other radiographic imaging should be avoided if at all possible.

Respiratory complications in a child with known primary immunodeficiency

In a child with known primary immunodeficiency, respiratory complications can be both infective and neoplastic. Pulmonary infective complications are common and may signal the need for a change in treatment, *e.g.* the introduction of immunoglobulin therapy in ataxia-telangiectasia. Suppurative airway disease is managed on standard lines, diagnosis of infection is by cough swab or sputum culture, and treatment is with airway clearance with consideration of mucolytic usage and antibiotics. If there is no response, induced sputum or bronchoscopy may be indicated to determine the infecting organism. If alveolar infection such as *Pneumocystis jirovecii* is suspected, then a diagnostic bronchoscopy may be indicated early, unless the clinical context is such that a blind antibiotic trial is appropriate. If BAL is negative and the child is not improving, consideration should be given to a lung biopsy rather than repeated BAL. Intrathoracic neoplastic disease may present as lymphadenopathy, infiltrates or a pleural effusion, and diagnosis will involve an appropriate biopsy or pleural tap.

Secondary immunodeficiency syndromes and immunosuppression

Other than HIV, secondary immunodeficiency syndromes and immunosuppression are not usually a diagnostic problem, but complications certainly are a major reason for referral (see also chapter "Lung involvement in the immunocompromised host"). In the appropriate context, the differential diagnosis of any pulmonary disease includes pulmonary toxicity of medications, both direct and *via* indirect effects on other organs, and recurrence of the original disease.

Pulmonary complications of chemotherapy for malignant disease

Opportunistic infections are the main complications of therapeutic immunosuppression, especially in neutropenic patients. The highest yield of infecting organisms is if bronchoscopy is performed early, but many units will treat empirically with cocktails of antibiotics, antifungals and antivirals, reserving bronchoscopy for those who do not respond. In such cases, the diagnostic yield is often poor. If the child is deteriorating and the cause is not known, rather than perform bronchoscopy repeatedly it is better to perform a lung biopsy (usually video-assisted thoracoscopic surgery). This may reveal a pattern of diffuse alveolar damage as the cause for deterioration. Another cause for apparently acute respiratory deterioration is pulmonary oedema secondary to drug-induced cardiomyopathy, pulmonary haemorrhage and pulmonary recurrence of the original malignancy.

Late sequelae after chemotherapy for malignant disease include pulmonary fibrosis and a picture similar to persistent bacterial bronchitis and bronchiectasis. Children with severe late fibrosis may be candidates for lung transplantation if they have been in remission for a sufficiently long period. The airway disease is treated on standard lines, with airway clearance, mucolytics and antibiotics, as well as attention to general respiratory health including exercise, immunisations and avoidance of tobacco exposure.

Infectious pulmonary complications of haematopoietic stem cell and solid organ transplantation

The morbidity and mortality of pulmonary complications following haematopoietic stem cell transplantation (HSCT) and solid organ transplantation are significant. Despite advances in prophylactic antimicrobial strategies, infections are common and follow a characteristic sequence in the post-transplant course. Nosocomial infections predominate in the first month, with opportunistic infections seen 1–6 months post transplant, coinciding with maximal sustained immunosuppression. Immunosuppression can usually be reduced after this time and infections are then generally due to common community-acquired organisms, except in a subset of patients who develop acute or chronic rejection. Cytomegalovirus (CMV) is the most common viral pathogen and infection can lead to graft failure. CMV pneumonitis is particularly prevalent post lung transplant (probably due to the lung being a site of CMV latency) and surveillance bronchoscopy is often performed in these patients along with regular PCR quantification of blood viral load. Oral valganciclovir prophylaxis for CMV is increasingly used in both solid organ and HSCT recipients. Epstein–Barr virus infection can cause malignant lymphoma, as immunosuppression blunts cytotoxic T-cell responses and allows abnormal proliferation of B-cells; this is termed post-transplant lymphoproliferative disorder (PTLD). Treatment requires reduction of immunosuppression or additional treatment, for instance immunotherapy with rituximab. Other viral infections include respiratory syncytial virus (RSV) and influenza, for which antivirals such as aerosolised ribavirin and amantadine or oral oseltamivir and baloxavir marboxil, respectively, may be used. Other organisms such as nontuberculous mycobacteria, *Mycobacterium tuberculosis* and *P. jirovecii* are less common (the latter due to the availability of effective chemoprophylaxis), although incidence varies; TB can affect up to 15% of transplant recipients in endemic areas. In HSCT recipients, invasive pulmonary aspergillosis is the leading cause of death secondary to infection, due to early diagnosis being difficult and to a lack of effective prophylactic therapy.

Other pulmonary complications of solid organ transplantation

Lung transplantation is discussed in detail in the chapter "Lung transplantation and management after transplantation". Perioperative complications of lung and liver transplant include acute respiratory distress syndrome (alternatively termed "primary graft failure" following lung transplantation), which has a mortality rate of 40–80%. Diaphragmatic dysfunction due to crush injury of the phrenic nerve can occur following heart, liver and lung transplant. Complications are fewer for renal transplants, although surgical manipulation of the pelvic veins leads to an increase in thromboembolic events. In addition to PTLD, other malignancies are reported such as bronchogenic carcinoma in heart transplant recipients and, in patients with hepatocellular carcinoma who receive a liver transplant, the lung is the most common site of recurrence.

Up to 75% of lung transplant recipients have at least one episode of acute rejection, mediated by T-lymphocytes, in the first year post transplant; regular surveillance transbronchial biopsy is undertaken during this period as histologically significant rejection may have no clinical signs. Signs and symptoms include dyspnoea, cough, a dip in spirometry parameters of ≥10% and infiltrates on chest radiographs. Chronic rejection, or bronchiolitis obliterans syndrome (BOS), is the main barrier to long-term survival following lung transplant. It is characterised by bronchiolar wall fibrosis and irreversible airflow obstruction and has a 2-year mortality of 40%. Photophoresis, total lymphoid irradiation and macrolide antibiotics have been used for treatment of BOS but there is no consensus on the best strategy and only re-transplantation is curative.

Other pulmonary complications of HSCT

Idiopathic pneumonia syndrome (IPS) is a diffuse lung injury following HSCT for which an infectious cause is not found. Toxicity from conditioning regimes and alloreactive T-cell-mediated injury have been implicated in IPS. Diagnostic criteria include dyspnoea, nonproductive cough and multilobar infiltrates on chest radiographs. Diffuse alveolar haemorrhage is usually seen in the first month after HSCT and has a similar aetiology and presentation to IPS. There is no accepted treatment for IPS, although etanercept has shown promise in children. Most IPS patients require intensive care, mortality is high and, although high-dose steroids are used in treatment of IPS, randomised controlled trials are lacking.

Graft *versus* host disease (GVHD) occurs after allogeneic transplantation, when donated cytotoxic T-cells attack the host as they recognise the recipient's cells as foreign. The risk of developing GVHD is greater if there is human leukocyte antigen mismatch between donor and recipient. GVHD can be acute or chronic and can affect many organs, including the skin, eyes, gastrointestinal tract and lungs. Chronic airflow obstruction, usually due to bronchiolitis obliterans, is associated with chronic GVHD. It is a common complication of allogeneic transplantation and rarely seen following HSCT. Onset is insidious so routine spirometry might detect it early; however, there is no consensus on effective treatment and disease progression can be rapid.

Pulmonary veno-occlusive disease is a rare complication of HSCT. Patients present with progressive dyspnoea due to fibrosis of pulmonary vasculature leading to pulmonary hypertension. The aetiology is thought to be related to endothelial injury from chemotherapy agents including bleomycin. Treatment options are limited, although there are reports of improvement with corticosteroids. This condition is discussed in more detail in the chapter "Pulmonary vascular disorders".

Cardiac disease

Systemic disease with cardiac and respiratory involvement

When considering multisystem diseases with cardiac and respiratory involvement, relevant diseases include trisomy 21 (congenital heart disease; may also have GOR and an incoordinate swallow leading to aspiration), TB (many pulmonary manifestations and may present with pericardial effusion and constrictive pericarditis), sarcoidosis (granulomatous lung disease with cardiomyopathy and arrhythmia) and ciliopathies, including PCD (chronic suppurative lung disease and may present with complex congenital heart disease). Non-motile ciliopathies, many of which have a mild pulmonary phenotype not dissimilar to that of PCD, are associated with congenital heart disease, generally without disorders of laterality.

Secondary relationships between the heart and lung

Primary respiratory diseases may present as a cardiovascular problem. For example, dilated cardiomyopathy may be a presentation of OSA. The differential diagnosis of "primary pulmonary hypertension with a normal chest radiograph" includes:

- OSA
- Occult ILD
- Pulmonary thromboembolism secondary to intravascular catheters or low flow circulation (including the right atrium as a potential source of emboli)
- Non-thrombotic pulmonary vascular occlusion, including emboli from liver or kidney
- Intravenous substance abuse (silica micro-emboli from injecting crushed tablets)

- Eisenmenger syndrome from occult congenital heart disease (see chapter "Pulmonary vascular disorders")

Cardiac diseases may also cause or be associated with secondary respiratory disease. Common causes include:

- Pulmonary oedema due to left heart obstructive lesions, heart muscle dysfunction, and left-to-right shunting (recurrent multifocal consolidation may be the presentation of left-to-right shunts, and pulmonary oedema may lead to an increased propensity for infection)
- Right ventricular outflow tract obstruction leading to secondary pulmonary hypoplasia
- Large airway obstruction, which may be from enlarged pulmonary arteries (absent pulmonary valve syndrome) or an enlarged cardiac chamber, usually compressing the left bronchial tree
- Complete cartilage rings, a known association of pulmonary artery sling
- Mediastinal disease such as vascular rings

Iatrogenic causes of the coexistence of cardiac and pulmonary disease

Medical cardiac treatments with an impact on the lungs include angiotensin-converting enzyme inhibitors causing chronic cough, and anticoagulants and antiplatelet therapies causing pulmonary haemorrhage. Surgical cardiac treatments may also affect the lungs, causing problems including nerve damage (phrenic palsy, left recurrent laryngeal nerve damage), subglottic stenosis secondary to repeated or prolonged intubation, large airway compression from implanted shunts or conduits, complications of the Fontan procedure (pulmonary arteriovenous fistulae, plastic bronchitis), tracheal infarction secondary to unifocalisation, and superior caval vein thrombosis leading to secondary pulmonary lymphangiectasia and chylothorax. Primary respiratory treatments with an impact on the heart include the use of intravenous β_2-agonists for asthma causing pulmonary oedema. Treatments for systemic disease that may have an impact on both the heart and lungs include chemotherapy for malignant disease, and mediastinal radiotherapy.

Clinical scenarios in cardiac disease

Repeated failed extubation after cardiac surgery despite favourable weaning parameters

In such a case, since significant pulmonary parenchymal disease is excluded by the ease with which gas exchange is maintained with minimal positive pressure ventilation, the problem lies either with large airway obstruction or dysfunction of the respiratory muscle pump. Key points on the history are 1) whether the child was genuinely symptom free before the procedure, and this is not the unmasking of a pre-existing complaint, 2) whether the child was stridulous and at least making vigorous respiratory efforts on extubation, suggesting upper airway obstruction (although the absence of stridor does not exclude this problem), or 3) whether there were weak respiratory efforts with an abnormal respiratory pattern, suggesting respiratory muscle weakness. A chest radiograph while the child is being ventilated with positive pressure is usually normal and cannot exclude diaphragmatic pathology. Abdominal ultrasound may be useful if the child is free-breathing, to assess diaphragm movement, as may simply watching the respiratory pattern with the child on low-level CPAP. If upper airway obstruction is the likely problem, a diagnostic fibreoptic bronchoscopy should be performed, preferably under a light general anaesthetic,

with the child breathing spontaneously. Vocal cord movement should be determined to exclude injury to the left recurrent laryngeal nerve, the extent of any subglottic stenosis should be delineated, and an unexpected cause of tracheal compression such as an undiagnosed vascular ring or pressure from a conduit should be excluded, as should tracheomalacia. Management should be for the underlying cause and may include 1) a trial of dexamethasone and nebulised adrenaline for subglottic stenosis, 2) referral to ENT if upper airway obstruction persists or laryngeal nerve damage is suspected, or 3) surgical plication of the diaphragm if there is unilateral phrenic nerve palsy. The child may need nocturnal NIV or even tracheostomy and long-term invasive ventilation as a last resort.

Lobar collapse or a unilateral whiteout after cardiac surgery

The context is the child who had a normal chest radiograph prior to the procedure, who now has radiological abnormalities showing either lobar collapse or a unilateral whiteout. Sepsis should obviously be excluded, and a history of blood or mucus plugs coming up the endotracheal tube sought. Especially in a complete whiteout, chest ultrasound should be performed to exclude the following causes of the abnormality: a large heart, fluid in the pleural space, paralysed hemidiaphragm, or subdiaphragmatic abscess. Once it is established that this is truly lobar or lung collapse, bronchoscopy should be performed to exclude extrinsic compression and intraluminal obstruction, usually from a mucus plug or blood clot. Bronchoscopy may relieve intraluminal causes of obstruction; large airway compression may mandate surgical revision.

Blue or breathless but apparently not due to the heart

It is due to the heart! Review the investigations with a senior consultant cardiologist and look for holes (in the heart and in the cardiological investigations).

Gastrointestinal, liver and kidney disease

Gastrointestinal disease

Systemic disease with gastrointestinal and respiratory involvement

CF has a pulmonary and gastrointestinal phenotype. The latter includes pancreatic insufficiency, rectal prolapse, liver disease (see later in this chapter), distal intestinal obstruction syndrome and constipation, and lactose intolerance (see also the chapter "Extrapulmonary manifestations of CF"). Oesophageal disease such as hiatus hernia, achalasia, H-type fistula and stricture, usually after repair of oesophageal atresia, may cause aspiration syndromes. Inflammatory bowel disease, especially Crohn's disease, has a respiratory phenotype, including airway and parenchymal manifestations. Airway disease includes upper airway obstruction, tracheobronchitis, granulomatous bronchiolitis and bronchiectasis, rarely with progression to respiratory failure. Parenchymal diseases described include bronchiolitis obliterans with organising pneumonia, noncaseating granulomatous inflammation and fibrosis, nodules and granulomas, alveolitis and alveolar filling. *Mycobacterium xenopi* infection has been described and enters the differential diagnosis of granulomatous lung disease in Crohn's. Pleural disease is very rare, but includes colopleural fistula and faecopneumothorax. Ulcerative colitis may be complicated by bronchitis, bronchiectasis and nongranulomatous ILD. Challengingly, respiratory disease may be the first presentation of inflammatory bowel disease. Rare cases of pulmonary haemorrhage have been described as complicating coeliac disease (Lane–Hamilton syndrome, also associated with IgA nephropathy).

Secondary relationships between the lung and the gastrointestinal tract

The most difficult secondary relationship is that between lung disease and GOR. GOR may cause aspiration of gastric contents and lung disease, and it may worsen bronchial responsiveness *via* an oesophago-bronchial reflex, without evidence of aspiration. GOR may be the result of multiple effects of respiratory disease on the gastro-oesophageal sphincter and it may be a coincidental finding, as in most cases of severe asthma. The complexity may only be sorted out by a trial of treatment, which should be discontinued if there is no clear-cut benefit. These syndromes are discussed in more detail in the chapter "GOR-associated lung disease and chronic pulmonary aspiration syndrome".

Iatrogenic causes of the coexistence of lung and gastrointestinal tract disease

Many medications used in inflammatory bowel disease affect the lungs, including immunosuppressants (as mentioned earlier in this chapter), sulfasalazine and infliximab; the latter is a risk for re-activation of TB.

Liver disease

Systemic disease with respiratory and hepatic involvement

CF has both a pulmonary and a hepatic phenotype, the latter including fatty liver, portal hypertension, macronodular cirrhosis and gall stones. Hepatocellular failure is a late and ominous sign. Non-motile ciliopathies (some of which have a mild PCD-like respiratory phenotype; see the section about kidney disease) are associated with polycystic liver disease and hepatic dysplasias. Alpha-1 antitrypsin deficiency causes liver disease, emphysema and bronchiectasis, but in childhood, liver disease dominates and significant lung disease is rare.

Liver disease causing or associated with secondary lung disease

There are two main pulmonary complications of liver disease, namely primary pulmonary hypertension and hepatopulmonary syndrome. There are no particular distinguishing features between pulmonary hypertension secondary to liver disease and other causes of pulmonary hypertension (see chapter "Pulmonary vascular disorders"). Hepatopulmonary syndrome is characterised by hypoxaemia and platypnoea-orthodeoxia, due to multiple microscopic pulmonary arteriovenous malformations, and should be suspected in the context of liver disease with or without apparent pulmonary manifestations, if hypoxaemia is disproportionately severe to the degree of respiratory impairment. A similar syndrome is caused by hereditary haemorrhagic telangiectasia, which also causes hepatic vascular abnormalities, and whose underlying cause is mutations in genes in the transforming growth factor-β superfamily signalling pathway, especially *Endoglin* and *ACVRL1*. There are rare reports of gene mutations in other pathways.

Iatrogenic causes of the coexistence of hepatic and pulmonary disease

Immunosuppression is the main treatment modality for hepatic disease that leads to respiratory complications.

Kidney disease

Systemic disease with renal and respiratory involvement

The most obvious systemic diseases with renal and respiratory involvement are the non-motile ciliopathies, many of which (*e.g.* Alström syndrome and Bardet–Biedl syndrome) have respiratory phenotypes similar to but less severe than that of PCD. The non-motile ciliopathies are complex multisystem disorders with multiple underlying gene mutations; the same mutation may lead to a very different phenotype even in the same family. Renal manifestations of the non-motile ciliopathies include

adult and juvenile polycystic kidney disease (due to mutations in the polycystin gene and for which there is a well-described association with bronchiectasis), as well as nephronophthisis and renal dysplastic syndromes (both due to multiple different genes). In addition to occasionally having a PCD-like respiratory phenotype, patients with Jeune syndrome (asphyxiating thoracic dystrophy) and Mainzer–Saldinho syndrome display chest wall deformities that affect the respiratory system. There may be respiratory effects secondary to cardiac and neurological disease related to non-motile ciliopathies. Of note, polycystin is expressed in respiratory epithelium, and there is a higher than expected prevalence of bronchiectasis in non-polycystic disease renal failure. Other associations between the two organs are pulmonary thromboembolism secondary to membranous glomerulonephritis and tumour emboli from Wilms tumour, vasculitic syndromes (see the section about vasculitis) and atypical haemolytic-uraemic syndrome. Amyloidosis, which is very rare in children, may also affect both the lung and the kidney.

Secondary relationships between the lung and the kidney

Fluid retention by the failing kidney and protein loss due to nephrotic syndrome can cause pulmonary oedema and pleural transudates. Renal failure can lead to dystrophic and metastatic pulmonary calcification. Pulmonary hypertension is increasingly recognised as a complication of end-stage kidney disease. There is an increased risk of TB and empyema in chronic renal failure patients.

Iatrogenic causes of the coexistence of renal and pulmonary disease

Immunosuppressive treatment may affect the lung, as may complications after renal transplantation (as mentioned earlier in this chapter). There are a number of pulmonary complications of dialysis. Peritoneal dialysis may lead to pleural effusions if there is a congenital small diaphragmatic defect. Haemodialysis is rarely associated with hypoxaemia, due to combinations of complement activation, intrapulmonary vascular white cell sequestration, and silicone emboli. Fracture of intravascular catheters for haemodialysis may lead to iatrogenic pulmonary embolism requiring transcatheter removal, and thrombi formed around such catheters may also embolise to the lungs. Levamisole, paraquat poisoning and chemotherapeutic agents, for example gemcitabine, may also affect both the lung and the kidney.

Haematological disease

This section considers only non-malignant haematological disease; haematological malignancies have been considered earlier in this chapter, in the section on secondary immunodeficiency syndromes. As with other systemic diseases, the effects of treatment should also be considered, as should secondary effects, especially *via* the heart (*e.g.* iron overload cardiomyopathy).

Pulmonary disease complicating haemoglobinopathy

Sickle cell disease

Sickle cell disease is a haemoglobinopathy that can affect the airway, lung parenchyma, chest wall and pulmonary circulation. The detailed management of the condition is beyond the scope of this chapter, and the issues are discussed in the chapter "Sickle cell disease". Acute chest syndrome is multifactorial, but sickling within the pulmonary microvasculature is a key finding. Around one third of cases is triggered by infection; the most common organisms are *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and RSV. Parvovirus has been implicated in a particularly severe form of crisis. Fat embolism secondary to bone marrow infarction is a factor in 10% of crises. Clinical presentation is with chest pain, cough, breathlessness and a new infiltrate.

If there has been bone marrow infarction, bone pain may be severe. Management should be organised in conjunction with haematologists, and should include pain relief, antibiotics, correction of hypoxaemia and attention to fluid balance and the need for transfusion. It is important to be aware of and avoid the complication of transfusion-induced hyperviscosity. If oral steroids are used, the course should be <3 days to reduce the risk of rebound vaso-occlusive disease.

There are numerous manifestations of chronic sickle cell disease. There may be restrictive lung disease with diffuse interstitial fibrosis. Haemosiderin-laden macrophages have been reported in the BAL of children who have undergone multiple transfusions, to a similar extent to that seen in idiopathic pulmonary haemosiderosis. Sleep disordered breathing is common and should always be actively sought. Understanding the airway disease is clouded by the irrelevant question "Do children with sickle cell disease have asthma?" Some children with sickle cell disease certainly do have an airway disease. If present, the airway disease should be deconstructed into treatable traits, for example the presence or absence of eosinophilic airway inflammation. We have found that the airway disease in sickle cell disease is characterised by fixed airflow obstruction with no evidence of type 2 inflammation, unless the child is coincidentally atopic. Pulmonary hypertension requires careful evaluation in the presence of anaemia and potentially raised left ventricular end-diastolic pressure (see chapter "Pulmonary vascular disorders"). Measurement of cardiac index and hence pulmonary vascular resistance is essential. True pulmonary vascular disease may be related to hypoxaemia secondary to OSA, and to alveolar and pulmonary vascular damage after recurrent sickle cell crises. Obstructive and restrictive patterns of lung function are common.

Thalassaemia

The pulmonary complications of thalassaemia are much less studied than those of sickle cell disease. Pulmonary function abnormalities are commonly found if sought, and there may be restrictive spirometry, impaired carbon monoxide transfer, and proximal and distal airway obstruction. Potential pathophysiological mechanisms include pulmonary oedema and fibrosis related to iron overload, cardiac damage, elevation of the right hemidiaphragm by an enlarged liver and microembolisation secondary to coagulopathy. Most of these abnormalities are subclinical.

Blue but not breathless: haemoglobins with abnormal oxygen-carrying capacity

The differential diagnosis of the well, blue child includes right-to-left shunting through pulmonary arteriovenous malformation(s) (which if microscopic may be invisible on chest radiographs) and congenital or acquired abnormality of the haemoglobin oxygen dissociation curve. In methaemoglobinaemia, which may be congenital or acquired, the iron moiety is in the ferric not ferrous state, greatly reducing oxygen-carrying capacity. If this diagnosis is suspected, a detailed medication history is necessary. Sulfhaemoglobinaemia arises from the interaction between a sulfur atom and the ferric moiety, and is usually drug induced.

Obesity

Obesity is becoming a pandemic, with ever-rising prevalence across the world fuelled by the junk food industry. Definitions vary across the world, but a reasonable one is that a child is overweight if their BMI is >91st centile and clinically obese if BMI >98th centile. The World Health Organization estimates that there will be 70 million overweight children in the world by 2025. Obesity is a systemic, pro-inflammatory

disease, which affects the upper and lower respiratory tracts. Respiratory complications of obesity usually only arise after the BMI is grossly elevated. A minority of cases relate to an underlying syndrome such as Prader–Willi, ROHHAD (rapid-onset obesity (RO) with hypothalamic dysregulation (H), hypoventilation (H) and autonomic dysregulation (AD)) or Bardet–Biedl, which should be managed on their merits (see chapter "Central sleep apnoeas and hypoventilation syndromes").

Physiological effects of obesity

Obesity leads to a reduction in expiratory reserve volume and hence in FRC. The layers of fat reduce lung and chest wall compliance leading to hypoventilation, atelectasis and ventilation/perfusion mismatch. Tidal volume may be reduced. The effect on spirometry of childhood obesity is controversial: FEV_1/FVC ratio is reduced, but different groups have reported elevated or reduced FEV_1 and FVC. In adults, moderate obesity is reported as causing a restrictive defect, morbid obesity as causing an obstructive defect. There is no association between obesity and airway hyperresponsiveness.

Obesity and control of ventilation

Pickwickian syndrome is a diagnosis of exclusion and consists of obesity with nocturnal hypoventilation and daytime hypercapnia. Clinical features include hypersomnolence (memorably described in Fat Joe in "The Pickwick Papers" by Charles Dickens, although Joe almost certainly did not have Pickwickian syndrome!), morning headaches, polycythaemia, pulmonary hypertension and cor pulmonale. The pathophysiology is mechanical overloading of the respiratory muscle pump, which overwhelms compensatory mechanisms, leading to chronic hypoxia and hypercapnia with subsequent blunting of chemoreceptor responsiveness. Treatment is with NIV and attempted weight reduction.

Obesity and the upper airway

The general issues of OSA are discussed in the chapter "OSAS and upper airway resistance syndrome". Obesity is a significant risk factor for OSA: each increment in BMI of 1 $kg \cdot m^{-2}$ above the 50th percentile is associated with a 12% increased risk of OSA. There is a near 40% prevalence of OSA in obese children, so PSG should be a routine part of investigation. These children may have fatty infiltrates within neck and upper airway structures, leading to upper airway narrowing and increased pharyngeal collapsibility. Additionally, the tonsils and adenoids may be enlarged. Gas exchange may be worsened by lower airway physiological changes such as reduced FRC. Treatment of obesity is weight loss in the first instance, either by dieting or, in extreme cases, bariatric surgery. If there is adenotonsillar hypertrophy, surgery is indicated, but residual OSA is common and post-operative cardiorespiratory polygraphy should always be performed. If OSA persists despite these measures, treatment with CPAP or sometimes even NIV, titrated in the usual way, is indicated.

Obesity and the lower airway

The first question to be determined in the child with breathlessness and noisy breathing ("wheezing", a term that covers a multiplicity of noises) is whether there is an airways disease at all, or whether the child is deconditioned or over-perceiving symptoms. If there is any doubt, a formal exercise test to document whether there is exercise-induced bronchoconstriction should be performed before escalating asthma treatment. If an airway disease is present, its nature should be determined. Obviously being obese does not preclude the development

of atopic, eosinophilic childhood asthma, but there may be a different airway phenotype in at least some obese children. This, and treating obese children who do not have an airway disease, are probably the main reasons for the steroid resistance described in the obese.

Obesity is associated with dysanapsis, in which the lung size and airway length are increased, but with a normal airway calibre, leading to airflow obstruction (consider Poiseuille's law). Physiologically, there is a normal FEV_1, a raised FVC and a reduced FEV_1/FVC ratio. Dysanapsis is associated with an increased risk of asthma attacks.

Whether obese asthmatics have type 2 inflammation is controversial; recent transcriptomic data suggest that obesity is not associated with airway type 2 inflammation. There is evidence that the airway may in fact be the target of systemic inflammation modulated by plasma interleukin-6 and unrelated to atopy. However, each child should be assessed and treated on an individual basis.

To summarise, in the breathless obese child, be sure there really is an airway disease. Determine whether the child has fixed obstruction (dysanapsis) and, if so, avoid over-prescribing medications; only prescribe bronchodilators if the child responds, and, before prescribing inhaled corticosteroids, make every effort to determine if the child has airway eosinophilia, using induced sputum (ideally), exhaled nitric oxide fraction and blood eosinophil count as markers.

Does obesity cause asthma?

The prevalence of both obesity and asthma is increasing, and this has led to the suggestion that obesity causes asthma (often without particular details of what sort of asthma is being discussed). There are a number of potential and complex interrelationships between the two conditions, and the answer is unlikely to be simple; some of the issues are discussed in the chapter "Difficult and severe asthma". The effects of obesity on the airways have been described. Another explanation is that airway disease causes obesity (known as "reverse causality") because of reduced activity and increased use of systemic steroids. A further (and in many cases, more likely) hypothesis is that the association is attributable to confounding factors. These may include shared genetic polymorphisms, prenatal factors (*e.g.* maternal nutrition) and medical comorbidities (*e.g.* GOR disease or OSA). Obesity is a disease of poverty, which brings with it other confounders, such as tobacco smoke exposure, low socioeconomic status, pollution exposure and overcrowding. Finally, Berkson's fallacy is likely to be a factor: selection bias arises when a sample is taken from a subpopulation not a general population, *e.g*. both cases and controls sampled from a hospital rather than a community population.

Connective tissue diseases

Inflammatory disease

There are numerous rheumatological and vasculitic diseases in childhood that may directly affect the respiratory system or cause indirect effects, *e.g. via* the kidney and heart, and which are treated with medications with direct pulmonary toxicity and immunosuppressive effects. These diseases can only be considered in outline here; there are more details in the chapter "Interstitial lung diseases". Respiratory manifestations may be the first presentation of a systemic disease, or may complicate the course of a child with a known rheumatological diagnosis. They should all be managed in conjunction with a paediatric rheumatologist. Serological investigations are shown in table 1.

Table 1. Serology of juvenile inflammatory connective tissue disorders

Serology	Disease entity
ANA	SLE, oligoarticular JCA, juvenile dermatomyositis, scleroderma; also seen in normal children
Anti-dsDNA	MCTD, SLE
Anti-Sm	SLE
Anti-Ro/La	SLE, Sjögren
Anti-RNP	SLE, MCTD, scleroderma
Anti-cardiolipin	SLE, anti-phospholipid antibody syndrome
Anti-Jo-1	Myositis
Anti-Scl-70	Scleroderma
Anti-centromere	Limited scleroderma
ANCA	Vasculitides
PR3	GPA
MPO	MPA
Rheumatoid factor	Rheumatoid factor-positive JCA

ANA: antinuclear antibody; SLE: systemic lupus erythematosus; JCA: juvenile chronic arthritis; dsDNA: double-stranded DNA; MCTD: mixed connective tissue disease; RNP: ribonucleoprotein; ANCA: antineutrophil cytoplasmic antibody; PR3: proteinase 3; MPO: myeloperoxidase; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis.

Juvenile chronic arthritis

Juvenile chronic arthritis (JCA) is a heterogeneous group of diseases, which may present with systemic features or be oligo- or polyarticular. JCA may be complicated by pleuritis, sometimes with pericarditis, in which case systemic lupus erythematosus (SLE) must be excluded. Other pulmonary manifestations are so rare as to warrant reconsideration of the underlying diagnosis. Systemic JCA may be complicated by ILD, including pulmonary alveolar proteinosis.

Systemic lupus erythematosus

Typical paediatric presentations of SLE are fever, rash and arthralgia. There is pulmonary involvement in up to 80% of patients. This includes pleuritic and pleural effusion. There is an increased risk of many different infections, due both to the underlying disease and to iatrogenic immunosuppression. Other complications include acute pneumonitis, pulmonary haemorrhage, pulmonary hypertension, pulmonary embolism secondary to thrombosis related to the lupus anticoagulant, bronchiectasis and shrinking lung syndrome. There may be asymptomatic pulmonary function abnormalities and nodules.

Juvenile dermatomyositis

The typical presentation of juvenile dermatomyositis is with rash and inflammatory myopathy. Unlike in the adult form of the disease, pulmonary manifestations are rare in children. Occasional cases of ILD have been described, and aspiration due to abnormal swallow and diaphragm involvement must be remembered. Respiratory muscle dysfunction should always be considered, and rheumatologists must be deterred from trying to diagnose diaphragmatic (inspiratory) muscle failure with a peak flow meter (an expiratory manoeuvre).

Scleroderma

The onset of scleroderma is usually insidious, with skin changes and constitutional symptoms including arthralgia. Pulmonary involvement is, by definition, only seen in the diffuse form of the disease, and includes ILD (typically nonspecific interstitial

pneumonia), pulmonary hypertension (isolated or associated with ILD), complications of cardiomyopathy, and aspiration due to oesophageal disease. Other manifestations include bronchiectasis, pleuritic and pleural effusions, alveolar haemorrhage and, very rarely, pneumothorax. Chest wall expansion may be limited by skin changes. Pulmonary manifestations are typically detectable at presentation, or very early in the disease.

Mixed connective tissue disease

Mixed connective tissue disease is rare in childhood, and pulmonary complications are a major cause of morbidity and mortality. These include ILD, pleural effusions, pulmonary hypertension, thromboembolic disease, diaphragm weakness and complications of aspiration.

Sarcoidosis

Compared with adults, a multisystem presentation of paediatric sarcoidosis, a much rarer disease, is common. There is an overlap with Blau syndrome, an early-onset autoinflammatory disease causing chILD. Sarcoid granulomas can occur in almost any organ. Pulmonary manifestations include lymphadenopathy, peribronchovascular nodules, bronchiectasis and bronchiolectasis, and large airway involvement, including laryngeal sarcoid. Extrathoracic organ granulomas may have secondary effects, *e.g.* sarcoid granulomatous cardiomyopathy.

Vasculitis in childhood

There is an extensive list of childhood vasculitic conditions, which can be classified by the size of the vessels involved, and which may be confined to the lung (as in the neutrophilic vasculitis underlying some cases of apparent idiopathic pulmonary haemosiderosis) or be part of a systemic syndrome, as some of these may have a pulmonary presentation. Henoch–Schönlein and Kawasaki disease are the most common vasculitides in childhood, although pulmonary involvement is very rare in both, with all other causes of vasculitides combined having an incidence of about one in 400 000. The most important paediatric pulmonary vasculitides are those affecting the small vessels, comprising granulomatosis with polyangiitis (GPA; proteinase-3 antineutrophil cytoplasmic antibody (PR3-ANCA) positive), microscopic polyangiitis (MPA; myeloperoxidase-ANCA positive), eosinophilic granulomatosis with polyangiitis (EGPA; formerly known as Churg–Strauss syndrome) and isolated pulmonary capillaritis, which may evolve into a renal form. The first three are multisystem diseases. GPA typically presents with upper and lower airway disease and multisystem involvement (eyes, kidney, skin, musculoskeletal, cardiac and nervous systems). MPA is characterised by necrotising glomerulonephritis and pulmonary haemorrhage, again with multisystem involvement. EGPA is suspected in children with severe asthma, rhinosinusitis, pulmonary infiltrates, constitutional symptoms, multisystem involvement and peripheral blood eosinophilia. Confirmation of these diagnoses includes the serological tests (table 1) in an appropriate clinical context.

Non-inflammatory disease

Marfan syndrome

Marfan syndrome is a rare genetic disorder caused by mutations in *FBN1*, which encodes fibrillin-1. Pulmonary manifestations include pneumothorax, which may be related to apical fibrobullous disease, and pectus excavatum or pectus carinatum. The syndrome is frequently associated with OSA, possibly due to contributions by craniofacial abnormalities. It is important to consider this diagnosis, because cardiac

abnormalities are a common feature, and early detection of such abnormalities improves prognosis.

Ehlers–Danlos syndromes

There are at least 13 types of Ehlers–Danlos syndrome, most very rare. Of interest to the pulmonologist are the kyphoscoliotic and vascular forms. Importantly, the vascular form may present with spontaneous haemothorax or pneumothorax, before any arterial or intestinal complications.

Williams–Campbell syndrome

Williams–Campbell syndrome is characterised by congenital deficiency of bronchial cartilage, leading to generalised bronchomalacia and bronchiectasis. The aetiology is unknown.

Mounier-Kuhn syndrome

Mounier-Kuhn syndrome is a description of congenital tracheobronchomegaly, bronchomalacia and bronchiectasis, and may be associated with Ehlers–Danlos, cutis laxa or Kenny–Caffey syndrome.

Musculoskeletal and neuromuscular diseases

The key components of the neuromuscular system that affect the respiratory system are:

- Neural reflexes that control breathing
- Upper airway reflexes, which protect the airway
- Inspiratory muscles: pivotal in achieving adequate ventilation
- Expiratory muscles: key to achieving sputum clearance
- The chest wall, disorders of which may affect inspiratory and expiratory muscle function

The paediatric pulmonologist also needs to deal with increasingly complex ethical issues in terms of ventilator support for disabled children.

Control of breathing

A detailed discussion of the control of breathing can be found in the chapter "Central sleep apnoeas and hypoventilation syndromes". Congenital central hypoventilation syndrome (also known as Ondine's curse) is due to mutations in the *PHOX2B* gene (paired-like homeobox 2b). Most patients have a polyalanine repeat mutation in *PHOX2B*, while a few have a different mutation. Prevalence is estimated as one in 150 000–200 000. It usually presents with severe infantile hypoventilation, and may be associated with diffuse autonomic nervous system dysfunction, Hirschsprung disease and neural crest tumours. Late presentation is with apnoeas or hypoventilation after anaesthesia or respiratory infection. There may be failure of perception of dyspnoea. Treatment is with ventilatory support, either nocturnal *via* NIV or 24 h·day^{-1} *via* tracheostomy, depending on severity.

Myasthenic crises are defined as acute respiratory failure in a child with a congenital myasthenic syndrome. These require assisted ventilation, and often bag and mask ventilation and NIV are sufficient. Factors associated with myasthenic apnoeic crises include heat, tonsillar hypertrophy, GOR and emotional stress, including temper tantrums. These are more likely in those who present early in life with apnoea, vocal cord palsy or bulbar/feeding issues, and who have mutations affecting pre-synaptic proteins (*e.g.* choline acetyltransferase (CHAT))

or post-synaptic proteins (*e.g.* acetylcholine receptor subunit epsilon (CHRNE) or RAPSN (which also affects acetylcholine receptor function)). Note that the need for NIV during acute apnoeic decompensation is not predictable from a sleep study when the child is stable.

Upper airway reflexes

An incoordinate swallow is caused by a defect in upper airway reflexes, and is a feature of many neuromuscular diseases that cause bulbar palsy and pseudobulbar palsy. If there is any question of this, assessment by a speech and language therapist is mandatory. GOR should also be excluded. Other issues include upper airway obstruction related to laryngeal neuropathy or myopathy, or bilateral vocal cord palsy due to severe spinal muscular atrophy.

Inspiratory muscle dysfunction

Inspiratory muscle dysfunction manifests initially with nocturnal hypoventilation and may then be followed by daytime respiratory failure. In some conditions, *e.g.* nemaline rod myopathy, congenital muscular dystrophy and central core disease, peripheral muscle function may be well preserved. Diagnosis is commonly attempted in nonrespiratory wards by measuring the peak expiratory flow rate, but it makes no sense to use an expiratory manoeuvre to diagnose inspiratory muscle disease. Severe bilateral diaphragm paralysis presents as profound orthopnoea with relatively preserved exercise tolerance. A drop in vital capacity (VC) of >25% between sitting and supine is a specific but not sensitive diagnostic test. Sniff inspiratory nasal pressure is another useful test. Nocturnal hypoventilation should be screened for regularly in any patient with neuromuscular or chest wall disease, especially if there is one or more of the following: a high thoracic scoliosis, early-onset disease, the patient is non-ambulant, the VC is <60% predicted (if standing height cannot be measured, then relate VC to arm span or ulna length). Nocturnal hypoventilation is usually readily corrected by NIV, which may also improve nutritional state and reduce the risk of infection by re-recruiting alveoli during the night. Patients with borderline inspiratory muscle function may decompensate into frank respiratory failure in association with upper or lower respiratory tract infections, atelectasis, cardiac failure secondary to cardiomyopathy and/or arrhythmia, sedatives, aspiration, pneumothorax (which is a complication of NIV), pulmonary embolism (a complication of immobility or cardiomyopathy and right atrial stasis) and acute gastric distension (also a complication of NIV).

Expiratory muscle dysfunction

Expiration is usually a passive process, but expiratory muscles are essential for the powerful cough that is needed to protect the airway. There are five components to cough: 1) the sensation of an irritant in the airway (not usually a problem in neuromuscular disease); 2) inspiration to TLC; 3) glottal closure with a rise in pressure in the airway and increased distal collateral ventilation; 4) acceleration of expiratory flow against a closed glottis; and 5) glottal opening and secretion expulsion. Cough strength should be monitored by regular cough peak flow (CPF) measurements in clinic. Children >12 years of age who have a CPF <270 $L \cdot min^{-1}$ are vulnerable to respiratory failure complicating relatively trivial viral respiratory disease; if the CPF is <160 $L \cdot min^{-1}$ they will are not be able to clear secretions. Airway clearance can be augmented by standard physiotherapy airway clearance, by using NIV to augment inspiration, or by using the cough in-exsufflator, which aids lung inflation but then also administers a negative pressure to suck secretions

out of the lungs. There is no evidence base for other therapies, but consideration should be given to the use of nebulised hypertonic saline or even recombinant human deoxyribonuclease (rhDNase), and antibiotics for infection, including prophylactic azithromycin and also nebulised antibiotics for chronic infection with *Pseudomonas aeruginosa*.

Chest wall disease

Chest wall diseases such as scoliosis and kyphoscoliosis reduce TLC, as well as reducing the mechanical efficiency of the respiratory muscles. The effects are compounded if scoliosis is secondary to neuromuscular disease. Patients should be screened regularly for nocturnal hypoventilation, especially during puberty when scoliosis may worsen rapidly. This issue is further discussed in the chapter "Chest wall disorders".

Secondary effects

Cardiomyopathy associated with neuromuscular disease, for example in Duchenne muscular dystrophy (DMD), may cause lower airway compression and pulmonary oedema. Obesity due to immobility may have respiratory consequences, as already discussed, especially OSA. Other secondary effects of cardiac disease on the lungs have also been described earlier in this chapter.

Ethics of respiratory support

Whereas, in the past, the downhill course of neuromuscular diseases such as DMD was accepted fatalistically as inevitable, now, increasingly, patients and families are demanding active interventions. What were once paediatric diseases are now also in the domain of adult physicians, with DMD patients surviving into their fifth and sixth decades. This has been driven by at least four factors: 1) the use of NIV, and increasingly of elective tracheostomy ventilation; 2) increasingly efficient ways of supporting airway clearance; 3) the realisation that professionals and carers hopelessly underestimate the quality of life as perceived by the patients themselves, and the rejection by disabled people of the right of the able-bodied to determine their quality of life; and 4) the dawning of a new age of specific treatments, such as nusinersen and gene therapy for spinal muscular atrophy. The ethical challenges are considerable and beyond the scope of this chapter. The great fear of performing a tracheostomy is the patient surviving in a "locked in" state. This is an area where multidisciplinary evaluation is recommended, including obtaining second opinions and involving palliative care consultants and, where possible, an external ethical review body.

Summary

There is no more dangerous place for a child than in a specialist clinic if s/he has a disease or complication outside that speciality. So it is important for us to remind nonrespiratory specialists that the lungs exist and are quite important!

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GOR-associated lung disease and chronic pulmonary aspiration syndrome

Charmaine Chai, Anna Rybak and Osvaldo Borrelli

Chronic pulmonary aspiration (CPA) syndrome is defined as the entry of food materials, gastric contents and/or saliva into the subglottic airways in a manner sufficient to induce chronic or recurrent respiratory symptoms. These symptoms include:

- Asthma and wheezing
- Recurrent pneumonia
- Choking on feeds or secretions
- Failure to thrive
- Apnoea of prematurity
- Brief resolved unexplained events
- Bronchiectasis and pulmonary fibrosis
- Delayed resolution of chronic neonatal lung disease

CPA constitutes one of the most serious challenges to the normal development of the respiratory tract, and although it is more common in premature infants, it remains a major health risk in all children throughout infancy and childhood.

Different mechanisms have been suggested in the genesis of CPA, including swallowing dysfunction, salivary aspiration and GOR. GOR is a physiological phenomenon occurring in healthy infants and children several times a day. In contrast, GOR disease (GORD) is defined as a condition which develops when the reflux of gastric contents causes troublesome symptoms and/or complications, and represents one of the most common causes of foregut symptoms in children. Although several studies in children have emphasised the role of GOR in the

Key points

- Chronic pulmonary aspiration (CPA) constitutes one of the most serious challenges to the normal development of the respiratory tract, and it represents a major health risk throughout infancy and childhood.
- Several studies have reported an association between GOR disease and CPA.
- Both acid and non-acid reflux may play a role into the pathophysiology of some parenchymal lung diseases.
- The diagnosis of GOR-related aspiration remains challenging due to the absence of a sensitive and specific test.

pathogenesis of upper and lower airway respiratory disorders, the likelihood of interactions between GOR and the respiratory system is still one of the areas of controversy in paediatric GORD. It is now generally agreed that certain underlying disorders predispose children to a higher risk of severe GORD, and thus to a higher risk of GOR-induced respiratory manifestations. These include neurological disorders (*e.g.* cerebral palsy), genetic or metabolic diseases (*e.g.* Stickler syndrome), congenital abnormalities, (*e.g.* oesophageal atresia with tracheo-oesophageal fistula), and chronic lung disease (*e.g.* CF).

The relationship between GORD and CPA has been investigated by different epidemiological and clinical studies. In children with severe neurodisability, severe lower respiratory infections are associated with severe GOR only with coexistence of swallowing dysfunction. GOR seems to be involved in pathogenesis of recurrent pneumonia in ~6% of cases. In children with GORD without co-existing neurological disabilities or congenital oesophageal anomalies, the prevalence of pneumonia and bronchiectasis is three to six times more frequent than amongst controls. In children with severe neurological impairment, a history of GOR is a significant risk factor for the development of bronchiectasis in children with CPA. Finally, several studies have reported an association between GORD and CF. The prevalence of GORD in children with CF ranges between 25% and 100%, which is six to eight times the rate of GORD in the non-CF population. One-fifth of newly diagnosed infants and 25–55% of CF children older than 1 year show abnormal reflux. Moreover, GOR may contribute to poor CF control at the end stage of disease, and may cause bronchiolitis obliterans syndrome (BOS) after lung transplantation.

Although a significant body of literature in children has emphasised the role of GOR in the pathogenesis of lower airway respiratory disorders, it should be stressed that the range of methodologies used hampers the interpretation of the results. Examples include the lack of standardised definitions for respiratory symptoms and/or diseases, and the lack of temporal relationships between the onset of respiratory symptoms and/or signs and GORD symptoms and/or signs. Moreover, it is difficult to evaluate whether GORD children are at increased risk of respiratory disorders in studies that do not assess the prevalence of same disorders in a representative control group. Similarly, the estimation of the prevalence of GORD in children with respiratory disorders by using investigational tools cannot be extrapolated to the general population, as the children are investigated by paediatric gastroenterologists after the failure of conventional therapy. Finally, although it is now generally agreed that the presence of abnormal GOR extending into the proximal oesophagus and cricopharyngeal region is a risk factor for aspiration, its finding does not inevitably imply aspiration.

Pathophysiology of GOR-induced CPA

Proximal reflux episodes followed by direct irritation of the airway epithelium is the pathophysiological mechanism of GOR-related CPA. Through elaborate reflex mechanisms, a close functional relationship exists between the oesophagus and the airway, which ensures the safety of the airway against aspiration of material during an episode of GOR. For instance, microaspiration of gastric contents into the lung can be prevented by protective mechanisms such as oesophageal clearance and reflex closure of the upper oesophageal sphincter and/or vocal cords. However, even if aspiration occurs, gastric aspirate may be rapidly cleared from the lung. In experimental animals, acute instillation of gastric contents in the main bronchus leads to a wide array of histopathological changes both in areas directly in contact

with acid as well as in distant areas, including alveolar haemorrhage and pulmonary oedema. These changes seem not to be related to direct tissue damage induced by acid, but to the inflammatory cascade triggered by release of preformed cytokines from damaged cells, such as leukotriene B4 and thromboxane A2. These in turn stimulate the synthesis of other cytokines, such as interleukin (IL)-1, tumour necrosis factor-α and IL-8, followed by neutrophil recruitment. Repetitive chronic aspiration induces loss of parenchymal architecture, collagen deposition with fibrosis, bronchiectasis and obliterative bronchiolitis.

Several experimental and clinical studies have suggested a role of acid microaspiration in the pathophysiology of bronchial inflammation and bronchoconstriction. However, more recently the focus has turned to weakly acidic and non-acidic reflux events, which make up the majority of reflux. A study reviewing children with predominantly acidic refluxate (pH <4) and those with predominantly weakly acidic refluxate showed a higher epithelial cell concentration in BAL and similar substance P and pepsin concentrations in the weakly acidic group, indicating airway inflammation is comparable in both groups, although it probably occurs *via* different mechanisms. Bile acid and pepsin from patients on antisecretory therapy stimulate the production of transforming growth factor-β *via* a p38 mitogen-activated protein kinase-dependent pathway, connective tissue growth factor and IL-8 secreted by bronchial epithelial cells, suggesting their ability in provoking a significant bronchial reaction. Moreover, it has been shown that non-physiological levels of pepsin and acid are able to induce inflammation and death of airway epithelial cells, with an effect inversely related to the acid concentration.

Diagnosis

Before considering GOR as cause of CPA, the clinician needs to rule out the presence of swallowing dysfunction, and consequently, a direct aspiration of fluid/food with swallowing. The following sections describe the steps to determine whether pathological GOR is occurring, with gastric contents entering the lung, and to assess the likelihood of an association between GOR and respiratory symptoms and/or signs. Unfortunately, at the present time, there is no sensitive, specific test for GOR-related aspiration, and the diagnosis is made by combining clinical, laboratory and radiological tests.

Biomarkers

Many attempts have been made to identify a biomarker for reflux aspiration. Ideally, a biomarker for aspiration should be a noninvasive measure of a quantifiable marker within the lung, which is specific for reflux aspiration and reliably detectable over a sustained period after aspiration.

Lipid-laden macrophages (LLMs) in BAL have been reported as useful markers of GOR-related pulmonary aspiration. First described in 1985 by Corwin and Irwin, these are macrophages in which ingested lipid can be seen under the microscope. The amount of lipid per single macrophage is determined after Oil Red O staining of BAL using a semiquantitative method, which assigns a score ranging from 0 to 4 to each cell according to the amount of lipid in the cytoplasm (figure 1). The number of cells graded 0, 1, 2, 3 and 4 is calculated for each patient and the final LLM index (LLMI) is determined by evaluating 100 cells, with the highest possible score being 400. A LLMI of 165 is considered to be consistent with aspiration. A rapid increase in LLMs occurs after intratracheal milk instillation, lasting for ≥2 days after a single instillation and longer with recurrent instillation. In one study, LLMI seemed to correlate with

Figure 1. Fluid from BAL stained with Oil Red O. The lipid is seen within the cytoplasm of alveolar macrophages. Courtesy of F. Midulla, Paediatric Emergency Service, Dept of Maternal, Infantile and Urological Sciences, Sapienza University, Rome, Italy.

total number of non-acid reflux episodes and the number of non-acid reflux episodes reaching the proximal oesophagus (Borrelli *et al*., 2010); however, these findings are highly debated. The role of LLMI as a standard test for aspiration is widely debated, as studies have shown significant variation in its sensitivity (57–100%) and specificity (57–89%). An increase in LLMs has been described in other pulmonary conditions, such as CF, infections, use of intravenous lipid infusion, and pulmonary fat embolism in sickle cell disease, suggesting that any pulmonary insult severe enough to cause tissue destruction may result in an increase in LLMs by releasing lipids from cell membrane. Despite these significant limitations, an elevated LLMI may provide supporting evidence of aspiration in a selected group of children.

Another possible biomarker is pepsin. Pepsin is a proteolytic enzyme of gastric origin and should not be detectable in the lower respiratory tract. In theory, its detection in the BAL fluid should be a highly sensitive and specific marker for GOR-related aspiration. The presence of pepsin in the BAL fluid is detected in a high percentage of children with GORD and chronic respiratory symptoms (83%), and its level correlates with proximal acid GOR. Pepsin has been used as marker of aspiration in both preterm infants and children ventilated in intensive care settings. Finally, increased BAL pepsin has been found in adults and children with CF, before and after lung transplantation. However, recent studies have shown conflicting evidence as to its utility. Abdallah *et al*. (2016) discovered the presence of pepsin in the BAL fluid of their control group. This is hypothesised to be due to the aspiration of nasopharyngeal secretions during sleep. In this study, pepsin was found to have a sensitivity of 62% and a specificity of 55% compared with abnormal oesophageal combined impedance-pH in a group of wheezy infants. It has been suggested that the role of pepsin in BAL could be in assessing children with negative oesophageal combined impedance-pH studies but ongoing typical GORD symptoms. Salivary pepsin has also been assessed as a possibly noninvasive biomarker by several groups and the results have been conflicting. A study in adults found a sensitivity and specificity of 87% (Yuksel *et al*., 2012), but a paediatric study found a sensitivity of 42% and a specificity of 58% (Dy *et al*., 2016). Notably, 50% of the paediatric cohort were unable to produce saliva for this test.

Radiology

An upper gastrointestinal contrast study is not a reliable test for discriminating between physiological and pathological GOR. However, it is useful to confirm or rule out anatomical abnormalities of the upper gastrointestinal tract that may predispose to GOR-related aspiration. Scintigraphy has been widely used for the evaluation of

GOR in children. However, its low sensitivity and specificity compared with 24-h oesophageal pH monitoring makes this test unsuitable for the routine diagnosis and management of GOR in infants and children. Evidence of pulmonary aspiration during the test is usually assessed through images obtained up to 24 h after administration of the radionuclide. However, a negative test does not exclude the possibility of infrequent aspiration. Furthermore, even in the presence of aspiration, the technique is unable to discriminate between aspiration due to swallowing dysfunction and GOR-related aspiration.

Oesophageal studies

Although oesophageal pH monitoring has been regarded for many years as the most sensitive and specific diagnostic tool for diagnosing GORD, its sensitivity and specificity are not well established. In fact, pH monitoring has significant limitations because of its inability to detect non-acidic retrograde bolus movement in the oesophagus, especially in infants who are frequently fed milk and/or milk-based formulas. Multichannel intraluminal impedance (MII) monitoring has the advantage of being able to detect anterograde or retrograde bolus movement into the oesophagus, in a pH-independent fashion. Combined MII and pH (MII-pH) monitoring can characterise the reflux episodes as acid or non-acid (figures 2 and 3) and determine the composition (liquid, gas or mixed), as well as the height reached by the refluxate. However, there are some limitations of MII-pH monitoring. First, there is a degree of subjectivity in the interpretation of the results, but improvements in automated software analysis will help to overcome this pitfall. Secondly, a positive test in a child with symptoms and signs of aspiration does not inevitably imply a cause–effect relationship, and a negative test does not exclude the possibility of GOR-related aspiration. There have been attempts to use full column refluxate data to assess for risk of aspiration; however, there was no correlation with pepsin positivity in full column reflux, with 46% of reflux events being full column. Finally, the results of MII-pH monitoring are still difficult to interpret given the absence of normal paediatric reference values.

Figure 2. Example of an acid reflux episode reaching the proximal oesophagus. Impedance measurements from the proximal, intermediate and distal oesophagus, and pH are shown. The episode is categorised as acid because of the presence of a pH drop to <4 during the impedance-detected episode (arrow and shaded area).

Figure 3. Example of a non-acid reflux episode reaching the proximal oesophagus. Impedance measurements from the proximal, intermediate and distal oesophagus, and pH are shown. The episode is categorised as non-acid, based on the absence of a pH drop to <4 during the impedance-detected episode (arrow and shaded area).

High-resolution oesophageal manometry is becoming more widely available for use in the diagnosis of motility disorders. This allows measurement of the function of the sphincters and oesophageal body motor activity. Its role in the assessment of CPA is limited; it may be of use in diagnosing underlying oesophageal stasis, which puts patients at higher risk of aspiration. The current recommendation is that manometry should not be routinely performed unless an underlying motility disorder is suspected.

Treatment

Medical and conservative therapies are the initial choice for children with GORD and features of aspiration. This includes thickened feeds, prokinetics and acid secretion inhibitors. Proton pump inhibitors (PPIs) have been widely used to decrease acid reflux and the perceived risks are low. Although the efficacy of PPIs has been shown for the treatment of patients with oesophageal symptoms and signs, no data are available for GORD-related respiratory symptoms. It is important to point out that, although PPIs change the gastric pH, they do not prevent episodes of reflux-related microaspiration. Given the increased evidence that non-acid reflux probably leads to respiratory symptoms more than acidic reflux, their utility should be reviewed in these patients. Feed thickener should be used as the first line of treatment in these patients.

Nasal or gastrojejunal feeding provides an approach to prevent reflux-related pneumonia, especially in children with severe neurological impairment; sometimes it needs to be combined with fundoplication.

Fundoplication has become the surgical antireflux procedure of choice in children with severe and persistent respiratory symptoms due to GOR refractory to medical treatment. It represents one of the three most commonly performed major operations in childhood. Resolution or improvement of respiratory symptoms after fundoplication occurs in 48–92% of patients. It has been demonstrated that fundoplication could reverse BOS in some lung transplant recipients with pathological reflux. Unfortunately, in children with neurological impairment, who represent the group with the greatest incidence of GOR-related aspiration, symptom relapse has been reported in up to 60% of them following the first antireflux surgery, and there is a high failure rate even

after redo-Nissen fundoplication. For this reason, the selection of patients undergoing Nissen fundoplication needs to be accurate and alternative surgical strategies, such as jejunostomy feeding, need to be considered.

The insertion of a gastrojejunostomy tube has the advantage of allowing gastric venting as well as establishing jejunal feeding. However, the tendency for accidental displacement renders this option impractical for long-term use, and surgical jejunostomy represents a more permanent solution. Although with either type of jejunal feeding, aspiration of gastric juice may still occur, they show a similar rate of aspiration pneumonia and mortality compared with fundoplication. Finally, in children with severe, irreversible neurological impairment and intractable aspiration despite the medical and surgical treatments previously described, a more aggressive surgical approach, such as oesophagogastric disconnection with oesophagojejunal anastomosis, may be required.

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Laryngeal cleft, tracheo-oesophageal fistula and oesophageal atresia

Colin Butler, Richard Hewitt, Paolo de Coppi and Colin Wallis

Laryngeal cleft and tracheo-oesophageal fistula (TOF) are congenital anomalies of the upper aerodigestive tract that are the result of failure of midline structures to develop appropriately *in utero*. This leads to abnormal communication between the proximal airways (larynx, trachea and bronchus) and the oesophagus. Oesophageal atresia (OA) is an associated congenital malformation; it is a failure of the oesophagus to form that can occur with or without the presence of a fistula.

Most children with these anomalies will be identified in the neonatal period, with airway obstruction, recurrent chest infections, swallowing and/or feeding difficulties. The spectrum of congenital abnormality is diverse, with equally broad symptoms depending on the pathology. While predominantly identified in the neonatal period, in some children, with smaller clefts and TOFs with no atretic component, the diagnosis may be extremely subtle and overlooked and only subsequently found in the older child when persistent symptoms have been investigated further. These children will present with a history of recurrent chest infections due to aspiration or a chronic cough. A high index of suspicion is required to identify the underlying cause.

Laryngeal clefts and TOF/OA share many symptoms, but often occur in isolation. Both pathologies presenting together is rare but is sometimes seen.

Laryngeal clefts

Laryngeal clefts account for 0.3–0.5% of all congenital anomalies of the larynx. The incidence has been reported as one in 20 000 births, with a male preponderance (male to female ratio of 5:3). However, the incidence may be higher, with laryngeal clefts identified in 7.6% of airways undergoing investigation for chronic cough

Key points

- A laryngeal cleft is a congenital anomaly where there is a posterior defect in the trachealis leading to a cleft of variable size between the trachea and the oesophagus.
- A tracheo-oesophageal fistula is an abnormal connection between the large airway (trachea and bronchus) and the oesophagus.
- Both pathologies are associated with respiratory symptoms that can be life-threatening in severity.

Figure 1. Laryngeal cleft classification: type 1 supraglottic inter-arytenoid cleft; type 2 partial cricoid cleft; type 3 total cricoid cleft extending into cervical trachea; type 4 laryngo-oesophageal cleft extending beyond thoracic inlet. Reproduced from Benjamin et al. *(1989) with permission.*

and/or aspiration. While mainly sporadic in inheritance, there are reports of an autosomal dominant pattern.

The larynx is derived from the fourth and fifth branchial arches and during fetal development the trachea and the oesophagus share a common lumen. The respiratory system develops from the primitive foregut at 20 days with the formation of the tracheo-oesophageal septum. The process is typically complete at 6–7 weeks with complete fusion of the cricoid cartilage. Failure of this septal advancement leads to development of a cleft, with longer clefts a result of early failure during gestation. Risk factors include maternal drug and alcohol exposure and polyhydramnios.

Laryngeal clefts can be variable in length, ranging from just the supraglottic inter-arytenoid region, extending to beyond the carina. The most used classification system is that of Benjamin *et al.* (1989), which classifies clefts into the following four types (figure 1):

- Type 1: the cleft involves the supraglottic inter-arytenoid region but no further than the level of true vocal cords
- Type 2: the cleft extends beyond the true vocal cords into the cricoid (but not completely through it)
- Type 3: the cleft extends through the cricoid and up to cervical trachea
- Type 4: the cleft extends into the posterior wall of the thoracic trachea as far as the carina

Laryngeal clefts can occur in isolation or associated with other abnormalities. These abnormalities include those of the respiratory tract (affected in ~50% of cases), TOF (in 20–37%), and vocal cord palsies and malacia (in 65%). Other malformations include cardiac defects (atrial and ventricular septal defects), gastrointestinal and genitourinary anomalies. They are also associated with syndromes, particularly those with midline malformations. These include Opitz G syndrome, which is associated with cleft lip and palate, and typically inherited through 22q deletion. It is associated with conditions such as velocardiofacial, DiGeorge and Cayler cardiofacial syndrome.

Figure 2. Anatomical configurations seen with TOF/OA: a) OA with distal TOF; b) Pure OA without a fistula; c) H-type without OA; d) OA with proximal and distal fistula; e) OA with proximal fistula. Adapted from Frank Gaillard, Radiopaedia.org.

Laryngeal clefts can be also seen in VATER/VACTERL and CHARGE associations, as well as in Pallister–Hall syndrome, an autosomal dominant condition associated with mutations in Gli3 gene.

Tracheo-oesophageal fistula and oesophageal atresia

TOF/OA has an incidence of one in 3500 births. The anomalies are classified according to their anatomical configuration. Broadly, this includes OA with distal TOF (the most common at 84%), an isolated OA without a fistula (8%), an H-type configuration without OA (4%), OA with both proximal and distal fistula (3%), and OA with a proximal fistula (1%) (figure 2). In a similar manner to laryngeal clefts, embryological TOF/OA arises due to abnormal separation of the respiratory system from the primitive foregut, with failure of posterior positioning of the tracheo-oesophageal septum, leading to a retained connection between the trachea and oesophagus. OA occurs due to failure of the oesophagus to recanalise at 8 weeks of embryonic development.

TOF/OA is considered part of VACTERL (19% of patients) and is associated with many midline anomalies. Overall, cardiac anomalies (ventricular septal defects being the most common) are seen in ~30% and spinal anomalies occur in 24%. VACTERL is thought to be related to sonic hedgehog (SHH) signalling anomalies and downstream transcription factors Gli2 and Gli3. Associated chromosomal anomalies include trisomy 18 and trisomy 21 (the latter occurring less frequently).

Clinical diagnosis

Laryngeal clefts

Presentation of symptoms is variable, and typically determined by the length of the cleft and associated anomalies. Type 1 and 2 clefts may have minimal symptoms and can remain undiagnosed. Severe clefts will be immediately apparent at birth with obstructive airway symptoms, including stridor and cyanotic episodes, necessitating airway intervention. In those with smaller clefts, symptoms may be more related to recurrent aspiration. Other symptoms may include poor feeding and failure to thrive. Differential diagnosis includes a TOF, oesophageal stricture, cricopharyngeal spasm, neuromuscular abnormalities, laryngomalacia, reflux, and vocal cord paralysis.

A persistent cough on swallowing free fluids should alert clinicians to the possibility of a laryngeal cleft. A videofluoroscopic swallow study (VFSS) will show contrast penetrating the posterior aspect of the glottis. It is, however, important to note that it can be difficult to distinguish the impact of a cleft and neuromuscular incoordination on the VFSS. Other investigations may include chest radiography, which may show pulmonary infiltrates as a result of aspiration. Diagnosis is ultimately *via* direct

Figure 3. Endoscopic images of a laryngeal cleft from a) proximal to c) distal (left to right), demonstrating a long laryngeal cleft extending to the thoracic inlet. The cleft is not so apparent at a) the glottis, due to excess mucosal edges of the cleft. This becomes more apparent at b) the subglottis and c) the trachea.

visualisation through microlaryngoscopy and tracheobronchoscopy (MLB), although it can be missed even on direct endoscopy due to redundant laryngeal and oesophageal mucosa prolapsing into the cleft. Careful examination is required, with palpation or probing of the larynx to ensure the diagnosis is not missed (figure 3).

Tracheo-oesophageal fistula and oesophageal atresia

Antenatal diagnosis of TOF with OA is typically suspected with a maternal history of polyhydramnios and the antenatal ultrasound scan may show absence of a fetal stomach bubble. The atresia will usually lead to overt symptoms in the newborn with excess secretions leading to drooling, choking and respiratory distress. Feeding may exacerbate symptoms and will not be possible. Gastric distension is a common feature and can lead to respiratory compromise. Failure to insert a nasogastric or orogastric tube more than 10–15 cm, with radiographic evidence of coiling of the catheter in the upper oesophageal pouch, will usually confirm the diagnosis. A lateral chest radiograph will demonstrate the distal TOF and air will be seen in the gastrointestinal tract. In anatomical configurations where there is no OA, symptoms may not be as severe and only be apparent on feeding. The lungs will be at risk due to reflux of gastric contents leading to recurrent infections. In H-type configurations, delayed diagnosis has been reported up to 4 years of age or completely missed and only confirmed as an adult. In these cases, diagnosis can be confirmed by a dynamic prone tube oesophagogram.

Airway management

A large laryngeal cleft will present with acute respiratory distress in a newborn infant. Intubation may be difficult as the endotracheal tube (ETT) is likely to displace posteriorly into the oesophagus. Face mask ventilation may be possible, but can lead to difficulty as air enters the stomach. This leads to distension and splinting, compounding the respiratory distress. Placement of a nasogastric tube will aid stomach decompression and can be helpful in ETT placement as it will encourage anterior positioning of the tube in the tracheal lumen. In these situations, advancing the ETT into the distal trachea can be helpful and aid adequate ventilation. Placement under direct endoscopy is sometimes required.

A newborn infant with TOF/OA may present with acute respiratory distress and difficulties with ventilation due to distal communication with the trachea. Proximal placement of the ETT with inadvertent ventilation of the gastrointestinal tract will exacerbate this compromise; distal positioning of the ETT may overcome this.

Surgical management

Laryngeal clefts

Small clefts, when they are diagnosed, may be initially treated with the use of thickened feeds and antireflux medication prior to surgical correction. Larger clefts (type 3 and type 4) will not usually tolerate a trial period of conservative management and will need an early surgical repair. Repair can be either endoscopic or open, which is largely dependent on the cleft length. Endoscopic repair is usually performed on type 1 and 2 clefts and involves excising the edges of the cleft with closure either as a single layer or two-layer technique. In all cases, attention to gastrointestinal reflux is required with optimisation of medical management. If necessary, a Nissen fundoplication should be considered in severe cases, which can be combined with the initial repair. Long laryngeal clefts will typically be approached using an open approach with exposure of the laryngotracheal framework. Access to the posterior wall of the trachea is through a midline incision over the larynx and trachea (laryngofissure), the cleft is identified and mucosal excess excised. The edges of the cleft are sutured in a two-layer technique. In some cases, graft material (either periosteum or cartilage) is used between the layers for additional support. Intubation is usually required for 1 week to allow the cleft to heal prior to extubation.

With a short cleft repair a child can return to their normal oral diet immediately (normally with thickeners due to aspiration risk). Following a speech and language therapy (SALT) assessment, a subsequent trial on free fluids can be attempted.

Tracheo-oesophageal fistula and oesophageal atresia

Operative repair of a TOF with or without OA is dependent on the configuration. With an OA and a distal TOF (the most common variant), the fistula is ligated *via* a right posterolateral (extrapleural) thoracotomy and a primary oesophageal anastomosis. If there is a right aortic arch, a left-sided thoracotomy is preferred. A primary oesophageal anastomosis may not be possible if there is a long gap (considered >2 vertebral bodies). In these cases, a gastrostomy will be required for feeding. Options for reconstruction include delayed primary repair using native oesophagus or replacement with stomach or colon. Timing of this is variable, but it is often delayed until 9–12 months of age. In the H-type TOF, the approach depends on whether the fistula is in the neck or in the chest. A proximal fistula (in the neck) is approached by lateral neck dissection and repair by a primary anastomosis. Thoracoscopic approaches may be possible if the fistula is low in the chest.

Outcomes

Laryngeal clefts

Outcomes from laryngeal clefts are related to the length of the cleft. Type 1 and 2 clefts generally have excellent prognosis, with almost all surgeries leading to symptom improvement for children identified at risk of recurrent aspiration. Immediate complications are rare, but an overtight repair at the glottic level can lead to immediate respiratory compromise due to limited vocal cord movements. Post-operative oedema at the laryngeal level has been reported and has led to emergency tracheostomy post-operatively. Other complications include failure of the cleft to close, which can be related to dehiscence at the site of repair. Longer clefts, particularly those that extend to the thoracic inlet and beyond, have a protracted recovery due to inherent structural malacia associated with the cleft. There is also often a degree of oesophageal dysmotility and the need for a gastrostomy is not uncommon.

Tracheo-oesophageal fistula and oesophageal atresia

Survival is generally reported at >97% in neonates with >1500 g birthweight without cardiac lesions; however, this drops to 22% if <1500 g and a severe heart anomaly coexists. While low birthweight is often seen, following repair children rapidly grow and "catch up". Feeding aversion is common, particularly if OA requires a delayed repair. Other gastrointestinal problems encountered include strictures at the anastomosis and oesophageal dysmotility. These lead to problems in managing secretions, with the risk of aspiration, food bolus obstruction and "choking spells". Strictures may need repeat dilatations and children will often adapt to feeding issues with the aid of SALT, skilled nursing and dietetic support. In general, long-term quality of life measures are good, with reports from adults with corrected TOF/OA showing minimal/no impairment.

Respiratory issues

Respiratory problems are common in children with long laryngeal clefts and those with TOF/OA, with the most common issue being severe airway malacia. This is seen in 10–20% of cases and may lead to significant difficulty in extubation. Post-operatively the residual tracheal malacia at the site of the connection leads to a characteristic brassy cough and even episodes of profound desaturation. Breathing difficulties can occur during mealtimes. NIV may be required in the short term and if the malacia is considered severe, an aortopexy may be indicated to improve ventilatory requirements.

Reflux is equally common and may require treatment to reduce the risk of aspiration. The vast majority of respiratory symptoms improve as children get older and approach adolescence.

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Foreign body aspiration

Iolo Doull

Foreign body aspiration (FBA) is a serious and potentially fatal condition in infants and children. Choking may occur with obstruction in the oral cavity, and insertion injuries may occur when foreign objects are present in either the nose or nasopharynx. Ingestion injuries can occur with a foreign body in the oesophagus or stomach. Depending on the age of the child and the size of the foreign body, airway obstruction and aspiration can occur anywhere in the respiratory tract. Large airway obstruction preventing adequate ventilation can be fatal, while more distal obstruction can lead to overinflation, atelectasis and subsequent chronic changes including bronchiectasis.

Aetiology and predisposing factors

Infants <3 years of age are at greatest risk. Infants have smaller airways than adults. Flow through an airway is inversely proportional to the radius to the fourth power, thus small changes in airway radius lead to proportionately greater changes in airflow, so even a small foreign body can be dangerous. Compared with adults the larynx is in a relatively high position in infants with the epiglottis close to the root of the tongue, increasing the risk of aspiration. Infants have gag, cough and glottic closure reflexes to protect against aspiration, but they may not always be fully developed from birth, and swallowing, in particular, may be delayed. Children with developmental delay are at increased risk of aspiration.

Incisors are necessary to bite through food, and molars are necessary to masticate the food in preparation for swallowing. However, incisors erupt ~6 months before molars and so food may not be appropriately pulped, remaining as a small smooth or rounded mass, the ideal shape to obstruct an airway if aspirated. Infants and children are less able to cough out a foreign body aspirated into the airway; peak cough flows at

Key points

- Children <3 years of age are at greatest risk of foreign body aspiration (FBA).
- FBA must be suspected for any witnessed choking episodes.
- FBA cannot be excluded on either normal physical examination or chest radiograph.
- Removal of the foreign body is the primary objective and mainstay of treatment.

4 years of age are approximately a quarter of that of adults. Once lodged in an airway, mucus and local inflammation will quickly result in complete airway obstruction, thus diminishing the possibility of forced clearance. Finally, infants are easily distractible and often inattentive, are more likely to talk and to run around while chewing, and more likely to put a non-organic foreign body in their mouth while playing.

Epidemiology

The exact incidence of fatal and non-fatal FBA and choking-related injuries in children is unclear; the available data are probably an underrepresentation, and international comparisons are difficult. Analysis of the US National Electronic Injury Surveillance System in 2001 identified 17 537 children aged ≤14 years treated in emergency departments for choking-related episodes (rate 29.9 per 100 000 population). Rates were highest for infants (140.4 per 100 000), decreasing with each successive age cohort to a rate of 4.6 per 100 000 for those aged 10–14 years of age. Many choking-related episodes were mild and included minor pharyngeal irritation without FBA, but ~10% required hospitalisation and for every 110 children treated there was one death. The most common food substance was candy/gum (19%), while the most common non-food item was coins (12.7%). Mortality is between 0.7% and 1.8%, but a further 2.2% may suffer anoxic brain injury, suggesting that up to 4% may have fatal or significant sequelae. Infants <1 year of age appear at greatest risk, with ~4% mortality.

A review of 13 266 cases (91 reports) of FBA from high-income countries and 24 731 (83 reports) from low/medium-income countries (total 37 997) demonstrated similar demographics in both populations (Foltran *et al*., 2013). 60% of subjects were male and 40% female, and the majority were aged ≤3 years (high-income countries 75%, low/middle-income countries 60%). The diagnosis of an inhaled foreign body was delayed by >24 h in ~60% of the cases.

In a review of 30 reports comprising 12 979 children with suspected FBA, of whom 11 145 had aspirated an object (14% false negative rate), over 80% of foreign bodies were organic materials, with nuts and seeds being the most common. Approximately 90% were lodged in the bronchial tree, with the remainder in the larynx or trachea. Foreign bodies were more likely to lodge on the right side (52%) than the left (33%), while a small number of objects fragmented and lodged in different parts of the airways.

Presentation

A history of a witnessed choking or gagging event is very suggestive of FBA. A child aged <3 years is rarely able to give a clear history, and an adult is present in over half of such cases.

The clinical findings will depend on the level at which obstruction has occurred, although most patients will initially have a paroxysmal cough, but this may then resolve leaving no symptoms. Respiratory distress and/or cyanosis suggest obstruction of a large airway and warrant emergency treatment. Laryngeal obstruction may cause a hoarse voice or aphonia, drooling, stridor and/or wheezing and respiratory distress. Tracheal obstruction may present with biphasic or monophonic wheeze and bilaterally decreased breath sounds and respiratory distress. More distal obstruction may result in unilateral monophonic wheeze and unilateral decreased breath sounds. Cough and wheeze are the most sensitive signs, while stridor and cyanosis are the most specific.

Up to 20% may be misdiagnosed and inappropriately treated before FBA is diagnosed. Late presentations may be misdiagnosed as pneumonia, asthma or laryngitis

presenting with decreased chest movement, decreased breath sounds, wheezing and possibly crackles and pyrexia.

Investigations

A chest radiograph is mandatory for all cases of suspected FBA to localise potential foreign bodies and assess chest asymmetry, but also to exclude other causes for respiratory distress. Flat objects, such as coins, tend to align in the sagittal plane in the trachea, whereas objects in the oesophagus tend to align in the anterior plain. Lateral chest radiographs can sometimes be helpful.

Chest radiograph abnormalities may include asymmetry, such as air trapping and overinflation, infiltrates and possibly mediastinal shift. For older children who are able to cooperate, a combination of inspiratory and expiratory films can be helpful. Partial airway obstruction may cause a valve-like effect resulting in air trapping and mediastinal shift being more prominent on expiratory films. The majority of foreign bodies are organic material and not usually radio opaque. Thus, although plain chest radiographs are very sensitive for non-organic foreign bodies, only 10% of foreign bodies will be visible on the chest radiograph. Pneumothorax and pneumomediastinum are infrequent findings. Chest radiographs may be normal in ~17% of children subsequently shown to have FBA. Later radiographic features include segmental collapse, consolidation or atelectasis. Fluoroscopy is unhelpful.

CT can be useful in assessment of FBA in stable children, offering greater sensitivity than plain radiographs. The CT scan should ideally be performed in volumetric acquisition with multiplanar reconstructions without contrast using a low-dose protocol. The radiation dose should be <2 mSv. A large multicentre prospective study of CT scans in FBA reported a sensitivity of 94–98% and a specificity of 95–97% (Manach *et al*., 2013). A CT scan is also useful in delineating other airway pathologies that might mimic the signs of FBA.

Treatment

Immediate treatment of FBA by parents or carers may dislodge the foreign body. In infants, back slaps in a head down position with or without chest thrusts are the treatment of choice. Abdominal thrusts including the Heimlich manoeuvre appear more appropriate for older children.

FBA must be suspected for any witnessed choking episodes. Although a history of inhalation can be elicited from the parent in many cases, FBA cannot be excluded on either normal physical examination or chest radiograph.

Removal of the foreign body is the primary objective and mainstay of treatment. Rigid bronchoscopy is the classical investigation and treatment of choice, although a common strategy is to use rigid bronchoscopy for children with convincing evidence of FBA, while children with a less clear-cut history or findings undergo flexible bronchoscopy. If removal of a foreign body is attempted by flexible bronchoscopy, the airway must be secured either with a laryngeal mask or endotracheal tube.

The majority of cases of FBA in Europe are treated in ENT departments where rigid bronchoscopy may be the primary intervention, although there is increasing use of flexible bronchoscopy. False negative bronchoscopies are preferable to false positives, and thus a proportion of bronchoscopies for FBA should be negative, with the reported incidence varying from 9% to 16.5%.

Rigid bronchoscopy allows control of the airway at the same time as instruments can be advanced to remove the foreign body in a safe way, while also facilitating removal

of mucous plugging and installation of saline or mucolytics to areas of lung collapse. Sometimes it is helpful to control the airway with a rigid bronchoscope, and then pass the flexible bronchoscope inside the rigid bronchoscope. Direct removal is usually undertaken either with alligator jaw or cup forceps; alternatively, an expandable wire basket can be passed distal to the foreign body, and expanded and withdrawn. For organic material, considerable care is required to prevent disintegration of the foreign body resulting in multiple smaller foreign bodies. Balloon-tipped catheters can be used to dislodge foreign bodies, particularly round foreign bodies, which may be lodged with surrounding granulation tissue. The catheter is passed distal to the foreign body before inflation, and once dislodged the foreign body can then be removed using conventional instruments. There is limited evidence for the use of a cryoprobe, which rapidly freezes tissue and leads to tissue adhesion (cryoadhesion), for foreign body removal. It appears particularly attractive for organic foreign bodies with high water content, although it has been used for retrieval of non-organic foreign bodies. Once the foreign body is grasped, it is imperative to position the foreign body close to the distal end of the bronchoscope and then withdraw the whole instrument (rigid or flexible bronchoscope). Where a foreign body has obstructed a large airway, care must be taken to avoid the potentially catastrophic loss of the foreign body into the contralateral lung. Once manoeuvred to the larynx it should be removed *via* the lower triangle of the glottis to avoid trauma to the vocal cords. If the child is clinically stable and it is impossible to remove the foreign body due to inflammation and granulation tissue, it is reasonable to abort and administer systemic corticosteroids and antibiotics for a few days before repeating the procedure.

In the rare circumstance where the foreign body is too large to pass through the subglottic space (the so-called monkey trap phenomenon), a temporary tracheostomy may be required. For life-threatening respiratory compromise there are case reports of open thoracotomy or cardiorespiratory bypass support to facilitate foreign body extraction.

Although the vast majority of foreign bodies are removed with a rigid bronchoscope, there is increasing evidence of the use of flexible bronchoscopy. In a study of over 1000 children, foreign bodies were successfully removed by flexible bronchoscopy in over 90% (Tang *et al*., 2009). Flexible bronchoscopy may be superior to rigid bronchoscopy in the removal of foreign bodies from distal airways and particularly upper lobe bronchi. If foreign body extraction is attempted by flexible bronchoscopy, it is imperative that rigid bronchoscopy is immediately available should removal appear difficult or complications occur.

There is lack of consensus on the best anaesthetic regime, with some authors advocating paralysis while others advocate spontaneous ventilation. Positive airway pressure during the procedure and particularly afterwards is useful for re-inflation of atelectatic lung areas. It is important that after removal of a foreign body the rest of the airways are checked to ensure there are no smaller objects. If there is significant bleeding during the procedure, diluted (100 $mg \cdot L^{-1}$) adrenaline can be administered topically. Pre-operative antibiotics are usually administered and continued for a 5-day course while systemic corticosteroids may decrease airway oedema.

For patients presenting with respiratory distress or cyanosis, emergency bronchoscopy is essential. However, for patients who are clinically stable without respiratory compromise, it is reasonable to take the child to theatre in a planned manner during normal working hours, even if this incurs a delay. It is unlikely that a delay of <24 h in removal of the foreign body will have any significant long-term effects on the lung. A review of over 3000 FBAs suggested that sequelae were more common where a

foreign body had been present for >1 week: 27.2% *versus* 6.7% for those <1 week. Long-term sequelae include focal bronchiectasis distal to the site of obstruction.

Complications

In a meta-analysis of 26 studies where major complications were specified, deaths occurred in 43 (0.42%) out of 10 236 cases. Death rates in individual studies varied between 0.21% and 0.94%, with approximately a third presenting with hypoxic arrest and a third arresting during the procedure. Major non-fatal complications occurred in 0.96% and included severe laryngospasm or bronchospasm requiring tracheostomy or intubation, pneumothorax or pneumomediastinum.

Prevention

Public health strategies can reduce the risk of FBA in children. There are European and US recommendations about the types of food that are inappropriate for younger children, and choking hazard warnings on small toys that pose particular risks of FBA. Parents should receive education and basic instructions on what to do in an emergency.

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Primary ciliary dyskinesia

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PCD is a rare inherited disease with an estimated prevalence of one in 10 000 births. PCD is clinically heterogeneous, complex to diagnose and requires multidisciplinary management throughout life. Despite being compared to diseases such as CF and non-CF bronchiectasis, PCD has a unique pathophysiology, and even without the existence of disease-specific therapy, its diagnosis and management by a specialist PCD team is extremely important.

This chapter summarises important aspects of PCD relevant for the paediatric pulmonologist; these include the pathophysiology, epidemiology, clinical manifestations, diagnosis and management of PCD.

Pathophysiology

PCD is caused by genetic mutations encoding proteins involved with motile cilia, leading to abnormal ciliary function. Motile cilia are found throughout the airways including the trachea, bronchi, Eustachian tubes, nose and sinuses. Normal ciliary beating comprises a coordinated forward and recovery stroke, clearing the mucus and secretions that accumulate in upper and lower airways, along with bacteria, particles and allergens. Ciliated epithelium also lines the fallopian tubes, predominantly on the apex of the mucosal folds, playing a role in the transport of egg cells to the uterus. The flagellum, which controls sperm motility, has a similar structure to respiratory cilia.

Key points

- The individual symptoms of PCD are nonspecific; combinations of symptoms starting in infancy are typical and require diagnostic testing.
- Diagnosis of PCD is complex and is based on a combination of tests including measurement of nasal nitric oxide, high-speed video-microscopy analysis, transmission electron microscopy, genetic analysis and immunofluorescence.
- Current management aims to prevent progressive and irreversible lung damage, hearing loss and developmental/educational delay, but there is limited evidence to guide patient treatment.
- PCD is a multisystem disease and therefore patient management requires a multidisciplinary approach.

Figure 1. Diagram depicting the ultrastructure of a normal ciliary axoneme in transverse section displaying the "9+2" formation. The boxes list all PCD-causative genes known to date, coupled with illustrative images of the ultrastructural defect seen by transmission electron microscopy (TEM). ODA: outer dynein arm; IDA: inner dynein arm.

In the brain ependyma, motile cilia propel cerebrospinal fluid through the cerebral ventricles.

Each motile cilium consists of a cytoskeleton (axoneme) covered by a cell membrane (figure 1). The axoneme comprises nine outer microtubule doublets and a central pair of singlet microtubules running along its length. Inner and outer dynein arms are anchored to the outer microtubules where they generate the force for the cilia's beating action. The axoneme also includes radial spokes and nexin links, which contribute to normal cilia motility.

PCD is usually inherited as an autosomal-recessive disorder; however, X chromosome-linked cases have also been identified. More than 40 disease-causing genes accounting for ~70% of PCD cases have been reported. These include genes that encode the many proteins that form the cilia axoneme, as well as genes important in the assembly of these proteins and the docking of ciliary structures. Most PCD-causing mutations are nonsense, frameshift or splice mutations and result in defects in the ciliary ultrastructure and/or ciliary beating (figure 1). This abnormal ciliary function impairs mucociliary clearance, typically leading to a persistent daily wet cough, recurrent sinopulmonary infections, bronchiectasis and serous otitis media.

Epidemiology

Although PCD has been estimated to affect approximately one in 10 000 people, its prevalence is probably underestimated. Many people remain undiagnosed or are

diagnosed late in life, despite symptoms starting soon after birth. This may occur because of a low awareness among physicians about PCD and the difficulty accessing a diagnostic service. In populations with a high proportion of consanguinity, the prevalence has been reported to reach one in 400 to one in 2000 people.

As is common in rare diseases, routine health statistics are a poor source of information for PCD epidemiological data. There are no PCD-specific identifier codes in the systems used in hospital records (*e.g.* the International Classification of Diseases). There is therefore a lack of data concerning incidence and mortality. Data on the spectrum and severity of clinical manifestations are dependent on case series and cohort studies, which have many biases, and there are only a few established national registries.

Growth, nutrition and lung function are affected in PCD patients from an early age. Height and BMI are generally lower than in healthy small children, and both are associated with worse lung function. Most patients "catch up" their BMI with age, but final height remains lower than in healthy peers. However, classical failure to thrive, which is often seen in untreated CF patients with pancreatic insufficiency, has not been reported in PCD. However, data on lung function in children with PCD show that FEV_1 is reduced, similar to the situation in CF. Lung function continues to decline throughout life; however, the decline from young adulthood onwards is less steep than in CF patients.

Historically, PCD was considered a relatively benign disease. However, several studies have shown that PCD can have a relatively severe course. For example, in addition to the progressive decline of FEV_1, the majority of patients have bronchiectasis by adulthood, mostly affecting the middle and lower lobes as opposed to the usual upper lobe compromise seen in CF. Many adults have severe lung disease with chronic *Pseudomonas* infection, and some become oxygen dependent. Although little is known about the life expectancy of people with PCD, there are patients who live to late adulthood.

There is mounting evidence that specific ultrastructural and genetic defects may lead to worse disease progression and worse lung function. Further research is needed on predictors of long-term prognosis, including the effect of sex, early diagnosis and different management strategies. There are no data on how environmental factors that are relevant for other lung diseases (*e.g.* breastfeeding, immunisations, active and passive smoking, pollution) might influence the clinical course of PCD.

Clinical manifestations

Motile ciliated cells are situated in different locations of the human body and thus ciliary dysfunction results in a wide range of clinical manifestations involving several organ systems. In the respiratory tract, impaired mucociliary clearance causes upper and lower respiratory symptoms throughout life. Symptoms usually start in early infancy. Neonatal respiratory distress is common in full-term neonates with PCD and often requires prolonged oxygen therapy and admittance to intensive care. Neonatal respiratory distress usually starts several hours after birth and is often accompanied by lobar collapse on chest imaging. From early life, patients have a persistent daily wet cough and suffer from recurrent lower respiratory infections. Pulmonary infections persist in adulthood, and almost all patients develop bronchiectasis.

Neonatal rhinitis might also appear hours after birth, and persistent rhinitis is often a feature of PCD. Recurrent sinusitis and acute otitis media are common, and many children have chronic serous otitis media with effusion (glue ear) with conductive

Table 1. Who should be referred for PCD diagnostic testing?

1) Patients with several of the following features:
Persistent wet cough since early childhood
Situs anomalies
Congenital cardiac defects
Persistent rhinitis
Chronic middle ear disease with or without hearing loss
Term infants with neonatal upper and lower respiratory symptoms or neonatal intensive care admittance
2) Patients with normal situs presenting with other symptoms suggestive of PCD
3) Siblings of PCD patients, particularly if they have symptoms suggestive of PCD
4) Patients identified by the use of combinations of distinct PCD symptoms and predictive tools (*e.g.* PICADAR)

Adapted from Lucas *et al*. (2017b) with permission.

hearing impairment. Although ear symptoms are often reported to improve with age, sinonasal symptoms persist and the majority of patients develop chronic rhinosinusitis.

Normal functioning of motile nodal cilia is responsible for development of normal left–right asymmetry of organs in the developing embryo. Therefore, ~50% of patients have situs inversus and another 10% have other heterotaxy syndromes (situs ambiguous). Congenital heart disease is found in 5–10% of patients and can range from simple malformations to complex defects, which can affect morbidity and mortality.

Many male patients report infertility, and fertility problems have also been reported in women, but data are scarce. There are very rare case reports describing hydrocephalus due to dysfunction of ependymal cilia. Rarely, PCD is associated with dysfunction of nonmotile as well as motile cilia, and it can therefore be associated with conditions such as retinitis pigmentosa and polycystic kidney disease.

The prevalence of clinical symptoms varies among published studies, and clinical features may differ among genetic variants, resulting in phenotypic variability. As shown in table 1, patients who report symptoms suggestive of PCD should be referred for diagnostic testing.

Diagnosis

Despite important advances in recent years, diagnosis of PCD remains complex and requires a combination of tests, using expensive equipment conducted by specialist technicians. In 2017, a European Respiratory Society (ERS) task force published evidence-based guidelines for the diagnosis of PCD, and the North American PCD Foundation published guidelines in 2018. Both guidelines highlight the lack of a gold standard test and emphasise the need for access to a combination of tests. The ERS guidelines suggest access to nasal nitric oxide (nNO) measurement, high-speed video-microscopy analysis (HSVA), transmission electron microscopy (TEM) and genetic testing (figure 2). Immunofluorescence labelling of ciliary proteins also contributes to the diagnostic certainty. Before proceeding to any diagnostic algorithm, it is important to have a strong clinical history compatible with PCD. This improves the predictive value and usefulness of all available tests. Diagnostic predictive tools (*e.g.* PICADAR) can aid in the appropriate selection of patients to be referred for diagnostic testing.

Figure 2. Diagnostic algorithm showing the combination of tests required to reach a diagnostic outcome and the subsequent steps for patient management after the diagnostic work-up.

An abnormal cilia ultrastructure seen by TEM (figure 1) or pathogenic biallelic mutations in PCD genes can confirm the diagnosis, but TEM and genetic tests are normal in a significant minority of people who almost certainly have PCD. Patients with low nNO and/or persistently abnormal HSVA are "highly likely" to have PCD and should be treated as if they have the disease while investigating any other possible causes for their symptoms. No single test or combination of tests can exclude the diagnosis, particularly in patients with a strong clinical history. However, further testing is not usually recommended for patients with only modest clinical suspicion and normal nNO and HSVA. Even after all available tests, the diagnosis remains uncertain in a significant minority of patients (figure 2).

nNO

Levels of nNO are usually extremely low in patients with PCD. nNO measurement is a relatively easy and noninvasive diagnostic test with excellent sensitivity and good specificity but does not always differentiate PCD patients from those with other diseases and will miss some patients. It is recommended that nNO is measured during a velum closure manoeuvre using a chemiluminescence analyser in adults and children aged >6 years. This manoeuvre is not always feasible, particularly in younger children, and measurement during tidal breathing can be helpful.

HSVA

For imaging tests, a brush biopsy of nasal (preferably) or bronchial respiratory epithelium is analysed *ex vivo*. A healthy sample improves the diagnostic accuracy of these tests, and therefore it is preferable that the patient is free of upper respiratory infections for 4–6 weeks to avoid secondary motility disorders.

HSVA assesses ciliary motility using a light microscope with an attached camera recording at high speed. Videos are played back slowly to assess the ciliary beat pattern. Abnormal patterns typically associated with PCD are static cilia, stiff hyperkinetic cilia and rotating cilia. Along with nNO, HSVA is particularly useful to decide whether a

patient is very unlikely to have PCD (if the beating and nNO are entirely normal), or to decide whether the diagnosis remains highly likely even if TEM and genetic testing are normal (figure 2). However, HSVA does not provide a definite positive or negative diagnosis in isolation.

Repeating HSVA following culture of the sampled epithelial cells further improves the diagnostic accuracy, because primary cilia defects persist while secondary defects (*e.g.* infection or inflammation) disappear.

TEM

For many years, TEM was considered the "gold standard" test for PCD diagnosis. "Hallmark" ultrastructural defects of the axoneme confirm a diagnosis of PCD (figure 1); however, it is now recognised that 15–30% of PCD patients have genetic variants that are characterised by a normal ciliary ultrastructure (*e.g.* patients with *DNAH11* mutations). TEM defects that are considered "hallmark" and can confirm diagnosis are: 1) absence of outer dynein arms; 2) absence of inner and outer dynein arms; and 3) microtubular disorganisation with absence of inner dynein arms.

Genetic testing

Biallelic mutations in a known PCD gene can confirm the diagnosis in ~70% of patients with supportive HSVA and/or TEM. It is important to demonstrate consistency between genotype and HSVA, TEM or immunofluorescence findings (figure 1).

Immunofluorescence labelling of ciliary proteins

Immunofluorescence labelling of ciliary proteins has high sensitivity and specificity. The method can be used in combination with other diagnostic tests to support diagnosis. Variability of quality of commercially available antibodies currently limits the application of this diagnostic test.

Management

As there is no cure for PCD, the aim is to prevent progressive and irreversible lung damage, and to minimise upper airway disease such as hearing loss and speech impairment, as well as to optimise health-related quality of life and psychosocial well-being. There is a limited evidence base for patient treatment, with only two randomised controlled trials published to date (Paff *et al*., 2017; Kobbernagel *et al*., 2020). Management of this lifelong disease is often based on expert consensus and experience from other diseases such as CF, non-CF bronchiectasis and chronic rhinosinusitis, despite different underlying pathophysiology.

Lower airways

Management of the lower airways consists of facilitating mucus clearance from the airways and preventing and treating repeated chest infections. Airway clearance therapy twice a day during periods of stability, with more frequent sessions during exacerbations, is usually recommended. Airway clearance physiotherapy techniques include combinations of an active cycle of breathing manoeuvres, manual techniques, positioning, positive expiratory pressure adjuncts and oscillatory positive expiratory pressure. The choice of technique is individualised and depends on the patient's age, preference, ability, mucus properties and disease severity, as there is no evidence base to indicate the most appropriate technique for PCD patients. Respiratory physiotherapy should be coupled with aerobic fitness; however, the latter should not be used as a substitute for airway clearance therapies.

Adjunct therapy can include nebulised treatments such as hypertonic saline to assist with mucus clearance. Recombinant human DNase is often used in CF but is not routinely recommended for use in PCD due to the lack of sufficient evidence of its efficacy. Equally, inhaled corticosteroids and bronchodilators are not routinely recommended unless patients have concomitant asthma or reversible airway disease.

Effective treatment of pulmonary infections aims to impede or delay the progression of irreversible lung damage. Antibiotics are usually prescribed to treat pulmonary exacerbations following CF guidelines, although the high doses used in CF may need modifying. The choice of antibiotic should be directed, when available, by sputum culture results. Typical respiratory pathogens include *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Pseudomonas aeruginosa*.

The first multinational randomised controlled trial on pharmacotherapy in PCD showed that azithromycin maintenance therapy halved the rate of respiratory exacerbations (Kobbernagel *et al*., 2020). Treatment based exclusively on positive cultures in asymptomatic patients is contentious, although treatment of new isolates of *P. aeruginosa* is universally recommended. Despite the lack of studies showing that cross-infection is a problem in PCD, patient segregation is sensible as it can minimise exposure to potentially harmful and resistant pathogens.

Upper airways

Management of the upper airways aims to improve hearing, prevent speech and developmental delays, and relieve symptoms of rhinosinusitis and otitis media.

Management of recurrent acute otitis media, otitis media with effusion and chronic otitis media in PCD is extrapolated from treatments used in the general population. Treatment of acute otitis media includes antibiotics covering common upper airway pathogens such as *Streptococcus pyogenes*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *H. influenzae* and *M. catarrhalis*. Antibiotic treatment should be guided by culture and sensitivity results where possible. The use of ventilation tubes in PCD is controversial due to a reportedly high incidence of troublesome otorrhoea after surgery. Hearing aids should therefore be considered to support hearing impairment.

Sinonasal irrigation with saline is often used to remove mucus, as it offers a cheap, safe and well-tolerated option for symptomatic patients. It is unclear whether topical steroids have any effect on PCD patients and therefore they are not routinely recommended. Local or oral prophylactic antibiotics might be an option for long-term therapy of chronic sinonasal symptoms but have not been evaluated in PCD. Endoscopic sinus surgery could be useful to eradicate pathogenic bacteria from the sinuses in refractory cases and is normally reserved for cases where medical therapy has failed.

Immunisations

Routine childhood immunisations are recommended, including pneumococcal vaccine and annual influenza immunisations to protect children with PCD from common viral and bacterial pathogens.

Investigations

Baseline assessments should take place soon after diagnosis and consist of spirometry, audiometry, sputum culture and chest imaging. Additionally, investigation for cardiac comorbidities and for abdominal and thoracic organ situs should be arranged. As PCD is a chronic disease, monitoring of lung function, structural lung damage, ENT

symptoms and health-related quality of life is essential. European and North American expert consensus statements recommend evaluation of lung function for pulmonary disease monitoring at every patient appointment, which ideally should take place every 3 months.

Microbiology surveillance

Surveillance cultures from sputum or oropharyngeal cough swabs should be obtained regularly (*e.g.* every 3 months).

Monitoring of lung disease

Lung function is often compromised from an early age, disputing earlier claims that PCD is a mild disease. Spirometry and body plethysmography are widely used to monitor the progression of lung disease, as they are widely available, easy and quick to perform. However, these tests can usually only be done in children >5 years of age. Additionally, they can miss signs of early structural damage or peripheral airway disease. Multiple-breath washout provides an alternative method to investigate and monitor peripheral lung disease but lacks standardisation in PCD.

Standard chest radiography can be used for occasional monitoring and for assessment during exacerbations but is insensitive to structural changes such as bronchiectasis. Additionally, the risk of ionising radiation should be considered, as there may be little clinical benefit in conducting chest radiographs during exacerbations. Chest HRCT is more reliable and sensitive for identifying bronchiectasis, air trapping, airway thickening, mucus plugging, opacities, and consolidation or collapse. However, CT also uses ionising radiation so might not be suitable for frequent monitoring, particularly in younger children. New modalities of HRCT with reduced radiation exposure could present a good alternative to monitor lung compromise in the future. Similarly, lung MRI could play an important role in disease monitoring in the future but is still mostly used as a research modality. Lung disease generally occurs in the middle and lower lobes in PCD, as opposed to the upper lung involvement seen in CF.

Monitoring of ENT disease

Children should be seen at least annually by an ENT clinician with expertise in PCD. Hearing should be assessed by audiometry soon after diagnosis and repeated annually or more often if required. An open-field audiogram is recommended for patients <6 years and a pure-tone audiogram for those above that age. Sinus HRCT scans are not routinely recommended for ENT monitoring in PCD but can be useful to assess disease in symptomatic patients.

Cardiac abnormalities

Imaging of thoracic and abdominal organ situs should be conducted soon after diagnosis. An echocardiogram should be scheduled to investigate cardiac abnormalities, which occur in ~10% of PCD patients.

Other investigations

Height, weight and BMI should be monitored in PCD patients, as there are emerging data suggesting that growth can be compromised from an early age and that low BMI is associated with lower FEV_1 compared with PCD patients with normal BMI.

The possibility of future fertility problems should be discussed at a sensible time. Investigations are likely to be conducted during adulthood.

Prognosis and delivery of care

A patient-centred multidisciplinary approach is essential for patients with rare, chronic, multisystem diseases such as PCD. Appropriate patient referral, diagnosis and management are often suboptimal due to a lack of awareness by treating physicians. Patients often visit multiple physicians and remain undiagnosed, which is troublesome considering early intervention might improve prognosis.

The ideal service delivery model will depend on a variety of factors, including the country's healthcare setting, geographical distribution, accessibility to diagnostic and management centres, national and local funding structures, and socioeconomic and cultural factors. Diagnostic testing requires the concentration of high-cost equipment and a highly specialised team, and therefore service models that centralise PCD diagnostics in specific locations. A centralised model for patient management can also be advantageous, as seen in CF where patient outcomes have improved with the establishment of CF expert centres.

As an example, since 2006, the National Health Service in England has commissioned a centralised and highly specialised paediatric service operating through three national diagnostic centres and, since 2012, four national management centres. All diagnostic cases are reviewed by a team of specialised diagnostic scientists and pulmonary paediatricians, and confirmed cases are managed by a multidisciplinary PCD team consisting of respiratory physicians, ENT specialists, specialist nurses and physiotherapists, and physiologists (for lung function measurements). All patients undergo annual reviews, where an individualised management plan is developed. Regular management appointments are conducted every 3 months for those who attend clinics at one of the PCD management centres and every 3–6 months for those in shared care with the patient's local specialist respiratory team.

Transition of care

The establishment of adult PCD centres is important for the continuation of highly specialised care after patients leave the paediatric service. Transition programmes prepare older children for self-management and empower them for care with adult physicians who may have little experience of PCD. This ensures that patients are prepared for issues that might face them as an adult, such as infertility. Programmes like "Ready, Steady, Go" offer a simple and structured questionnaire and can be used as a framework to guide transition for PCD patients.

Summary

PCD is a complex genetic disease with a prevalence of approximately one in 10 000 births. Symptoms can be nonspecific and, due to lack of awareness of the disease by treating physicians, diagnosis is often delayed. Patients with a suggestive clinical history, particularly from early life, or with siblings diagnosed with PCD should be referred to specialist centres for diagnostic testing. Patients with PCD should be managed by a multidisciplinary team to prevent progression of irreversible lung damage, hearing impairment and developmental delays.

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Bronchiolitis obliterans

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Bronchiolitis obliterans (BO), or obliterative bronchiolitis, is a rare chronic obstructive lung disease that follows a severe insult to the respiratory tract and results in narrowing and/or complete obliteration of the small airways.

Historically, the term has been used by pathologists to describe two histologically distinct patterns: 1) the constrictive pattern, characterised by subepithelial inflammation and peribronchiolar fibrosis with various degrees of lumen constriction (currently defined as BO), and 2) the proliferative pattern, characterised both by an inflammatory process (primarily involving alveolar ducts and interstitium) and by fibroblast polypoid proliferation in airway lumen, defined as BO with organising pneumonia (BOOP) or cryptogenic organising pneumonia.

In children, BO is a long-term sequela of severe infections occurring most commonly after acute pneumonia or bronchiolitis. The term post-infectious BO (PIBO) is currently used to indicate BO that develops following an infectious insult. Other causes include haematopoietic stem-cell transplantation (HSCT) or lung transplantation (LT), drug toxicity, noxious inhalation injury, vasculitis and autoimmune disorders.

The onset of BO is frequently insidious and symptoms may be misinterpreted, resulting in delayed diagnosis. The mortality rate remains high, and most patients die of respiratory failure complicated by additional infections.

Key points

- Bronchiolitis obliterans is a rare paediatric chronic obstructive lung disease that follows a severe insult to the respiratory tract and results in narrowing and/or complete obliteration of the small airways.
- The most common cause is severe lower airway infection, followed by bone marrow or lung transplantation, drug toxicity, noxious inhalation injury, vasculitis and autoimmune disorders.
- Open-lung biopsy for histological confirmation of the diagnosis is rarely necessary. In the appropriate setting, after exclusion of other chronic obstructive lung diseases, HRCT provides adequate evidence for a correct diagnosis.
- Lung function is characterised by a moderate-to-severe fixed airflow obstruction that may slowly progress to fatal deterioration even a few months after diagnosis.

Epidemiology

Childhood BO is a rare condition; nevertheless, in recent decades its prevalence has increased unexpectedly, particularly in some countries in the southern hemisphere (Argentina, Chile, Brazil and New Zealand). Race has been suggested as a predisposing factor for PIBO. However, while in the PIBO population from Argentina there is an increased frequency of the human leukocyte antigen (HLA) DR8-DQB1*0302 allele, 70% of PIBO children from Brazil were Caucasian. This suggests that the local racial composition may affect the prevalence of the disorder in individual centres.

BO after HSCT ranges from 5.5% to 14% in the presence of extrathoracic chronic graft-*versus*-host disease (cGVHD). BO affects ≥50% of LT recipients, representing the major noninfectious cause of chronic lung allograft dysfunction.

Pathogenesis

The pathogenesis of BO is not fully understood. Epithelial injury following triggers of different origin (*i.e.* lower respiratory tract pathogens, toxics, ischaemia–reperfusion injury after LT) represents the first step of the process: epithelial denudation and prompt activation of humoral, cellular and innate immunological responses result in the development of small airways chronic inflammation. The immune cells release matrix metalloproteinase and profibrotic cytokines, which lead to matrix degradation, collagen deposition, fibroblast proliferation and finally peribronchiolar fibrosis.

Transplant-related BO can be considered a chronic allograft rejection in LT and cGVHD in HSCT recipients. Potential factors implied in transplant-related BO are polymorphisms in innate immune-system genes, the presence of circulating antibodies to donor HLA molecules, activation of a T-helper 17 immune response and autoimmunity against airway proteins (*i.e.* collagen and K-α1 tubulin). Furthermore, the protective role of the re-establishment of pre-transplant respiratory microbiota in LT patients has recently emerged, which seems to induce an immunogenic tolerance against BO development.

Pathology

BO is primarily a lesion of terminal and respiratory bronchioles with a fibrosing inflammatory process surrounding the lumen, which results in progressive airways narrowing, distortion and obliteration. Histological features comprise a wide spectrum of patterns, from chronic inflammation to bronchiolar scarring without extensive changes in alveolar ducts or walls, and show a patchy distribution.

The term BOOP identifies an airspace-filling process with granulation tissue plugs extending to small airways, and is distinguished from BO on the basis of clinical, functional and radiographic features, including the response to corticosteroids and the final prognosis. It has long been considered a small airways disease, but the current classification lists BOOP among interstitial pneumonias.

Clinical entities

Post-infectious bronchiolitis obliterans

PIBO should always be suspected in previously healthy children who develop chronic respiratory symptoms lasting for >4–8 weeks after an episode of acute, usually severe, lung infection at preschool age.

Several pathogens are associated with paediatric PIBO, and adenovirus (serotypes 3, 7, 11 and 21) is most frequently implicated. Other micro-organisms include:

- Influenza virus
- Parainfluenza virus
- Measles virus
- Varicella virus
- Metapneumovirus
- HIV
- *Mycoplasma pneumoniae*
- *Chlamydophila pneumoniae*
- *Staphylococcus aureus*
- *Streptococcus pneumoniae*
- *Bordetella pertussis*

Although respiratory syncytial virus (RSV) is frequently associated with bronchiolitis, evidence for its causative role in determining PIBO is lacking. Increased serum interleukin-6 and -8 and tumour necrosis factor (TNF)-α in children with adenovirus infection suggest that the host immunological response may play an important role in the development of PIBO.

The acute infection leading to PIBO usually requires hospital admission for oxygen therapy and sometimes demands mechanical ventilation. Despite appropriate initial treatment, hypoxaemia, cough, breathlessness, wheezing, tachypnoea, exercise intolerance and crackles on auscultation are common clinical findings. Oxygen may be required for months or years after the acute infection. Failure to thrive, clubbing, chest deformity and pulmonary arterial hypertension are reported in severe cases.

BO following a bone marrow transplant

BO is the most common late, noninfectious pulmonary complication of allogeneic HSCT. Generally, BO does not develop after autologous HSCT. Although there are reports of BO as early as 30 days following HSCT, 80% of cases occur 6–12 months post-transplantation.

The presentation is usually insidious, and the main symptoms include dry cough and dyspnoea. Approximately 20% of patients are asymptomatic, and diagnosis may be suspected based on lung function. In the advanced stages, patients are physically limited because of severe airway obstruction and may require home oxygen. Almost all patients also display symptoms and signs of cGVHD.

BO following LT

LT recipients who develop BO often have a variable period of good graft function, followed by an insidious onset of symptoms. Clinical presentation of BO may vary from asymptomatic disease to nonspecific symptoms such as dyspnoea, cough and exercise intolerance, while wheezing and chest pain are less common.

Compared with a deceased donor transplant, the incidence of BO is lower in living-donor lobar transplant recipients, probably due to the minor impact of rejection episodes in terms of frequency and severity. Moreover, children aged <3 years undergoing LT have a lower risk of BO, probably because of the decreased incidence of acute rejection. The differential expression of fibrosis and apoptosis-related genes that occurs in peripheral blood cells, as well as in BAL, may be used in the future to develop biomarkers for disease prediction.

BO following autoimmune disorders or vasculitis

The majority of described cases of collagen vascular diseases and associated BO (*i.e.* rheumatoid arthritis, scleroderma, systemic lupus erythematosus, Crohn's disease) are in adults, in whom a history of tobacco use may play a role as a confounder. BO as a complication of toxic epidermal necrolysis and Stevens–Johnson syndrome is rare and is characterised by late insidious onset with an often progressive course that may require LT or lead to death.

Risk factors

Pathogen load, immunological response, and genetic and environmental factors may be associated with the onset of BO. Possible risk factors for PIBO are prolonged hospitalisation, multifocal pneumonia, the need for mechanical ventilation and hypercapnia. It remains unclear whether the need for mechanical ventilation is an indicator of disease severity or is itself responsible for the direct induction of airway injury.

The presence of cGVHD is the most important, but not the only, risk factor for developing BO after HSCT. Other probable and possible risk factors are shown in table 1.

Recurrent acute cellular rejection episodes following LT, as well as high-grade acute cellular rejection, are primary risk factors for BO. As a result, early and aggressive treatment of acute cellular rejection represents an important preventative strategy. Nonimmunological factors leading to BO include Epstein–Barr virus re-activation and infection of the lung allograft by cytomegalovirus, adenovirus, influenza and parainfluenza viruses, RSV, fungi and bacteria. BAL analysis of the pulmonary microbiome has been used to predict susceptibility to BO. LT recipients harbouring

Table 1. Probable and possible risk factors for developing bronchiolitis obliterans

Probable risk factors
Airflow obstruction (FEV_1/FVC ratio <70%) prior to HSCT
Older recipient age (*i.e.* >20 years)
Early respiratory viral infections (*e.g.* influenza virus, parainfluenza virus and RSV) within 100 days following HSCT
Possible risk factors
Busulfan-based conditioning regimen
Mismatched or unrelated donor
Hypogammaglobulinaemia (especially IgG and IgA)
Methotrexate prophylaxis against GVHD
Older age of donor
HSCT for chronic myelogenous leukaemia
Blood-derived stem cells
Interval from diagnosis of leukaemia to transplantation >14 months
Female donor to male recipient
Prior interstitial pneumonitis
Total body irradiation
Cytomegalovirus infection
GOR disease
Underlying disease (*i.e.* chronic myelogenous leukaemia)

distinct *Pseudomonas* spp. in BAL show significantly different outcomes. In addition, a Gram-positive-enriched pulmonary microbiome seems to predict resilience to BO. Examination of the cellular composition, matrix metalloproteinases and cytokine profile in BAL fluid may offer a useful tool to predict the risk of bronchiolitis obliterans syndrome (BOS) or to assess treatment response in LT recipients. The LT type may also be a risk factor, with single-transplant recipients being at higher risk than bilateral ones. GOR may contribute to allograft rejection, and bile acids and pepsin in BAL fluid from LT recipients indicate aspiration.

Diagnosis

Although diagnosis is based on clinical, functional and radiographic criteria, lung biopsy remains the gold standard to diagnose BO. As parenchymal involvement is patchy, transbronchial biopsy has a small yield, and transthoracic biopsy from two sites should be recommended.

Because BO after LT is difficult to detect due to a patchy distribution, a persistent 10–19% decrease in FEV_1 and/or a ≥25% decrease in forced expiratory flow at 25–75% of FVC (FEF_{25-75}) from baseline (defined as the average of the two highest, not necessarily consecutive, post-transplantation values measured ≥3 weeks apart) are considered surrogate markers of probable BO. This change in pulmonary function after careful exclusion of other post-transplant complications that can cause delayed lung allograft dysfunction is defined as BOS and represents the indication to perform bronchoscopy and to modify the immunosuppressive therapy.

The development of BO after HSCT is associated with the presence of cGVHD. The diagnosis requires the absence of overt infection in the respiratory tract documented by clinical symptoms, radiological procedures or microbiological cultures. PFTs show new-onset airflow obstruction with a decrease in FEV_1 of <75% predicted with ≥10% decline over <2 years.

PIBO may also be diagnosed without performing a biopsy, based on a combination of clinical, imaging and laboratory criteria:

- A history of a severe respiratory infection, especially in early childhood
- Evidence of persistent airway obstruction after the acute event, unresponsive to treatment (*i.e.* systemic steroids and bronchodilators)
- A mosaic pattern or air trapping on chest HRCT
- The exclusion of CF, PCD, immunodeficiency, BPD, congenital heart disease, severe asthma, an inhaled foreign body, extrinsic bronchial compression and α_1-antitrypsin deficiency

PFTs provide information about disease severity and progression over time. Infant PFTs, when available, suggest early severe obstruction, diminished lung distensibility and increased airway resistance. Older children exhibit severe and irreversible airflow obstruction, with no or a small response to bronchodilators, and increased RV and RV/TLC ratio due to air trapping. The decreased FEF_{25-75} is the typical functional marker of the disease, often associated with reduced FEV_1 and FVC. Furthermore, children and adolescents with BO exhibit a compromised pulmonary function during exercise with a significantly reduced 6-min walk distance and a reduced peak aerobic capacity in a cardiopulmonary exercise test.

The single-breath nitrogen washout in LT recipients may reveal heterogeneous ventilation and alteration in expiratory flow rates 6–12 months before conventional PFTs.

The LCI has been shown to be effective in early detection of post-bone marrow transplant BO in adults and children. This finding has been confirmed in adults who underwent repeated LCI measurements after HSCT and, recently, in children with PIBO.

Elevated levels of exhaled nitric oxide (F_{ENO}) may predict BOS development post-LT, and follow-up F_{ENO} measurements are useful to identify LT recipients with an unfavourable course. Conversely, data on F_{ENO} in HSCT recipients are discordant, with lower levels in cases with BO than in those without BO, probably due to a different pathophysiology of BO after HSCT and LT.

In children with PIBO, the impairment of T_{LCO} related to poorly ventilated lung units with marked small airways obstruction may be helpful in the differential diagnosis with severe asthma, which often shows normal or even increased T_{LCO} due to hypervascularity.

Chest radiographs are often unspecific or even normal. Rarely, there is a predominant unilateral hyperlucency (Swyer–James or MacLeod syndrome), with the affected lung being smaller on inspiration.

Chest HRCT is extremely helpful for diagnosis, and structural changes include the following (examples also given in figure 1):

- Mosaic perfusion
- Air trapping
- Bronchial wall thickening
- Bronchiectasis
- Thickening of septal lines
- Narrowing of the pulmonary vessels due to reflex vasoconstriction secondary to tissue hypoxia

Expiratory scans are helpful in identifying air trapping that may be missed on inspiratory scans. The characteristic mosaic perfusion on HRCT, due to patchy distribution of areas of attenuated density alternated with areas of increased attenuation, may be useful in discriminating between patients with BO and those with severe asthma and irreversible obstruction.

Given the relative risk of lung biopsy, it has been emphasised that, in the appropriate setting, once other congenital or acquired disorders have been excluded, HRCT provides clear evidence for a correct diagnosis without the need for biopsy. Thus,

Figure 1. a) HRCT scan of a 4-year-old boy with bronchiolitis obliterans following M. pneumoniae *infection. Bilateral areas of increased and decreased parenchymal attenuation (mosaic perfusion), bronchiectasis and air trapping can be seen. b) Bronchiolitis obliterans in a 13-year-old boy 2 years after bone marrow transplantation for acute lymphoblastic leukaemia. The HRCT scan shows a bilateral mosaic perfusion pattern, air trapping and bronchial dilatation.*

lung biopsy is recommended if HRCT is inconclusive or not available, or when severe progression and gradual deterioration occur despite treatment.

Ventilation–perfusion scintigraphy with the typical matched ventilation–perfusion defect in one or more pulmonary segments provides a valuable assessment of the extension, distribution and severity of lung involvement but does not disclose the nature of BO.

Finally, in severe BO, overnight oximetry and/or PSG may reveal nocturnal hypoxaemia with a high desaturation index that should prompt a thorough cardiovascular assessment to detect pulmonary arterial hypertension.

Treatment

Patients should be treated by a multidisciplinary team including:

- A paediatric pulmonologist
- A paediatric cardiologist
- A physical therapist
- A nutritionist
- A psychologist
- A social worker

BO treatment for children has not been clearly defined, and pharmacological approaches are often based on the clinical experience of different healthcare workers.

The therapeutic approach is mainly supportive, and includes prolonged oxygen supplementation, antibiotics in acute respiratory infections, annual influenza vaccination and chest physiotherapy for cases complicated by bronchiectasis. Adequate nutritional support is fundamental, as up to 20% of children with BO may have some degree of malnutrition. GOR must be adequately treated.

The use of corticosteroids in PIBO is controversial because no controlled clinical trials have confirmed their efficacy. Early administration of corticosteroids and azithromycin in PIBO may restrain the effects of inflammation before its severity is fully established. Analysis of 42 cases of PIBO reported the effectiveness of treatment with corticosteroids and azithromycin in 85.7%, although the lack of a control group hampered a definitive conclusion. The body of evidence is based mainly on anecdotal clinical reports describing the beneficial effects of pulse methylprednisolone (25–30 $mg \cdot kg^{-1} \cdot day^{-1}$ for 3 days) in children with PIBO. Conversely, in GVHD occurring after HSCT, high-dose systemic prednisone (1–1.5 $mg \cdot kg^{-1} \cdot day^{-1}$ for 2–6 weeks) or methylprednisolone (10 $mg \cdot kg^{-1} \cdot day^{-1}$ for 3 days on a monthly basis for 1–6 cycles) should be prescribed, and immunosuppressive therapy should be reinstated or augmented. Inhaled corticosteroids and/or bronchodilators may be considered an option in the treatment of BO, but they should be discontinued in the absence of benefits.

In paediatric LT recipients, the development of BO should lead to augmentation of immunosuppression. Indeed, available studies suggest that LT recipients treated with immunosuppressive therapies and azithromycin had a lower incidence of BOS. BAL neutrophilia appears to represent a subgroup of patients who respond to azithromycin therapy. To date, it has been shown that azithromycin may improve BO symptoms, lung function and exercise tolerance, probably because it exerts anti-inflammatory and immunomodulatory activity. However, the current body of evidence is not conclusive in either supporting or rejecting the benefit of azithromycin in HSCT-related BO. A timely use of extracorporeal photopheresis was shown to be a promising adjunct treatment

in BO after LT, probably by inducing regulatory T-cells. Empirical monthly intravenous immunoglobulin administration has been used in a few cases. There are also some reports of symptom improvement after chloroquine and hydroxychloroquine use in BO, and after TNF-α monoclonal antibodies (infliximab) and tyrosine kinase inhibitors (imatinib) in BO complicating bone marrow transplantation. Severe cases with oxygen dependency, important physical limitation and extremely impaired lung function should be referred for LT.

Prognosis

The long-term prognosis of BO is variable and depends on several factors, including the underlying causes and speed of development. Most patients with PIBO improve slowly and progressively, but this may be due to airways growth rather than resolution of inflammation. Nevertheless, most patients continue to have mild symptoms, especially during exercise.

The mortality rate in HSCT recipients with BO from different studies ranges from 14% to 100% with a median of 65%. Factors associated with mortality include rapid FEV_1 deterioration, progressive cGVHD, underlying disease relapse and no response to the primary treatment. Chronic airways bacterial colonisation in LT recipients with BO is commonly associated with poor outcome. Moreover, BO or its complications are the single most common cause of death in LT recipients, accounting for ~40% of deaths after the first year following paediatric LT.

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Interstitial lung diseases

Nadia Nathan, Laura Berdah and Annick Clement

ILD in children (chILD) is a heterogeneous group of respiratory disorders that are mostly chronic and impair the respiratory function of the lung. These diseases, which are associated with high morbidity and mortality, are characterised by the presence of diffuse infiltrates on lung imaging and abnormal PFTs with evidence of a restrictive ventilatory defect and/or impaired gas exchange.

Epidemiology

ChILD prevalence is difficult to assess and is probably underestimated due to a variety of definitions, differences in the studied patient populations and the absence of organised reporting systems. Several studies have reported prevalence ranging from 0.1 to 16.2 cases per 100 000 children. The published data are mainly composed of case reports and small series. However, it seems that paediatric ILD occurs more frequently at a younger age and in boys. In addition, based on the existence of family cases, at least 10% appears to be familial.

Pathophysiology

The term ILD refers to disorders affecting the interstitium but also the alveolar structure, the distal part of the small airways and the conducting zone (*i.e.* the

Key points

- ILD in children (chILD) represents a heterogeneous group of respiratory disorders that are mostly chronic and impair the respiratory function of the lung.
- Classifications remain unsatisfactory but four main aetiological groups are recognised: ILD related to exposure/environment insults, to systemic disease processes or to primary lung parenchyma dysfunctions, and ILD specific to infancy.
- Knowledge on the genetic contribution to chILD pathogenesis is growing; surfactant disorders play important roles in various forms of chILD and other disease-causing genes are increasingly implicated.
- Treatment protocols remain difficult but include supportive measures and pharmacological therapy, mainly anti-inflammatory (corticosteroids) and immunosuppressive molecules, with some targeted therapeutic strategies.

terminal bronchioles). Therefore, the term diffuse parenchymal lung diseases has been proposed instead of ILD. However, in keeping with clinical practice habits, the term ILD will be used here. As the pulmonary structures responsible for the diffusion of gases between blood and air are involved, gas exchange and consequently lung function are impaired.

The current concept of ILD pathogenesis highlights the central role of genetically predisposed "vulnerable" alveolar epithelial cells that fail to respond correctly to repetitive micro-injuries. Consequently, complex mechanisms including epithelial cell apoptosis and altered epithelial–mesenchymal interactions, with disturbed epithelium homeostasis, a dysregulated inflammatory response and lung remodelling, are involved. Changes in cellular phenotype and function are observed, with epithelial cells acquiring phenotypic and functional characteristics of mesenchymal cells including the production of collagen and extracellular matrix components. Progenitor cells may also be affected by an acceleration of the ageing process leading to stem-cell exhaustion.

Together, these changes induce the onset of symptoms, with subsequent acute exacerbation episodes precipitating lung failure. The role of inflammation seems central in ILD development. The recruitment of inflammatory cells including collagen-producing fibroblasts seems to be involved the pathophysiology of alveolar injury and to participate in extracellular matrix accumulation. Ultimately, the activation of profibrotic growth factors such as transforming growth factor (TGF)-β1 is observed. In this context, T-regulatory (Treg) lymphocytes may play a role in the fibrosing process, as has been suggested in idiopathic pulmonary fibrosis. They are both responding to and secreting TGF-β1. In contrast, T-helper 17 (Th17) cells are involved in pro-inflammatory processes. An impaired Treg/Th17 ratio could compromise immune homeostasis, as has been shown in idiopathic pulmonary fibrosis.

Genetic factors appear to play a major role in the development of ILD. Mutations in the genes encoding surfactant proteins (SPs) were initially documented in chILD, followed by genes involved in inflammatory signalling. However, genetic factors cannot explain the whole ILD story, as illustrated by highly variable phenotypic expression in a single family. Recent findings also indicate that epigenetic regulatory mechanisms, such as DNA methylation, histone modifications or noncoding RNAs including microRNAs, play a role in the phenotypic heterogeneity of ILD. Environmental and host comorbidity factors are also important disease contributors, both in disease onset and progression. These mainly include virus infections, particularly Epstein–Barr virus, cytomegalovirus, herpesvirus and parvovirus, tobacco smoke, and exposure to contaminants in air, such as metal or wood dusts, and to livestock. Finally, intrinsic comorbidity factors include GOR, sleep apnoea syndrome and cardiovascular diseases.

ILD classification

ChILD classification was initially based on adult idiopathic interstitial pneumonia, mainly using the histological terms of usual interstitial pneumonia, desquamative interstitial pneumonia and nonspecific interstitial pneumonia. However, these terms lacked precision for childhood cases of ILD. Progressively, specific paediatric entities were defined. Various classifications have been proposed, including international multidisciplinary consensus classification of interstitial pneumonias published by the American Thoracic Society (ATS)/European Respiratory Society (ERS). These were instead based on clinical assessment, HRCT scans and histology. Because lung growth and maturation processes have been identified as key issues in the pathophysiology of ILD, two age groups have been defined by the ChILD Research Cooperative group and the European Union–ChILD collaboration network: 1) ILD that is more prevalent

in children <2 years old (infancy), and 2) ILD not specific to child age. ILD specific to infancy includes neuroendocrine cell hyperplasia of infancy (NEHI), pulmonary interstitial glycogenesis (PIG) and developmental disorders. The other paediatric ILDs are grouped into: 1) ILD related to exposure/environment insults, 2) ILD related to systemic and immune diseases, and 3) ILD related to primary lung parenchyma dysfunctions. Surfactant disorders are part of the latter group and are particularly prevalent in infancy.

Work-up for chILD diagnosis

A step-by-step aetiological diagnostic approach is necessary. The first step is taking a family medical history including the presence in relatives of ILD, pulmonary fibrosis or neonatal respiratory distress but also of extrarespiratory disorders. Consanguinity should be searched for, especially if a genetic cause of ILD is suspected. Careful attention to environmental exposures (infectious, inorganic, tobacco) is also crucial.

Apart from a few characteristic and subacute presentations with severe respiratory symptoms, in most cases the onset of symptoms is insidious or asymptomatic, explaining why a long diagnosis delay is often reported before chILD is considered. Respiratory symptoms are usually nonspecific with dry cough, dyspnoea on exertion or at rest, and frequent respiratory infections. Failure to grow and/or to thrive and oral feeding issues are also frequent symptoms. A history of wheezing may be observed. Clinical findings may be subtle. Tachypnoea is the most constant sign. Other signs include inspiratory crackles, retractions and, at a more advanced stage of the disease, digital clubbing and cyanosis during exercise or at rest. Extrarespiratory manifestations could be suggestive for lung involvement of a systemic disease and must also be searched for, such as joint pain, muscle pain, weakness, cutaneous rashes, neurological abnormalities, thyroid dysfunction signs and recurrent fever.

Chest radiography is usually performed as part of the initial consultation. However, an HRCT scan using thin sections offers better visualisation of the parenchymal structure and is the key tool for chILD diagnosis. The most common HRCT scan feature of ILD is widespread ground-glass attenuation, with some observations of intralobular lines and irregular interlobular septal thickening. Large subpleural air cysts in the upper lobes adjacent to areas of ground-glass opacities are also reported in young patients. These cysts are interpreted as paraseptal or irregular emphysema (figure 1). In advanced stages of the disease, honeycombing can reveal a fibrosing process. The repartition and the predominant HRCT scan sign are crucial tools both for diagnosis and also to guide lung biopsy or to monitor disease progression. In the future, the use of ultrasonography and MRI could provide interesting alternatives.

PFTs are performed mainly in older children and adolescents. In chILD, they show nonspecific lung function abnormalities such as a restrictive ventilatory defect with decreased lung volumes and, if feasible, a reduced lung compliance. TLC and vital capacity (VC) are variably diminished; FRC is also reduced but relatively less than VC and TLC, and RV is generally preserved; thus, the ratios of FRC/TLC and RV/TLC are often increased. Only a minority of patients also present an obstructive ventilator defect reflecting an airway involvement. T_{LCO} is often markedly reduced and may be abnormal before any radiological findings. Hypoxaemia on exertion, or at rest, as defined by reduced resting S_{aO_2} or reduced resting P_{aO_2}, is often present and can be highlighted by performing a 6-min walk distance test, an exercise tolerance test and/or an overnight pulse oximetry test. However, hypercapnia is observed only at the end stage of the disease.

Figure 1. Examples of chILD lung HRCT scans. a) Newborn with alveolar capillary dysplasia with misalignment of pulmonary veins, showing diffuse ground-glass attenuations. Note that there were complications of the disease and the invasive ventilation: an anterior pneumothorax and a bilateral pleural effusion. b) A 1-year-old boy with NEHI, showing ground-glass areas of attenuation with anterior and central predominance. c) A 5-year-old girl with diffuse alveolar haemorrhage (haemosiderosis), showing bilateral patchy areas of dense ground-glass attenuations with blurred limits. d) A 2-year-old girl with SP-C deficiency showing diffuse ground-glass attenuations with parenchymal cysts and interlobular septal thickening. e) A newborn with ATP-binding cassette subfamily A member 3 (ABCA3) deficiency showing diffuse dense homogeneous ground-glass attenuations. f) A 10-year-old boy with hypersensitivity pneumonitis showing heterogeneous ground-glass areas of attenuation, centrilobular nodules and septal thickening.

Bronchoscopy and BAL are usually part of the diagnosis process, as long as the clinical status of the patient allows for this. This provides a specimen for cytological, microbiological and molecular studies. Its primary usefulness is to search for infections. It may also orient the diagnosis in situations of alveolar haemorrhage, alveolar proteinosis or aspiration with lipid-laden macrophages, and can also allow transbronchial biopsy in specialised centres.

Despite being considered the gold standard for chILD diagnosis, due to its invasiveness, the histological analysis of lung tissue usually represents the final step of the diagnostic approach. Different methods of biopsy are reported, based on the expertise of the surgical teams and the balance between procedure invasiveness and the potential for obtaining adequate and sufficient tissue for diagnosis. The techniques of choice are open-lung biopsy and video-assisted thoracoscopy biopsy. All of the adult histological patterns appear to be observed in chILD, with nonspecific interstitial pneumonia being the commonest pattern. However, this is often atypical or coexisting within the same lung tissue sample as other described histological patterns, and can also be associated with pulmonary fibrosis. Usual interstitial pneumonia is reported rarely, as well as lymphoid interstitial pneumonia, which is often associated with either connective tissues disorders or immunodeficiency states. It is important to consider that in cases of extrarespiratory involvement of the disease, biopsy of another involved organ could be a less invasive and equally gainful procedure.

Molecular analyses are becoming more common in the aetiological approach to chILD and may be discussed as a noninvasive alternative to lung biopsy when specific genetic causes of chILD are suspected. As phenotypes are rarely typical for a disease, next-generation sequencing of a selected panel of chILD genes is currently used. The cost is becoming more affordable in a growing number of countries. However, this has to be balanced with the very few molecular centres worldwide that are able to provide expertise on the identified variants.

Other investigations in chILD diagnosis and evaluation include cardiac ultrasonography for estimation of pulmonary artery pressure, blood tests especially for evaluation of the immune function, searches for systemic inflammation and autoantibodies, searches for haematuria and proteinuria, a metabolic work-up including thyroid, liver and kidney function, and other biological parameters depending on the clinical situation and the suspected diagnosis.

ChILD aetiological diagnosis

ChILD is rare and the diagnosis approach is often tricky, hence the recent development of national and international multidisciplinary team meetings that gather together expert clinicians, radiologists, pathologists and geneticists. These reduce any diagnosis delay and optimise chILD diagnosis.

In keeping with other classifications, we will describe diagnoses within four groups: 1) ILD specific to infancy, 2) ILD related to exposure/environment insults, 3) ILD related to systemic and immunological disease processes, and 4) ILD related to primary lung parenchyma dysfunctions (table 1).

ILD specific to infancy

NEHI is usually well tolerated, without respiratory failure in very young infants. Neuroendocrine cells are the first specialised epithelial cells to appear in the lung, and are suggested to act as mechano- and chemosensors as they secrete amines

Table 1. Classification of chILD

ChILD aetiologies	Most frequent conditions	Genetic disorders
ILD specific to infancy		
NEHI		
PIG		
Diffuse developmental disorders	Acinar dysplasia	*TBX4*, *FGFR2*
	Congenital alveolar dysplasia	
	ACD/MPV	*FOXF1*
	Filamin A deficiency	*FLNA*
ILD related to exposure/environment insults		
Hypersensitivity pneumonitis	Bird fancier's diseases	
	Humidifier lung diseases	
	Chemical lung diseases	
Medication, drugs or radiation exposure		
ILD related to systemic and immunological diseases		
Connective tissue diseases	Rheumatoid arthritis	
	Systemic sclerosis	
	Systemic lupus erythematosus	
	Sjögren syndrome	
	Dermatomyositis and polymyositis	
	Mixed connective tissue disease	
Vasculitis	ANCA-associated vasculitis	
	Anti-GBM diseases	
	Purpura rheumatica	
	Cryoglobulinaemia vasculitis	
	DAH related to coeliac disease or cow's milk protein intolerance	
Autoinflammatory disorders	SAVI	*TMEM173*
	COPA syndrome	*COPA*
Granulomatous disorders	Sarcoidosis	
Metabolic disorders	Niemann–Pick diseases	*NPC1*, *NPC2*
	Gaucher disease	*GBA*, *PSAP*
	Hermansky–Pudlak syndrome	*HPS1*, *AP3B1*, *HPS3*, *HPS4*, *HPS5*, *HPS6*, *DTNBP1*, *BLOC1S3*
	Pulmonary alveolar proteinosis	*MARS*, *CSF2RA*, *CSF2RB*
ILD related to primary lung parenchyma dysfunctions		
Surfactant disorders	SP-A1, SP-A2, SP-B and SP-C defects	*SFTPA1*, *SFTPA2*, *SFTPB*, *SFTPC*
	ABCA3 defects	*ABCA3*
	Brain–lung–thyroid syndrome	*NKX2-1*
DAH related to primary haemosiderosis		
Eosinophilic lung diseases		
Lymphatic disorders		
Viral infections		

ACD/MPV: alveolar capillary dysplasia with misalignment of pulmonary veins; ANCA: antineutrophil cytoplasmic antibody; GBM: glomerular basement membrane; DAH: diffuse alveolar haemorrhage; SAVI: stimulator of interferon genes (STING)-associated vasculopathy of infancy; COPA: coatomer protein-α; ABCA3: ATP-binding cassette subfamily A member 3. Reproduced and modified from Nathan *et al*. (2020) with permission.

and vasopeptides such as gastrin-releasing peptide (bombesin). As normal bombesin levels decrease after midgestation, it has been suggested that NEHI could be related to nonregression of these neuroendocrine cells. However, the relationship between the observed symptoms and neuroendocrine cells remains unknown. Clinical presentation is often typical, with persistent mild tachypnoea, sometimes associated with a pseudo-asthmatic presentation with wheezing and air trapping. Lung imaging is characterised by limited ground-glass opacities, mainly in the anterior segments of the right middle lobe and lingula. The outcome is usually favourable without any treatment. However, in situations of prolonged evolution or severe forms of NEHI with growth alteration, corticosteroid medication has been proposed. Lung biopsy is performed in atypical or severe cases to confirm the diagnosis. The abnormal histological findings are minor, but bombesin staining highlights an increased number of neuroendocrine cells within terminal bronchioles. Recently, some molecular defects have been documented in NEHI.

PIG is also a nonlethal chILD. Its pathogenesis is unknown, but it is suggested that it could be linked to a maturation defect of interstitial cells that leads them to accumulate glycogen within their cytoplasm. PIG is reported in neonates with respiratory distress syndrome that develops shortly after birth. Because its evolution is reported to be spontaneously favourable, very few cases are confirmed by lung biopsy, and PIG is probably an underestimated condition. PIG can be associated with other pathological conditions such as meconium inhalation or other lung growth development anomalies.

Diffuse developmental disorders are severe and often lethal conditions of the newborn, manifesting as respiratory distress with persistent pulmonary hypertension and refractory hypoxaemia. Acinar dysplasia and congenital alveolar dysplasia are characterised by arrested development at the pseudoglandular or canalicular/saccular stages, respectively. Alveolar capillary dysplasia with misalignment of pulmonary veins (ACD/MPV) associates an aberrant parenchymal development of the lung with thickened interstitium, a poor capillary bed and, in most cases, the presence of pulmonary veins in the bronchovascular axis instead of at the periphery of the lobule. The diagnosis is usually made on autopsies. Mutations in the *TBX4* and *FGFR2* genes have been associated with syndromic acinar dysplasia, and the majority of described cases of ACD/MPV have been found to be related to mutations in *FOXF1* or its enhancer. ACD/MPV is associated with extrapulmonary disorders in more than half of the cases: congenital heart diseases, digestive malformations or malrotations, and genitourinary malformations.

FLNA mutations have been associated with syndromic ILD. *FLNA* encodes filamin A, a ubiquitous cytoskeletal protein that interacts with actin. *FLNA* is located on the X chromosome, and females have been described with this condition more often than males. Chest imaging shows marked emphysema of the lungs, lobular septal thickening and diffuse patchy atelectasis. Extrarespiratory manifestations include periventricular nodular heterotopias, dental and dermal anomalies, congenital heart diseases, and impaired psychomotor development and cognition.

ILD related to exposure/environment insults

Hypersensitivity pneumonitis (HP) is the main environmental chILD diagnosis, followed by ILD related to medication, drug or radiation exposure. HP is a cell-mediated immune reaction that can occur after organic or inorganic antigen inhalation in a susceptible person. Repeated lung exposure to a critical dose of such components is able to trigger the clinical and biological manifestations. Clinical symptoms are nonspecific, but asthenia is often marked. HP can be asymptomatic or pauci-symptomatic for

months. Thus, it is often diagnosed at the chronic stage of the disease. In children, fewer molecules of the antigen are involved than in adults. The most frequent types of HP include bird fancier's disease, humidifier lung diseases and chemical lung diseases. The diagnosis of HP can be established by a thorough environmental survey and by the intervention of an expert environmental adviser at home to confirm the exposure and eventually to perform environmental measurements. Specific serum-precipitating IgG antibodies against the offending antigen are of help in the diagnosis process and may even be present in asymptomatic exposed individuals. BAL is not specific for HP but shows a lymphocytic alveolitis with a $CD8^+$ T-cell predominance. The diagnosis is further confirmed by disease regression shortly after removing the offending antigen from the patient's environment. Although rarely necessary, a corticosteroid treatment may be used, and a quick and positive response to this treatment is a supplementary argument in favour of this diagnosis.

ILD related to systemic and immune diseases

Systemic diseases can be responsible for chILD, usually associated with extrarespiratory disorders. Connective tissue diseases are the most frequent group, followed by vasculitis, autoinflammatory disorders, granulomatous diseases such as sarcoidosis, metabolic disorders such as Niemann–Pick syndrome and rarer diseases such as Hermansky–Pudlak syndrome. In this chapter, we will not include ILDs related to immunocompromised children such as chronic granulomatous disease, common variable immunodeficiency, cytotoxic T-lymphocyte-associated protein 4 (CTLA4) deficiency, lipopolysaccharide-responsive and beige-like anchor protein (*LRBA*) and signal transducer and activator of transcription 3 (*STAT3*) mutations, but these should be excluded as differential diagnoses of chILD.

Connective tissue diseases are caused by autoimmune and inflammatory disorders of the connective tissues. In childhood, the main connective tissue disorders associated with chILD are rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, Sjögren syndrome, dermatomyositis and polymyositis, and mixed connective tissue disease.

Pulmonary vasculitis associated with chILD mainly affects small vessels (arterioles, venules and capillaries). This includes antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, and microscopic polyangiitis), anti-glomerular basement membrane (anti-GBM) diseases; and purpura rheumatica (Henoch–Schönlein purpura) and cryoglobulinaemia vasculitis. Diffuse alveolar haemorrhage (DAH) can also be related to vasculitis. DAH syndromes are caused by disruption of the alveolar capillary basement membrane. As only a few children with DAH present with haemoptysis, it is important to suspect this diagnosis in cases of chILD associated with anaemia. BAL samples assess the alveolar bleeding by the presence of haemosiderin-laden macrophages within the alveoli. In children, DAH can be associated with other systemic diseases, especially autoimmune, dysimmune and allergic disorders such as coeliac disease or cow's milk protein intolerance (Heiner syndrome).

Autoinflammatory disorders can also be revealed by isolated ILD or DAH. These are emerging causes of genetic forms of chILD. Stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI) was first described in paediatric patients with multiorgan disorders including mainly the skin, joints and lung. Dominant gain-of-function mutations of *TMEM173*, encoding the STING protein, have been associated with upregulation of interferon secretion, causing

autoinflammatory and autoimmune disorders. Since the first reports, this disease has also been reported in adult patients. Coatomer protein-α (COPA) syndrome was recently described. COPA is involved in the retrograde transport of cargo proteins between the Golgi and the endoplasmic reticulum. Dominant mutations in the *COPA* gene, located on chromosome 1, have recently been described and are associated with childhood onset of multiorgan disorders including ILD and DAH but also kidney, joint and immunological disorders. For both *TMEM173* and *COPA* defects, the penetrance of the disease is incomplete, with reported asymptomatic carriers.

Granulomatous disorders are characterised by the presence of granulomas defined as an aggregation of monocytic giant cells surrounded by a ring of inflammatory cells. Sarcoidosis is the most frequent cause of granulomatous ILD. Its cause remains unknown, but the current concept is a combination of an environmental organic or inorganic trigger in a genetically predisposed host. In children, sarcoidosis is extremely rare and mostly affects black pre-teenagers. The diagnosis is based on a combination of suggestive clinical, biological and histological features. The disease seems to be more severe in children than in adults, presenting as a multiorgan disorder with general symptoms initially (fever, asthenia). Clinical manifestations mainly include respiratory manifestations, lymphadenopathies, skin lesions, and ocular and central nervous system abnormalities. Chest radiography and HRCT can find hilar lymph node enlargements, with or without ILD. BAL usually documents a lymphocytic alveolitis, with an increased $CD4^+/CD8^+$ ratio. An elevated serum angiotensin-converting enzyme level is observed less often in children than in adults. Other granulomatous disorders should be considered in children, such as chronic granulomatous disease in immunocompromised patients, infectious diseases, Langerhans cell histocytosis and Crohn's disease.

Metabolic disorders are rarely revealed or complicated by chILD. Niemann–Pick diseases (types A, B and C) are rare recessive genetic diseases caused by biallelic mutations in the gene encoding sphingomyelinase. Sphingomyelin accumulates within lysosomes in the macrophage–monocyte phagocyte system, mainly in the brain, spleen, liver, lung and bone marrow. BAL shows lipid-laden macrophages, as well as "sea-blue histiocytes" on pathology. Gaucher disease, another autosomal-recessive disease, is rarely associated with chILD but is the most common lysosomal storage disease. It is also caused by a biallelic genetic deficiency of the enzyme lysosomal glucocerebrosidase. Hermansky–Pudlak syndrome is associated with accumulation of a ceroid-like substance in lysosomes of a variety of tissues. It is characterised by albinism, a bleeding tendency associated with poor platelet aggregation, and systemic complications linked to lysosomal dysfunction.

Genetic causes of pulmonary alveolar proteinosis (PAP) can also be considered as metabolic disorders. Methionyl-tRNA synthetase (MARS) deficiencies were first described in PAP, with a recessive pattern of inheritance. The patients presented mostly severe and early forms of PAP, with most of them being associated with liver and brain involvement. Most of the reported patients with *MARS* mutations originated from the island of La Réunion and carried the same ancestral mutated allele. However, many other mutations have also been described. The relationship between the *MARS* mutations and the PAP phenotype is not clearly understood. Apart from *MARS* mutations, PAP has also been associated with very rare cases of granulocyte–macrophage colony-stimulating factor (GM-CSF) receptor defects. The clinical presentation is heterogeneous, with one patient being diagnosed in adulthood. The effects of GM-CSF are mediated through its receptors (CSF2RA and

CSF2RB), which are expressed on a number of cell surfaces including macrophages, neutrophils and type 2 alveolar epithelial cells. It is reported that the lack of efficacy of GM-CSF on its receptor caused by genetic mutations could be responsible for a decrease in ability of the alveolar macrophages to recycle SP, which accumulates in the alveolar space.

ILD related to primary lung parenchyma dysfunctions

This group mainly includes surfactant disorders, primary DAH (idiopathic pulmonary haemosiderosis), eosinophilic lung disease, lymphatic disorders and lung infections.

Surfactant disorders are genetic dysfunctions of SP metabolism. The *SFTPB* gene, encoding SP-B, with biallelic mutations was the first surfactant disorder to be described. Patients are usually newborns presenting with immediate respiratory failure and a fatal evolution, despite aggressive managements. However, a few cases with late survival have also been described after lung transplantation. SP-B deficiency is an autosomal-recessive disorder. The frameshift mutation 121ins2, resulting in a premature termination codon, is reported in approximately two-thirds of cases, but more than 40 other mutations have been described.

SFTPC mutations seem to be the most frequent surfactant disorders in children. These are associated with heterogeneous phenotypes ranging from severe neonatal respiratory distress to childhood and adult ILDs and lung fibrosis. The inheritance pattern is autosomal dominant, with incomplete penetrance and severity. It seems that up to half of the mutations are *de novo* mutations. One missense mutation, c.218T>C (p.Ile73Thr), is reported to be the most frequent, occurring in about one-third of the cases. The molecular defect is believed to result in cell toxicity with increased endoplasmic reticulum stress, alveolar inflammation and enhanced apoptosis.

ABCA3 encodes the ATP-binding cassette subfamily A member 3, the transporter of the hydrophobic SP-B and SP-C in lipid lamellar bodies to the cellular membrane. *ABCA3* biallelic mutations are reported in full-term babies with fatal neonatal respiratory distress, as well as in adult patients with ILD or lung fibrosis. Heterozygous *ABCA3* mutations have also been associated with an increased risk of neonatal respiratory distress in late preterm newborns. The increasing number of mutations documented in a heterozygous state suggests that *ABCA3* defects may be the most common causes of inherited surfactant diseases. One variant, c.875A>T (p.Glu292Val), observed in 0.4% of the general population, was found in 4% of a cohort of infants with respiratory distress. To date, more than 200 mutations have been reported in *ABCA3*, and their functional significance led to the proposal of classification as “null” mutations for those that completely abolish the protein expression and function, “non-null” mutations for those with residual ABCA3 function, and “other”. It has been suggested that protein correctors, initially studied in the context of CF in *CFTR* mutations, could also be of efficacy in certain *ABCA3* mutations.

Mutations in the *NKX2-1* gene, encoding NK2 homeobox 1 are associated with brain–lung–thyroid syndrome. *NKX2-1* is a transcription factor in the lung, thyroid and diencephalon. It promotes *SFTPB*, *SFTPC* and *ABCA3* transcription in alveolar epithelial cells. The inheritance pattern is autosomal dominant, with incomplete penetrance and severity for each of the three involved organs, even in a single family. Approximately half of the mutations are *de novo* mutations. To date, over 50 mutations have been described, with no recurrent mutation identified.

SP-A is a hydrophilic protein that belongs to the C-type lectin family (collectins). It is the most abundant SP, and is a combination of SP-A1 and SP-A2 proteins, which are highly homologous, encoded by two functional genes, *SFTPA1* and *SFTPA2*. Mutations in *SFTPA1* and *SFTPA2* have been documented mainly in adult patients. The phenotype is heterogeneous and associated with various forms of fibrosing ILD and adenocarcinoma of the lung. A paediatric case who presented with severe ILD leading to death in infancy was also reported in a large family with *SFTPA1* mutation (Nathan *et al.*, 2016).

Idiopathic pulmonary haemosiderosis is a primary form of DAH with no systemic findings. It has to be considered after exclusion of other DAH causes in cases of acute, subacute or recurrent DAH. Lung biopsy, if performed, shows evidence of red blood cells in the alveolar space without parenchymal damage and/or inflammation of the alveolar capillaries. This pattern is called "bland" pulmonary haemorrhage (*i.e.* without capillaritis or vasculitis). In this particular situation, anti-GBM antibody as well as perinuclear ANCAs should be tested for at diagnosis, and repeated over time to screen a systemic disease onset.

Eosinophilic lung diseases are also a heterogeneous group. Eosinophilic lung diseases of known cause in children mainly include allergic bronchopulmonary aspergillosis, parasitic infections and drug reactions. Eosinophilic lung diseases of unknown cause include Löffler syndrome (characterised by migrating pulmonary opacities), acute eosinophilic pneumonia and chronic eosinophilic pneumonia. The diagnosis is suggested by the presence of interstitial and alveolar infiltrates on chest imaging together with eosinophilia. It is confirmed by the presence of an eosinophilic alveolitis in BAL and/or by the presence of a lung tissue eosinophilia. Idiopathic hypereosinophilic syndrome is a multiorgan system dysfunction caused by eosinophilic infiltration, with pulmonary involvement documented in almost half of patients.

Lymphatic disorders are rare and manifest as chylothorax more often than as chILD. Primary forms (congenital abnormalities of lymphatic development) include lymphangiomas, lymphangiomatosis, lymphangiectasis and lymphatic dysplasia syndrome (congenital yellow nail syndrome). Secondary forms of lung lymphatic disorders result from a variety of processes such as chronic airway inflammation that impair lymph drainage and increase lymph production.

Infections, mainly viral, must always be considered in the chILD diagnosis process. Latent viral infections may be involved in the pathogenesis of ILD through targeting of the alveolar epithelium. The main viruses implicated include adenovirus, members of the human herpesvirus family (Epstein–Barrr virus and cytomegalovirus) and respiratory syncytial virus. A number of other viruses may also be involved, such as influenza A virus, hepatitis C virus and even HIV in immunocompetent children.

ChILD management

The rarity and diversity of chILD conditions make it difficult to propose randomised trials or consensual treatment strategies. However, international groups have proposed management strategies, both for the stable state and for exacerbation treatments. Recently, multidisciplinary team meetings have largely participated in improving the standard of care for patients with chILD.

General measures are critical. These mainly include oxygen therapy for chronic hypoxaemia, maintenance of an adequate energy intake and immunisation with

influenza vaccine. In addition, the treatment of intercurrent infections and avoidance of tobacco smoke and other air pollutants are necessary.

Corticosteroids are the preferred pharmacological therapy in chILD, followed by immunosuppressive drugs. Oral prednisolone is most commonly administered at a dose of 1–2 $mg \cdot kg^{-1} \cdot day^{-1}$. Children with significant disease are best treated with pulsed methylprednisolone at least initially, given at a dose of 10–30 $mg \cdot kg^{-1} \cdot day^{-1}$ for 3 days with a 1-month interval. An alternative to steroids is hydroxychloroquine with a recommended dose of 6–10 $mg \cdot kg^{-1} \cdot day^{-1}$. The preferred choice between steroids or hydroxychloroquine is highly dependent on the severity of the disease and the local expertise. In cases of severe disease, steroids and hydroxychloroquine may be combined. In situations of inefficiency of steroids and hydroxychloroquine, other immunosuppressive or cytotoxic agents such as azathioprine, rituximab (especially in the case of ANCA-associated vasculitis), cyclophosphamide, cyclosporine or methotrexate may be used.

Other therapeutic options include macrolides, a class of antibiotics that display a number of anti-inflammatory and immunomodulatory actions. Of interest is the ability of macrolides to accumulate in parenchymal cells including epithelial cells and phagocytes.

Other specific treatments include whole-lung lavage in situations of alveolar proteinosis, and more recently, targeted therapies such as Janus kinase (JAK) inhibitors have been proposed in patients with SAVI.

In the future, therapies currently proposed in adult patients may be of interest in certain forms of chILD. These include pirfenidone, a compound with anti-inflammatory and antifibrotic properties, and nintedanib, a tyrosine kinase inhibitor initially developed as an antitumour agent, also having activity against fibroblasts through the inhibition of several growth factors.

Lastly, lung transplantation or heart–lung transplantation may be discussed as an ultimate therapy for end-stage disease. The outcome and survival do not seem to be different from those reported in other pulmonary conditions.

In addition to pharmacological treatments, a global management should be offered to the patient's family. Social care, physiotherapy, psychomotricity and nutritional monitoring with oral feeding care in infants and young children may be proposed, as well as specific genetic counselling in cases of genetic disorders.

ChILD outcome

ChILD outcome is extremely variable and very difficult to predict. It is highly dependent on the aetiology, management and individual response to treatment. Overall, a favourable response to anti-inflammatory therapy can be expected in almost two-thirds of cases, although significant sequelae such as limited exercise tolerance or the need for long-term oxygen therapy are often observed. Reported mortality rates are around 15%. chILD is often a long-lasting disorder that greatly affects the health-related quality of life. Its evaluation and monitoring are crucial issues and help in adjusting the therapeutic strategy and global care of the patient and their family.

Summary

chILDs are rare and highly heterogeneous respiratory disorders. The various classifications proposed so far may not be fully satisfactory; they need to be further evaluated and to integrate additional information on underlying molecular

mechanisms. Genetic factors are important contributors to the chILD aetiological spectrum and the place of molecular analyses is increasing in chILD work-up.

The aetiological and follow-up management of paediatric ILDs is tricky, and national and international multidisciplinary team meetings are strongly recommended to provide optimal care to the patient. Corticosteroids, hydroxychloroquine, azithromycin and supportive care are the main treatments for chILD. The prognosis is widely variable, and the individual outcome is difficult to predict.

International networking groups on chILD have been set up in the last decade. These allow critical issues to be addressed such as deciphering chILD molecular mechanisms, predicting disease courses, improving patient management with personalised care and structuring family genetic counselling.

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Surfactant dysfunction syndromes and pulmonary alveolar proteinosis

Elias Seidl, Christina Rapp, Matthias Kappler and Matthias Griese

Pulmonary surfactant is a complex mixture of surfactant protein (SP)-A, SP-B, SP-C and SP-D and lipids. It is the key component of alveolar integrity and function. The surfactant components are essential for lowering surface tension (mainly lipids, SP-B and SP-C) and regulation of the innate immune function of the lungs (mainly SP-A and SP-D). Detailed molecular knowledge of these components led to the discovery of primary disorders of the surfactant system. Deficiencies of SP-B and SP-C, the lipid transporter ABCA3 (ATP-binding-cassette transporter A3) located in type II pneumocytes and TTF1 (thyroid transcription factor-1) regulating the expression of SP-B, SP-C and ABCA3 lead to clinical entities that are summarised here as surfactant dysfunction syndromes. These diseases are rare and represent an underdeveloped area of pulmonary research. There are no reliable estimates, but the prevalence of surfactant dysfunction syndromes is likely to be less than one per 100 000 of the population. On histopathological examination, characteristic features include: 1) interstitial widening and hyperplasia of type II alveolar epithelial cells (nonspecific interstitial pneumonia pattern), or 2) filling of the alveolar spaces with macrophages (desquamative interstitial pneumonia pattern) or with proteinaceous material (pulmonary alveolar proteinosis (PAP) pattern). The latter is often present during the initial disease phases, but the extent of alveolar filling

Key points

- Surfactant dysfunction syndromes include diseases caused by mutations in the genes encoding surfactant proteins B and C, the lipid transporter ABCA3 and the transcription factor TTF1.
- Surfactant dysfunction syndromes may present at birth as respiratory distress syndrome or later in infancy as chronic dyspnoea and hypoxia (ILD in children (chILD)), whereas mutations in the granulocyte–macrophage colony-stimulating factor receptor α-chain present only as chILD.
- No controlled trials have been performed to evaluate different therapeutic options. For surfactant dysfunction syndromes, regimes may include anti-inflammatory therapy (corticosteroids), hydroxychloroquine, azithromycin or additional treatment with immunosuppressants, while the clinical course of patients diagnosed with pulmonary alveolar proteinosis can be stabilised with repetitive whole-lung lavages.

is often less than in PAP. Therefore, the term "congenital alveolar proteinosis" to describe newborns with surfactant dysfunction has led to some confusion and should be avoided.

In contrast to surfactant dysfunction syndromes, other clinical entities leading merely to a filling of the alveolar space with surfactant due to defective removal are classed as PAP. The interstitial space is not usually affected. More than 100 other diseases are known to cause PAP (table 1). These, as well as secondary surfactant deficiency syndromes, have to be included in the differential diagnosis of patients with disturbance of the surfactant system.

Surfactant dysfunction syndromes

Deficiencies of SP-B and SP-C, ABCA3 and TTF1 are caused by mutations in the *SFTPB*, *SFTBC*, *ABCA3* and *NKX2-1* genes, respectively. The resulting diffuse parenchymal lung diseases (also known as ILD in children (chILD)) present clinically with two major phenotypes: neonatal respiratory distress syndrome and chronic ILD.

Clinical presentation

At birth, the neonatal phenotype of the surfactant dysfunction syndromes typically manifests with acute respiratory distress syndrome without being preterm or having other explanations for the clinical manifestations (*i.e.* infections, congenital heart defects, blood vessel abnormalities or other anatomic abnormalities). The pulmonary symptoms are often so severe that the child will require mechanical ventilation. Depending on the underlying mutation, the clinical course is variable, ranging from rapid disease progression and death to mild forms. A transient response to medications such as systemic steroids or administration of surfactant may be observed. Chronic ILD in children often starts insidiously with dyspnoea, dry coughing, fine crackles and failure to thrive. Such clinical symptoms alone, or in particular in combination with a familial history of fatal or chronic lung diseases or the presence of consanguinity, must lead to specific genetic testing for the conditions that are potentially causing disease.

Diagnostic assessment

Surfactant dysfunction syndromes should be suspected in children who present at birth with respiratory distress syndrome or later in infancy with chronic dyspnoea and hypoxia, as well as diffuse radiological changes. As the clinical courses are variable and not yet well described, it is not feasible to determine the most common age at presentation. When there is clinical suspicion of a surfactant dysfunction syndrome, the following entities should be excluded before further investigations: CF, immunodeficiency, congenital heart defect, BPD, pulmonary infection, PCD and recurrent aspirations. After excluding these diseases, the probability of a diagnosis can be enhanced by a structured investigation. The purpose of chest CT is to evaluate the presence and extent of an ILD. However, the ability of CT to be completely diagnostic is limited to relatively few conditions (*e.g.* PAP, hypersensitivity pneumonitis, and persistent tachypnoea of infancy, usual form). Blood tests should include investigation of genetic abnormalities. As the phenotypic manifestation of single-gene disorders may overlap, multiple gene sequencing should be performed (including for the *ABCA3*, *FLNA*, *FOXF1*, *NKX2-1*, *SFTPB* and *SFTPC* genes). However, it should be noted that novel genetic variants causing surfactant dysfunction syndromes are constantly being described. Analysis of BAL fluid for SP-B and SP-C is generally not standard as it is susceptible to interference. If a diagnosis cannot be established, open or

Table 1. Diseases that have PAP as an important pulmonary manifestation

Surfactant dysfunction syndromes
Mutations of *SFTPB*, *SFTPC*, *ABCA3* and *NKX2-1*
Impaired GM-CSF signalling
GM-CSF receptor α-chain mutations, Turner syndrome with heterozygous GM-CSF receptor α-chain mutations, GM-CSF receptor β-chain mutations, autoimmune GM-CSF antibodies[#]
Haematological disorders and other malignancies
GATA2 deficiency, myelodysplastic syndrome, chronic myelomonocytic leukaemia, acute lymphatic leukaemia, congenital dyserythropoietic anaemia, Fanconi anaemia, haemophagocytic lymphohistiocytosis, sideroblastic anaemia and others
Systemic diseases
Lysinuric protein intolerance, MARS mutations, Niemann–Pick disease type C2/B, bone-marrow/stem-cell transplantation, rheumatological diseases, lung transplantation
Immunological diseases
Adenosine deaminase deficiency, agammaglobulinaemia, DiGeorge syndrome type 2, monoclonal gammopathy, selective IgA deficiency, severe combined immunodeficiency, X-linked hyper-IgM syndrome, OAS1 mutation
Infections
Cytomegalovirus, Epstein–Barr virus, HIV, *Mycobacterium tuberculosis*, atypical mycobacteria, *Nocardia* spp., *Pneumocystis jirovecii*
Drugs
Chemotherapy, antineoplastic, busulfan, sirolimus, everolimus, tyrosine kinase inhibitors (including imatinib, nilotinib and dasatinib), mycophenolate and cyclosporine combination, smoked fentanyl patches, leflunomide, hydrofluoric acid (inhaled)
Inorganic dust exposure
Aluminium, cement, marble, indium, iron, silica and silica-leaking breast implants, tin, titanium (and varnish)
Organic dust exposure
Bakery flour, chlorine, cleaning products, cotton, fertiliser, agricultural dust, fumes, gasoline, hydrofluoric acid, dust from parrots and pigeons, petroleum, sawdust
Miscellaneous conditions
Osteopetrosis caused by *TCIRG1* gene mutation, total anomalous pulmonary venous return with coarctation of the aorta

GM-CSF: granulocyte–macrophage colony-stimulating factor; GATA2: GATA-binding factor 2; MARS: methionyl-tRNA synthetase; OAS1: oligoadenylate synthetase 1; *TCIRG1*: T-cell immune regulator 1 gene. [#]: autoimmune PAP occurs mainly in adults and is rare in children. Reproduced and modified from Griese (2017) with permission.

thoracoscopic lung biopsy should be performed in centres capable of processing the biopsy correctly. An experienced histopathologist should evaluate the specimen to ensure the correct diagnosis.

Clinical course and therapeutic strategies

SP-B deficiency

Nogee *et al*. (1994) described a mutation in SP-B causing a severe neonatal respiratory distress syndrome in term infants, ultimately leading to death. The mode of inheritance is autosomal recessive and the most common mutation is the insertion of two amino acids (121ins2). Most mutations lead to an absolute or partial loss of SP-B. The diagnosis is confirmed by sequencing of the *SFTPB* gene. Currently, the only

therapeutic option is lung transplantation. Experimental therapy with inhaled *SFTPB* RNA has been shown to be successful in animals. Palliative therapy is indicated for children with the classic mutation.

SP-C metabolism dysfunction

The inheritance of this disease, which occurs more frequently than SP-B deficiency, is autosomal dominant. Besides neonatal respiratory distress syndrome, a frequent clinical presentation is the insidious start of dyspnoea, first on exercise or noted as remaining after a respiratory infection. In the early stages of the disease, the radiological findings may be similar to those in PAP with the typical alveolar filling pattern and ground-glass opacities (figure 1). During the individual disease course, increased interstitial markings are seen as pronounced interlobular septa, multiple cystic lesions and ground-glass opacification. Therapeutic options may include anti-inflammatory therapy (corticosteroids) and treatment with hydroxychloroquine or possibly azithromycin. Additional treatment with immunosuppressants has anecdotally been described for these and other entities. To date, no controlled trials have been performed and there are no data on the success rate of therapy or on the different strategies available for *SFTPC* gene mutations. Therefore, all treatments should be tried and assessed within the framework of expert centres for rare respiratory diseases in children.

ABCA3 transporter deficiency

ABCA3 is a lipid transport protein essential for the biogenesis of lamellar bodies of type II pneumocytes. More than 200 different autosomal-recessive mutations have been described. As the heterozygous frequency in the population is estimated to be between one in 33 and one in 70 individuals, ABCA3 transporter deficiency represents one of the most frequent genetic changes detected in ILDs in children and adolescents. The clinical course and prognosis are highly variable depending on the mutations and other factors that are not yet well defined. There is a strong genotype–phenotype correlation, with patients with mutations resulting in no functional protein and presenting in the neonatal period mostly dying within the first 6 months of life, and those with residual function presenting later in childhood. Effective therapeutic interventions should be determined empirically, evaluated systematically and registered prospectively. In addition to diverse systemic steroid therapy regimes (routinely oral or pulsed intravenous), hydroxychloroquine or azithromycin are used.

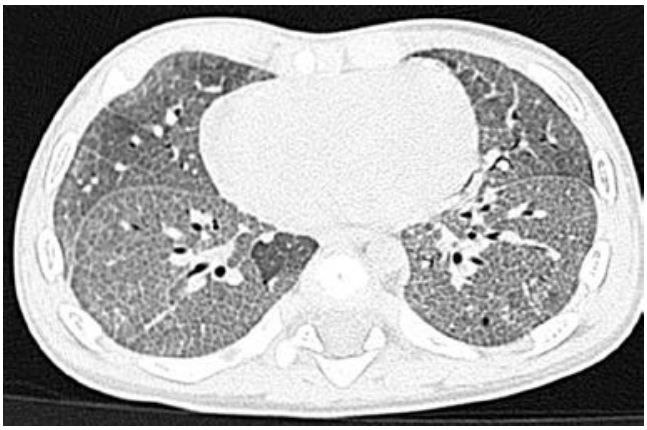

Figure 1. HRCT scan of an infant with SP-C deficiency and presentation of chILD at 6 months of age. Note the "crazy-paving pattern" in both lower lobes.

Brain–thyroid–lung syndrome

This disease, also known as TTF1 deficiency syndrome, is caused by haplo-insufficiency of the transcription factor TTF1, encoded by the *NKX2-1* gene. TTF1 modulates the expression of SP-B, SP-C and ABCA3 in the lung and other proteins in the thyroid and basal ganglia. The clinical triad of congenital hypothyroidism, neurological symptoms (muscular hypotonia, developing into chorea during infancy) and chronic or recurrent respiratory symptoms should alert the search for this condition. The spectrum of pulmonary symptoms is wide, ranging from neonatal respiratory distress to typical manifestations of chILD. Importantly, recurrent bronchopulmonary infections may represent the only primary symptoms in childhood. About 40% of cases present with respiratory symptoms alone. To date, there is still relatively little experience of treating this disease. A practical approach would be early antimicrobial and mucolytic treatment of respiratory infections. However, the empirical therapy should be evaluated and registered prospectively in order to establish and compare different therapeutic options.

Pulmonary alveolar proteinosis

PAP is defined by the accumulation of pulmonary surfactant in the alveolar space caused by disturbances of the surfactant homeostasis on the basis of altered surfactant production, removal of surfactant or both. Histologically, PAP is characterised by an accumulation of periodic acid–Schiff (PAS) reaction-positive material in the alveolar space. The alveoli are filled with eosinophilic, acellular and finely granular material. Additionally, clefts formed from cholesterol can be found. Sometimes detached type II pneumocytes, foamy macrophages or neutrophil granulocytes, as well as lamellar bodies of normal lung, can be identified. Many different underlying conditions can cause PAP and are classified as: 1) primary, involving disruption of granulocyte–macrophage colony-stimulating factor (GM-CSF) signalling, and 2) secondary, resulting from various underlying conditions. A detailed overview of the different entities causing PAP is given in table 1. Whole-lung lavage (WLL) is the cornerstone of treatment. Depending on the underlying condition causing PAP, there are a number of possible treatment approaches, although currently these remain experimental (including GM-CSF substitution, stem-cell transplantation, human induced pluripotent stem-cell-derived macrophages, pioglitazone, statins and immunomodulation).

Clinical presentation and diagnosis

The alveolar accumulation of surfactant leads to impaired gas exchange, detected early during physical exercise. Carbon dioxide transfer is not usually affected. Therefore, the clinical course typically starts insidiously at various ages ranging from infancy to senescence. The diagnosis is frequently made in the context of an acute respiratory infection that does not resolve appropriately or has a severe course. In other cases, primary presenting symptoms include exercise-induced nonproductive cough, at times developing into coughing with expectoration of whitish surfactant material. Other symptoms include exercise intolerance, weight loss or failure to thrive.

Diagnostic assessment

The physical examination may reveal dyspnoea with intercostal retractions and digital clubbing. Sometimes, fine crackles and reduced breath sounds are present. Chest radiographs typically show a bilateral alveolar filling pattern, often more prominent

in the perihilar regions and known as the "bat-wing pattern". HRCT initially shows a geographical distribution of reticulation and ground-glass opacification, the so-called "crazy-paving pattern" (figure 2). PFTs may show restrictive patterns and a reduction in the diffusion capacity. BAL typically recovers a milky fluid from large amounts of extracellular PAS-positive material. However, this is not pathognomonic for PAP, and in children without a clear molecular diagnosis, lung biopsy is the gold standard.

Whole-lung lavage

WLL represents the most important therapeutic option in PAP. A lavage of both lungs is performed to sequentially remove abnormal material. Different procedures and strategies are used. In younger children, an inflatable catheter is generally used. In older children, a double-lumen endotracheal tube is usually feasible. If the child is in a good clinical condition, there is no age limit, and lavaging both lungs is possible in the same session, if required. It is important to ensure a balanced fluid recovery and to avoid electrolyte displacements. Nevertheless, WLL is an invasive treatment and should only be performed in specialised centres by a trained team of pneumologists, anaesthesiologists and intensive care unit physicians.

Clinical course and therapeutic strategies

There are more than 100 underlying conditions associated with PAP. Here, we discuss a few examples.

GM-CSF receptor α-chain mutations

In paediatrics, the classic form of PAP is caused by GM-CSF receptor α-chain deficiency. Patients may have no clinical symptoms or suffer from dyspnoea, requiring oxygen supplementation initially during exercise and later at rest. The chest CT scan shows abnormalities in all cases, and BAL samples suggest PAP due to whitish recovered fluid in some cases. WLL is the established therapy to stabilise patients. GM-CSF receptor α-chain mutations cause a wide variety of clinical phenotypes, and identical variants can result in divergent disease courses. In fact, the clinical course cannot be predicted and ranges from clinically silent to acute respiratory failure; in most cases,

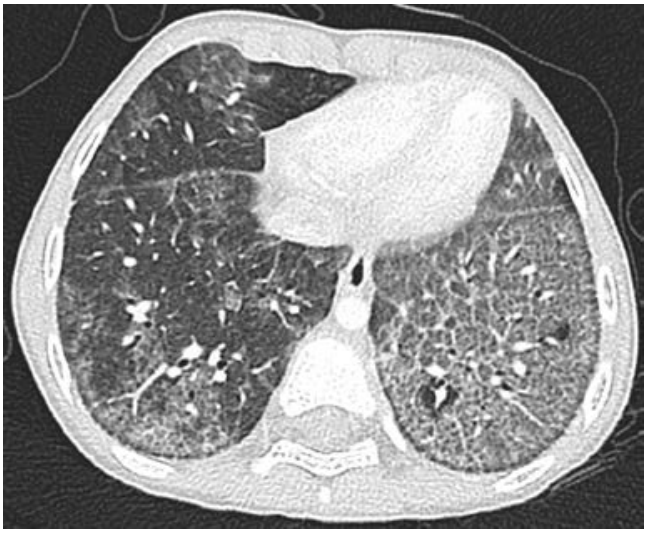

Figure 2. CT scan of the lungs of a patient diagnosed with PAP due to GM-CSF receptor α-chain mutations showing a "crazy-paving pattern" (diffuse ground-glass opacities and inter- and intralobular thickening).

patients improve over time. Some patients have to undergo WLL at regular intervals for long periods in order to enable physiological gas exchange and development. Nevertheless, such a therapy should be performed in specialised centres to offer a good long-term prognosis. Injection or inhalation of recombinant GM-CSF is ineffective and therefore not recommended. The clinical outcome of treatment with bone-marrow transplantation is highly contradictory: one case in the literature was reported to have completely recovered (Frémond *et al*., 2017), whereas another died due to complications soon after bone-marrow transplantation (Martinez-Moczygemba *et al*., 2008).

Niemann–Pick disease type C2

This disease often manifests with respiratory distress during infancy and childhood. The average age of death from respiratory insufficiency is 8 months. Accumulation of PAS-positive lipid material that, in contrast to normal surfactant, also contains high concentrations of ceramides, glucosylceramides and SP-A has been identified as the cause of respiratory distress syndrome in some cases. Furthermore, the widened interstitium is characterised by progressive fibrosis and lipoid pneumonia. WLL has been tried therapeutically, but was not successful.

Lysinuric protein intolerance

This is an autosomal-recessive disorder caused by defective plasma membrane transport of cationic amino acids in epithelial cells of the gastrointestinal tract and kidneys due to a mutation in the *SLC7A7* gene encoding Y+L amino acid transporter 1. So far, most cases have been reported in Finland, Italy and Japan. While there is a major focus on renal and gastrointestinal manifestations (*e.g.* pancreatic insufficiency), pulmonary affection in the sense of ILD is highly variable and can lead to respiratory insufficiency. In these cases, this is often due to PAP, probably caused by reduced expression of *SLC7A7* by GM-CSF. Therapeutically, and with variable success, WLL, inhaled GM-CSF and lung transplantation have been tried. However, recurrence of PAP after lung transplantation has been reported.

GATA2 deficiency

The zinc finger transcription factor GATA2 (GATA-binding factor 2) is essential for differentiation of immature haematopoietic stem cells regulating the phagocytosis of alveolar macrophages. Haplo-insufficiency in GATA2 accounts for a broad phenotype including immunodeficiency, myelodysplastic syndrome, pulmonary disease and vascular dysfunction. The hallmark of affected patients is recurrent respiratory tract infections or exacerbations. Nevertheless, it has to be noted that PAP is present in only about one-fifth of affected patients, and a specific variant does not inevitably cause PAP in different patients. Symptomatic treatment with WLL is feasible, even for children of a very young age. The reduced monophagocytic function of the alveolar macrophages might be corrected by stem-cell transplantation, as in one child clearance of PAP occurred shortly after stem-cell transplantation. It is noteworthy that no beneficial effects have been noted after the use of systemic corticosteroids.

OAS1 mutations

Recently, Cho *et al*. (2018) described an infantile onset of PAP with onset of respiratory symptoms within the first 6 months in combination with hypogammaglobulinaemia due to heterozygous OAS1 gain-of-function variants. OAS1 is a member of the 2′,5′-oligoadenylate synthetase family involved in the innate immune response to viral infections. The impaired removal of surfactant by alveolar macrophages expressing OAS1 mutations leading to PAP may be treated with bone-marrow transplantation.

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Pulmonary vascular disorders

Andrew Bush and Elizabeth Scotney

The cardinal manifestation of pulmonary vascular disorders is pulmonary hypertension. Normal pulmonary arterial pressure (PAP) is ≤20 mmHg, whereas patients with pulmonary hypertension have PAP >25 mmHg, and those with intermediate values are considered as developing pulmonary hypertension and require follow-up. For pre-capillary pulmonary hypertension, pulmonary capillary wedge pressure must be <15 mmHg and cardiac output normal or reduced. In post-capillary pulmonary hypertension (usually due to left heart disease), wedge pressure is >5 mmHg and cardiac output normal or reduced. If the transpulmonary pressure gradient is >12 mmHg with an elevated wedge pressure, a reactive component is present. There are no data to define pulmonary hypertension on exercise. Pulmonary hypertension does not, of itself, mean the child has pulmonary vascular disease; a high pulmonary venous pressure and a high pulmonary blood flow can both elevate PAP without there necessarily being any pulmonary vascular disease. In paediatric practice, it is wise to measure pulmonary vascular resistance (PVR), particularly in children with left-to-right shunts and anaemia. The normal PVR is ≤3 Wood units (transpulmonary vascular pressure gradient/pulmonary blood flow).

Classification of pulmonary hypertension in children

There are significant differences in the pathophysiology of pulmonary hypertension in children and adults. Abnormalities of growth and development are more likely in paediatric patients; for example, infants with pulmonary hypertension may have failed to reduce the antenatally physiologically high PVR during the post-natal

Key points

- The symptoms of pulmonary hypertension are nonspecific and the possibility of the condition should always be remembered. Syncope on exercise should never be ignored.
- If pulmonary hypertension is secondary to lung disease, this is usually obvious from the chest radiograph.
- In a child with pulmonary hypertension and a normal chest radiograph, remember that OSA and occult ILD are possible causes.
- Children with pulmonary hypertension should be referred to specialist centres for evaluation and consideration of treatment.

Table 1. Current clinical classification of pulmonary hypertension

1 PAH
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug- and toxin-induced PAH
1.4 PAH associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.5 PAH long-term responders to calcium channel blockers
1.6 PAH with overt features of venous/capillary involvement (PVOD/PCH)
1.7 Persistent pulmonary hypertension of the newborn
2 PAH due to left heart disease
2.1 PAH due to heart failure with preserved LVEF
2.2 PAH due to heart failure with reduced LVEF
2.3 Valvular heart disease
2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PAH
3 PAH due to lung diseases and/or hypoxia
3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders
4 PAH due to pulmonary artery obstructions
4.1 Chronic thromboembolic PAH
4.2 Other pulmonary artery obstructions
5 PAH with unclear and/or multifactorial mechanisms
5.1 Haematological disorders
5.2 Systemic and metabolic disorders
5.3 Others
5.4 Complex congenital heart disease

PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; LVEF: left ventricular ejection fraction. Modified from Rosenzweig *et al*. (2019) and del Cerro *et al*. (2011).

period. Chromosomal and genetic syndromes are also important, as are the effects of disease and treatment on the developing lung. Abnormalities of vasculogenesis and angiogenesis have increasingly been implicated in paediatric pulmonary hypertension. A recently proposed classification of pulmonary hypertension in children is given in table 1.

Epidemiology

Pulmonary hypertension may present at any age. There are numbers of national and international specifically paediatric registries, which have increased our information base. The European incidence is 4–10 cases per million, and prevalence is 20–40 cases per million. Of these, 87% were transient (persistent pulmonary hypertension of the newborn or repairable cardiac shunt defects). Of the persistent pulmonary hypertension cases, 34% were associated with developmental lung disease (BPD, congenital diaphragmatic hernia and congenital pulmonary vascular abnormalities)

and 27% with other causes (idiopathic, associated with congenital heart disease or connective tissue disease, and pulmonary veno-occlusive disease (PVOD)).

Pulmonary hypertension secondary to respiratory disease is usually dominated by obvious features of the underlying cause (for example, very severe bronchiectasis in CF). The underlying mechanism is usually intermittent or continuous alveolar hypoxia leading to pulmonary vasoconstriction and ultimately vascular remodelling; there may be elements of alveolar growth and developmental disorders. Systemic arterial hypoxaemia in the absence of alveolar hypoxia (for example, due to multiple pulmonary arteriovenous malformations) does not lead to pulmonary hypertension. Two important "occult" respiratory causes of pulmonary hypertension with a normal chest radiograph are ILD and sleep disordered breathing, usually OSA. Hence, every case of apparently idiopathic pulmonary hypertension should have these conditions excluded. The management of secondary pulmonary hypertension is largely of the underlying respiratory conditions, and this will not be discussed further here. If secondary pulmonary hypertension is thought to be disproportionate to the severity of lung disease, consideration should be given to the use of therapies used for primary pulmonary arterial hypertension (PPAH) (see later in this chapter), probably best as part of a randomised controlled trial. Any child thought to have primary pulmonary vascular disease should have Eisenmenger syndrome and other cardiological conditions excluded by a careful evaluation. The management of this latter group is usually medical in specialist paediatric cardiological centres, which is beyond the scope of this chapter.

Normal pulmonary vascular development

The pulmonary arteries develop embryologically from the sixth bronchial arches. The pre-acinar vessels follow the airway development and are largely complete by the end of the first 16 weeks of pregnancy, the end of the pseudoglandular phase. Blood vessels form by vasculogenesis (*de novo* formation of vessels in the mesenchyme) with the airways acting as a template for vascular development. Acinar vessels develop in parallel with the terminal bronchioles and alveoli. Alveolar development is largely a post-natal phenomenon and capillaries form by angiogenesis (sprouting from existing vessels). Antenatally, the lung is a fluid-filled, fluid-excreting organ with a very low blood flow and no role in gas exchange. At birth, profound adaptations must occur if the baby is to survive. The lung absorbs fluid and becomes "dry"; the alveoli expand, PVR falls and the pulmonary blood flow rises from <5% to equal that of the systemic circulation. The arterial duct and the foramen ovale become functionally, and later structurally, closed. In the subsequent weeks, there is thinning of the alveolar capillary membrane and profound increase in the number of alveoli, produced by secondary septation. Post-natally, alveolar development was thought to be largely complete by 2 years of life, but recent work in rhesus monkeys and also using hyperpolarised helium (He^3) to measure alveolar size in humans has shown that alveolar size is largely stable during the phase of somatic growth, implying neoalveolarisation, and by implication pulmonary capillary growth, continues to puberty. He^3 studies have also suggested catch-up alveolar growth in at least some preterm survivors.

Abnormal pulmonary vascular development

Most conditions with abnormal pulmonary vascular development present to the neonatologist and are only briefly discussed here:

- Persistent pulmonary hypertension of the newborn is the most dramatic example of failure of normal developmental homeostasis. Shortly after birth, the baby

becomes deeply cyanosed and very difficult to oxygenate. This is a neonatal intensive care unit emergency.

- Alveolar capillary dysplasia spectrum is an overlapping group of diseases, comprising acinar dysplasia, alveolar capillary dysplasia, and alveolar capillary dysplasia with misalignment of the pulmonary veins (MAPV). MAPV is a misnomer; the venous drainage, which is in the bronchovascular bundle instead of centrilobular, is in fact through dilated bronchial veins, which anastomose with pulmonary veins proximal to occlusions of the latter. Mutations in the *FOXF1* (forkhead box F1) and *STRA6* (stimulated by retinoic acid 6) genes should be sought. Presentation is usually in a term baby with relentlessly progressive respiratory distress. These conditions should be distinguished from disease due to mutations in *SFTPB* (surfactant protein B), *SFTPC* (surfactant protein C), *ABCA3* (ATP-binding cassette sub-family A member 3) and *TTF1* (thyroid transcription factor 1, *NKX2.1*), which may present in a similar way (see chapter "Interstitial lung diseases"). Diagnosis is on lung biopsy or at autopsy. There is no treatment and prognosis is poor. Late-presenting patchy forms of the disease with longer survival have been described.
- Early-onset primary pulmonary hypertension with MAPV comprises babies presenting at a few weeks of age with very severe pulmonary hypertension for which no underlying cause is found. It is thought to be related to failure of regression of the antenatal physiologically hypertensive pulmonary circulation. The prognosis is poor.
- Pulmonary hypoplastic syndromes result from alveolar maldevelopment, for which there are numerous causes. Congenital diaphragmatic hernia is the obvious example, and other causes include those secondary to cardiac disease (abnormal fetal blood flow), lack of space (fetal pleural effusion, Jeune syndrome) and impaired fetal breathing movements (for example, myotonic dystrophy with maternal inheritance). There are no specific treatments other than of any treatable underlying cause.

Presentation of pulmonary hypertension due to pulmonary vascular disease

The symptoms of pulmonary hypertension are nonspecific and the condition can be missed initially. Breathlessness may be attributed to airway disease and early cyanosis may be difficult to detect. Syncope, particularly on exercise, is an ominous symptom that should never be ignored. Once pulmonary hypertension is suspected, ECG, or better, echocardiography, confirms the diagnosis, as well as the underlying cause if related to congenital heart disease. If there is tricuspid or pulmonary regurgitation, PAP can be estimated reasonably accurately from the Bernoulli equation. The gold standard is right heart catheterisation, which also allows cardiac output and pulmonary capillary wedge pressure to be measured.

Causes of pulmonary vascular disease

The three main causes of primary pulmonary vascular disease encountered in paediatrics are PPAH, PVOD and pulmonary embolism (thrombotic and nonthrombotic). Other causes of pulmonary hypertension that will also be discussed in this section are invasive pulmonary capillary haemangiomatosis and secondary pulmonary hypertension in BPD.

Primary pulmonary arterial hypertension

Diagnosis of PPAH

PPAH is a diagnosis of exclusion, requiring the documentation of pulmonary hypertension and an elevated PVR, and the exclusion of any secondary cause. The differential diagnosis of apparent PPAH includes HIV infection, substance abuse (crack cocaine, amphetamines), occult liver disease, connective tissue disease (especially

scleroderma), pulmonary vasculitis, metabolic disease (Gaucher disease, Niemann–Pick disease) and sarcoidosis. Pulmonary hypertension and other vascular disease secondary to liver disease are described in more detail in the chapter "Effects of systemic and extrapulmonary conditions on the respiratory system".

The symptoms of PPAH are nonspecific, but fainting during exercise should always be taken seriously. Infants typically present with right heart failure and cyanosis. There may be suggestive physical signs, such as a loud pulmonary component of the second heart sound, the murmurs of pulmonary or tricuspid insufficiency, a parasternal heave or, in advanced cases, the signs of right heart failure. Blood tests should be directed to eliminating any underlying cause of pulmonary hypertension, as well as excluding thyroid disease, which is not uncommon in pulmonary hypertension. Elevated N-terminal pro-brain natriuretic peptide and brain natriuretic peptide have been reported in children with pulmonary hypertension and are likely to be increasingly used in the future as biomarkers. Chest radiography may lead to suspicion of PPAH diagnosis if there is peripheral oligaemia and enlarged central pulmonary arteries. The 6-min walk test may give useful functional information. The decision to proceed to right heart catheterisation and measurement of vascular reactivity is taken in conjunction with a paediatric cardiologist; the procedure is not without risk, especially in children with suprasystemic PAP. The Sitbon criteria for positive acute vascular reactivity are a decrease in mean PAP by >10 mmHg to a value <40 mmHg with sustained cardiac output; these identify children likely to respond to treatment. Overall, children appear to have a better-preserved cardiac output than adults and go into right ventricular failure later in the course of the disease. A diagnostic algorithm is given in figure 1.

Pathophysiology of PPAH

The pathophysiology of PPAH is unclear. Important components are vasoconstriction, obstructive remodelling of the pulmonary circulation, thrombosis and inflammation. Histopathology reveals combinations of arterial medial hypertrophy, concentric laminar fibroelastosis, plexiform lesions, necrotising vasculitis and fibrosis. There may be increased neuroendocrine cell numbers and positive endothelial staining for endothelin-1 immunoreactivity. Children tend to have more medial hypertrophy, less intimal fibrosis and fewer plexiform lesions than adults. The clinical correlate may be greater pulmonary vascular reactivity and a propensity to sudden death from pulmonary hypertensive crises, especially in infants. Endothelial dysfunction manifests as reduced production of vasodilator and antiproliferative mediators, such as nitric oxide and prostacyclin, and overproduction of vasoconstrictor and pro-proliferative agents, such as endothelin-1 and thromboxane A_2. Other endothelial mechanisms include increased sensitivity to apoptosis, release of pro-inflammatory mediators, smooth muscle-like mesenchymal formation and changes in migratory potential and metabolism. Mutations are found in 20–30% of sporadic cases and 70–80% of familial. The most common is in the *BMPR2* (bone morphogenetic protein receptor 2) gene, found in ~70% of familial PPAH. BMPR2 is part of the transforming growth factor (TGF)-β superfamily and, among other properties, contributes to the modulation of vascular proliferation. Mutations in other receptors for these polypeptides are associated with familial pulmonary hypertension, including activin receptor-like kinase 1 (encoded by the *ALK1* gene) and endoglin, both of which are also associated with hereditary haemorrhagic telangiectasia. Other genes implicated include *SMAD9*, *CAV1* (caveolin-1), *KCNK3*, *ABCC8*, *GDF2*, *EIF2AK4* and *TBX4*.

Treatment of PPAH

Any underlying condition should receive standard treatment. Oxygen should be given to prevent hypoxaemia, although this is of controversial benefit. A single, nonrandomised

Figure 1. Suggested scheme for investigating a child with suspected pulmonary hypertension (PH). CHD: congenital heart disease; V′/Q′: ventilation/perfusion; CTEPH: chronic thromboembolic pulmonary hypertension; CTA: computed tomography angiography; PEA: pulmonary endarterectomy; AVT: acute vasodilator testing; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary artery wedge pressure; WU: Wood units; 6MWT: 6-min walk test; CPET: cardiopulmonary exercise test; CTD: connective tissue disease; IPAH/FPAH: idiopathic/familial pulmonary arterial hypertension. Reproduced and modified from Rosenzweig et al. *(2019) with permission.*

study of pulmonary hypertension in children with congenital heart disease suggested that oxygen had a beneficial effect on survival. Calcium channel antagonists are prescribed only for those children with marked vascular reactivity. Anticoagulation should be considered in selected children, usually those with right heart dysfunction, indwelling lines or a hypercoagulable state, but is used much less often with the advent of advanced therapies. There are no paediatric studies suggesting benefit from anticoagulation. Blade atrial septostomy may help symptomatically by decompressing the right-sided circulation but may be associated with significant mortality. Patients with end-stage disease should be considered for heart–lung transplantation.

There are three groups of compounds that may be used to treat PPAH and that have been extended to other causes of pulmonary hypertension. These are 1) prostacyclin

and its derivatives, 2) phosphodiesterase-5 inhibitors (*e.g.* sildenafil), and 3) the endothelin receptor antagonists. Their use has led to enhanced survival.

- Continuous intravenous infusion of prostacyclin has been associated with improved survival in children as well as adults, but the logistic challenge of this treatment is considerable. The benefit may be not only by vasodilation but also by restoration of endothelial function. Inhaled iloprost has also been used but the need for six to eight nebulisations a day has limited its value in children; it may also cause bronchoconstriction when nebulised. Oral, subcutaneous and inhaled treprostinil are other options.
- Sildenafil is a phosphodiesterase-5 inhibitor that increases cGMP and thus promotes vasodilation and modulates remodelling. It is the only approved treatment of its class in Europe for pulmonary hypertension. The first ever randomised controlled trial in children with pulmonary hypertension showed that sildenafil reduced PVR and improved survival. However, in the 16-week STARTS-1 trial (sildenafil in treatment-naïve children, aged 1–17 years with pulmonary arterial hypertension) there was an unexplained increased mortality during trial extension on high dose (STARTS-2); hence, it is not approved for children in the USA. Serious adverse events are not uncommon, and include headache, flushing, hypotension, GOR, bronchospasm, nasal stuffiness and (rarely) priapism. Tadalafil is a long-acting member of the same class. An alternative future approach may be to use cGMP stimulators, of which riociguat is an exemplar.
- Endothelin-1 is a potent vasoconstrictor and mitogen for fibroblasts and smooth muscle cells. There are two isoforms of the endothelin receptor found in pulmonary vascular smooth muscle cells: ET_A and ET_B. ET_B receptors are also found in the endothelium and are involved in endothelin clearance and release of nitric oxide leading to vasodilation. However, despite these physiological differences, dual-receptor and selective ET_A receptor antagonists are equally effective. Bosentan, a dual-receptor antagonist, is licensed in children and observational studies suggest it may be beneficial. However, 10–15% of children discontinue therapy because of side-effects, including abnormal liver function tests especially during viral infections, ventilation/perfusion mismatch, hypotension and anaemia. Oedema and airway issues are rarely encountered in infants.

In general, these new options, alone and in combination, are expensive and potentially toxic medications that are best utilised in pulmonary hypertension accredited centres. There is a scarcity of randomised controlled trials in children and treatment algorithms are unfortunately often extrapolated from adult studies; this is dangerous, because the pathophysiology of pulmonary hypertension may not be the same.

Prognosis of PPAH

The prognosis in children is variable. Good prognostic signs are: 1) clinical stability with good functional status and well-maintained cardiac output, 2) absence of right ventricular hypertrophy, 3) absence of syncope, 4) diagnosis at >2 years of age, 5) brain natriuretic peptide studies normal, and 6) PAP <75% systemic with acute vasoreactivity. 5-year survival is of the order of 75%.

Pulmonary veno-occlusive disease

The presentation of PVOD is indistinguishable from that of PPAH. Physical examination may reveal digital clubbing (unusual in other forms of pulmonary arterial hypertension other than cyanotic congenital heart disease) and crackles. Chest radiography and HRCT will show signs of pulmonary venous congestion. The diagnostic gold

standard is open-lung biopsy but noninvasive testing may obviate the need for this. If lung tissue is obtained, the pulmonary veins and venules contain organised and recanalised thrombi with intimal fibrous pads and medial hypertrophy. The veins may show medial hypertrophy and arterialisation. There may be similar changes in pulmonary capillaries and the pre-capillary circulation, including fibrinoid necrosis in the latter. If cardiac catheterisation is undertaken, wedge pressure is often normal because the large pulmonary veins are not affected, and pulmonary vasodilator trials may precipitate pulmonary oedema. There is no medical therapy and referral to the local transplant centre is indicated at diagnosis.

The majority of cases are idiopathic; rare familial cases are described, and cases secondary to chemotherapy, bone marrow transplantation and congenital heart disease have been described. Differential diagnosis includes congenital absence or stenosis of the pulmonary veins, and pulmonary venous obstruction due to mediastinal pathology such as fibrosing mediastinitis.

Pulmonary embolic disease

Causes of pulmonary embolic disease are summarised in table 2. This condition is undoubtedly underdiagnosed in children because it is frequently not considered. Presentation may be with acute collapse due to a massive embolism or the more subtle onset of breathlessness due to repeated small emboli. There are four important questions if pulmonary embolic disease is suspected:

- Has there been embolic occlusion of part of the pulmonary arterial tree?
- Is the child cardiovascularly stable or is urgent intervention required?
- What is the material embolised?
- What has predisposed to the embolic event?

Table 2. Causes of pulmonary embolic disease

Thromboembolic disease	Nonthrombotic embolic disease
Indwelling venous catheters (>25% cases) **Low flow states** Cardiac failure Fontan circulation Dilated cardiomyopathy **Coagulopathy** Factor V Leiden Protein C deficiency (congenital or acquired) Protein S deficiency (congenital or acquired) Antithrombin III Dysfibrinogenaemias Miscellaneous, including oral contraception **Immobility** **Blunt thoracic trauma** **Axillary vein thrombosis** May be associated with acquired lymphangiectasia and chylothorax **Renal vein thrombosis** Membranous nephropathy, may also have a coagulopathy	**Tumour emboli** Right atrial myxoma Liver, renal or testicular tumours **Tropical** Schistosomiasis **Fat embolism** Trauma Burns Cardiopulmonary bypass Acute pancreatitis (always consider CF if no other obvious cause) **Adolescent issues** Pregnancy complications (amniotic fluid embolism) Intravenous drug abuse (talc emboli from injecting crushed up tablets)

The factors predisposing to thromboembolism are an intravascular foreign body (*e.g.* a portacath), a sluggish circulation, coagulopathy and immobility. More than one factor may be operative. Typical causes of a sluggish circulation include the post-Fontan situation and left atrial dilatation secondary to cardiomyopathy. Numerous congenital and acquired prothrombotic disorders have been implicated in pulmonary embolism or *in situ* thrombosis. Membranous glomerulonephritis is a notorious source of pulmonary thromboemboli from the renal veins.

There are numerous causes of nonthrombotic emboli. Tumour emboli originating from Wilms, hepatoblastoma or testicular teratoma are among the most common. In tropical regions, schistosomal ova are an important cause of pulmonary hypertension. Talc emboli from injecting crushed up tablets as a form of substance abuse is another cause. The presentation of infected emboli, another complication of intravenous drug abuse, is usually dominated by a septic picture.

Since these conditions are so rare in childhood, there is usually insufficient experience to rely on noninvasive diagnosis, for example with D-dimer. Suspicion may be aroused by a ventilation/perfusion scan, which typically shows normal ventilation but marked perfusion defects. Contrast-enhanced CT scanning will demonstrate filling defects in the proximal pulmonary arteries. If distal disease not visible on CT scanning is suspected and, in particular, if nonthromboembolic disease is a diagnostic consideration, then a lung biopsy may be indicated.

Management is of the underlying cause, for example, by removal of the indwelling line. For an otherwise well child who has had a pulmonary thromboembolism and is clinically stable, anticoagulation with heparin and warfarin is indicated, and referral to a paediatric haematologist is mandatory. If the child is critically unstable, then consideration should be given to thrombolysis and even embolectomy, in consultation with a paediatric cardiologist and cardiothoracic surgeon.

Invasive pulmonary capillary haemangiomatosis

Invasive pulmonary capillary haemangiomatosis is a rare condition that is considered a low-grade neoplasm, and is characterised by proliferating sheets of thin-walled vessels that infiltrate the pulmonary circulation leading to vascular occlusion. Rarely, there is extrathoracic spread of the abnormal vasculature. Presenting features include dyspnoea, thrombocytopenia and haemoptysis, and symptoms of pulmonary hypertension. There may be digital clubbing and pleural and pericardial effusions. Familial and congenital cases have been described. HRCT differentiates the condition from other causes of pulmonary hypertension. The distinction is important because vasodilator trials may cause pulmonary oedema in this condition. Typically, there is diffuse bilateral thickening of the interlobular septa and small centrilobular opacities, which are poorly defined. There may also be diffuse ground-glass opacities. Definitive diagnosis is by lung or other tissue biopsy. Occasional children have an associated connective tissue disease or other comorbidity. Localised forms may be treated surgically, disseminated disease with interferon-α2a or heart–lung or bilateral-lung transplant. However, most affected children die quickly.

Secondary pulmonary hypertension in BPD

Secondary pulmonary hypertension in BPD accounts for an increasing proportion of children with pulmonary hypertension, related to impaired alveolar and vascular growth and maturation. BPD is currently the most common primary lung disease causing pulmonary hypertension, and pulmonary hypertension is present in up to

20% of BPD patients. Although it may resolve over time, it is associated with an increased risk of death. A treatable cause is large aortopulmonary collaterals, which can be embolised. Another underlying cause, usually fatal, is acquired pulmonary venous stenosis, which may especially complicate necrotising enterocolitis.

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Pulmonary haemorrhage

Matthias Griese

Bleeding coming from the lungs, also called pulmonary haemorrhage, is a symptom and, as such, a sign for an underlying disease. Almost any disease affecting the respiratory tract may cause it, yielding an extremely broad differential diagnosis. However, some entities may be more prone and typical than others. Therefore, the clinical course, clinical modifiers, details on history and genetic factors will be helpful to rapidly come to the most likely diagnosis. To easily memorise possible entities, two groups of diseases can be distinguished: 1) those affecting the "lung only" (*i.e.* diseases affecting lung vessels), and 2) those related to systemic disease processes. In both groups, haemorrhage may occur at localised sites or be diffusely distributed in the lungs (table 1).

As the number of entities is very large, we will focus on a few to illustrate the underlying diagnostic and therapeutic principles.

Clinical presentation

Usually, spitting of blood is an alarming and terrifying event. Haemoptysis volumes obviously have to be related to age; often scant (<5 mL), mild-to-moderate (5–240 mL) or massive bleeding (>240 mL·day^{-1}) are differentiated. However, the younger the child, the less likely it is that blood will be coughed up, and in newborns, infants and young children, coughing alone, transient respiratory distress or anaemia may be the only symptoms.

Key points

- Pulmonary haemorrhage is a symptom.
- The underlying causes need to be clarified meticulously.
- Few, if any, cases remain idiopathic when the diagnostic work-up is thorough and repetitive.
- Alternative treatments to systemic steroids used in chronic "idiopathic" haemosiderosis should be sought to minimise side-effects.

Table 1. Causes of pulmonary haemorrhage for bleeding related to the lung only and to systemic disease processes

Lung only	Systemic
Local	**Local**
• Infection (acute, recurrent and chronic bronchitis, pneumonia)[#] Bronchiectasis, non-CF (post-infectious, immunodeficiency) CF PCD/Kartagener syndrome Lung abscess • Diffuse alveolar damage and acute interstitial pneumonia • Trauma (airway laceration, lung contusion, tracheostoma, endotracheal tube, suction catheter) Inhalation injury Foreign body aspiration • Vascular disorders (haemangiomas, atrio-venous malformations) Pulmonary vein atresia/stenosis Pulmonary mitral stenosis or other left-sided obstructions Other congenital heart diseases, left-to-right shunt Thromboembolic disease • Acute fibrinous and organising pneumonia • Factitious/Münchhausen syndrome/ Münchhausen by proxy • Catamenial (menstruation)/ endometriosis • Tumour or malformation Bronchogenic cyst Sequestration Congenital cystic adenomatoid malformation Bronchial carcinoid Bronchial inflammatory polyps Bronchogenic carcinoma Mucoepidermoid carcinoma	• Infections due to immunodeficiency (B-/T-cell deficiencies, phagocyte defects) • Vascular disorders Hereditary haemorrhagic telangiectasia (Osler–Weber–Rendu syndrome) • Metastasis
Diffuse	**Diffuse**
• Asphyxiation, abuse • Vascular disorder Pulmonary hypertension Veno-occlusive disease Idiopathic pulmonary capillaritis Pulmonary capillary haemangiomatosis • Toxic inhalation (*e.g.* tetrahydrocannabinol)	• Preterm birth • Vasculitis disorders Granulomatosis with polyangiitis Coeliac disease (Lane–Hamilton syndrome) Heiner syndrome (milk induced) Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) IgA vasculitis (Henoch–Schönlein purpura) Diffuse alveolar haemorrhage due to vasculitic disorders Antiglomerular basement membrane disease (Goodpasture syndrome) Cryoglobulinaemic vasculitis Microscopic polyangiitis Necrotising sarcoid granulomatosis Other rare causes of granulomatous arteritis Polyarteritis nodosa • Coagulopathy Von Willebrand disease Thrombocytopenia Pulmonary thrombotic microangiopathy (from atypical haemolytic uraemic syndrome) • Immune-mediated/collagen vascular disorders Systemic lupus erythematosus Behçet disease Juvenile idiopathic arthritis • Immune dysregulation COPA syndrome Lymphoid interstitial pneumonitis STAT3 loss of function (*e.g.* hyper-IgE syndrome) • Therapeutic intervention (aspirin, warfarin, other medications and interactions) • Chromosomal disorders (*e.g.* trisomy 21) • Transplantation and rejection • Acute idiopathic diffuse alveolar haemorrhage of infancy • Idiopathic pulmonary haemosiderosis

[#]: most prominently adenovirus, influenza virus, respiratory syncytial virus, *Mycobacterium tuberculosis*, nontuberculous mycobacteria, *Pseudomonas aeruginosa*, *Mycoplasma pneumoniae*, *Aspergillus* spp. and echinococcosis, among others.

Clinical course

Onset: neonatal and paediatric

Neonatal haemorrhage needs to be differentiated from that in older age groups due to the development of haemostasis. Because this is not concluded in the mature neonate, newborns and in particular preterm neonates and sick infants are very vulnerable and prone to haemorrhagic (or thrombotic) complications. Neonatal pulmonary haemorrhage has an incidence of ~1% and is frequently associated with comorbidities including respiratory distress syndrome, surfactant administration, persistent ductus arteriosus, fluid overload, cardiac failure and left-to-right shunts, as well as neonatal infection and birth asphyxia. Diagnosis is made by bloody fluid recovered from the nose, mouth or airways and supported by bilateral infiltrates on chest radiography. Treatment addresses underlying coagulation deficiencies and other causes identified, together with careful/restrictive blood substitution and fluid management.

Temporal pattern: acute, recurrent or chronic

Obvious bleeding and bleeding suspected to originate from the lungs need to be differentiated clearly from that coming from the nose (one side?) or the gastrointestinal tract. Adolescents may report a "bubbling sensation" over a certain area of their chest or a metallic taste. Acute major haemorrhage leading to hypovolaemic shock is frequently due to bronchial artery bleeding from aberrant vessels or chronic pulmonary infection. It is important to note that in many children only indirect signs, including pallor and anaemia, coughing, wheezing or reduced exercise tolerance, may be present. Some of these patients remain undiagnosed for some time so that failure to thrive and clubbing may develop. Tachypnoea, dyspnoea, fever, crackles and wheeze are important signs to note. Recurrent symptoms, in particular with symptom-free intervals, point to progressive underlying conditions such as autoimmune or vascular abnormalities.

Table 2. Diagnostic work-up to be used appropriate to the clinical situation and history information

Routine and immunological/rheumatological blood tests
Full blood count (including reticulocytes)
Chemical profile (including serum iron, ferritin, haptoglobin, lactate dehydrogenase, C-reactive protein and erythrocyte sedimentation rate)
Autoantibodies (including transglutaminase, cow's milk and antiglomerular basement membrane, antimyeloperoxidase, antiproteinase 3, double-stranded DNA, antinuclear, rheumatoid factor, anticentromere, Sjögren and Scl-70 antibodies)
Immunodeficiency screening (including IgE and HIV)
Coagulation studies (including prothrombin time, activated partial thromboplastin time, international normalised ratio, fibrinogen, D-dimer, lupus anticoagulant, von Willebrand factor, protein C and protein S activity, factor V Leiden and β_2-glycoprotein)
Microbiology
Culture or PCR for respiratory pathogens including bacteria, fungi, viruses and mycoplasma/chlamydia, acid-fast bacilli/Mantoux test
Bronchoscopy with BAL or lung biopsy
Include assessment of haemosiderin-laden macrophages (each lung separately)
Imaging
Chest radiography, chest CT, angiography

Clinical modifiers and past medical history

It is important to note that a pulmonary haemorrhage can be due to several causes at the same time, one of which may be underlying and the other(s) triggering (table 1). As the differential diagnosis is very broad, a detailed family, exposure/environmental, psychosocial and travel history must routinely be taken.

Diagnostic work-up

Due to the broad range of underlying diseases, a standardised diagnostic assessment including interdisciplinary consultation is appropriate (table 2). This involves the paediatric pneumologist, cardiologist, radiologist and haematologist.

PFTs are not helpful in the acute situation; however, in the long term, PFTs are useful to identify the development of restrictive lung disease (*i.e.* fibrosis from repetitive bleeding). Diffusion capacity is expected to be increased when intra-alveolar haemoglobin is present; with chronic fibrosing lung disease, it may be decreased. The testing, however, is rather difficult in small children and overall not much help.

Chest radiographs are important to gauge extent and for follow-up, whereas CT may reveal localised lung disease and bronchiectasis or aberrant lung vessels; otherwise, these are not very useful for specific diagnosis. Diffuse alveolar haemorrhage most commonly presents on CT with patchy or diffuse consolidation or ground-glass opacification. Interlobar septal thickening develops over days after the acute episode and combined with ground-glass opacities yields a “crazy-paving pattern”.

Bronchoscopy may identify localised lesions, while BAL is particularly helpful in small children who are not spitting blood to demonstrate increasing bloody return and, 48 h after the bleeding occurred, iron-laden macrophages. The normal level is 7.5±10.7%

Figure 1. a) Angiographic image of a patient with CF and massive haemoptysis (600 mL), showing a leading Cobra catheter in the aorta, with coils already positioned in the large bronchial artery and still filling with contrast agent. b) Chest radiograph of the same patient, with identification of the bleeding bronchial artery and closure by coils. The radiograph shows the overall position of the coils.

(mean±SD) of all macrophages. These haemosiderin-laden macrophages may persist for many months.

Lung biopsy is done in severe diffuse pulmonary haemorrhage to demonstrate capillaritis in the acute phase. This often appears risky; however, positive findings support aggressive anti-inflammatory treatments.

Management

Most frequently, pulmonary haemorrhage is caused by infections ranging from acute illnesses to chronic airway diseases with bronchiectasis, resulting in focal bleeding. In particular in the latter situation, antimicrobial treatment in combination with a transient reduction of vigorous airway clearance (recombinant human DNase should be halted for some time), while avoiding reduced mucus removal from the lungs, is indicated. With significant continuing or major bleeding, angiography to identify bronchial arteries or other aberrant large vessels is of importance, and interventional closure of feeding arteries is done in the same session (figure 1). If all of these methods are ineffective at controlling bleeding, targeted lung surgery may be a last resort.

Diffuse lung bleeding is rare and is most frequently caused by autoimmune and, rarely, generalised vascular disorders including pulmonary capillary haemangiomatosis and idiopathic pulmonary capillaritis. The latter condition is very elusive and a diagnosis is given only after all known causes of pulmonary haemorrhage have been excluded. Treatment is dependent on the acuity of bleeding and whether or not active bleeding is present (table 3).

Table 3. Management of haemoptysis

Active bleeding
Resuscitation
Free airway, intubation, positive expiratory pressure
Haemorrhage arrest
Stop nonsteroidal anti-inflammatory drug or others interfering with coagulation
Corticosteroids: 10–30 mg·kg^{-1}·day^{-1} for 3 days or 1–2 mg·kg^{-1}·day^{-1} for 1 week and taper to lowest level controlling disease
Other immunosuppressants (azathioprine, hydroxychloroquine, cyclophosphamide)
Plasmapheresis
Topical haemostasis (factor V, tranexamic acid)
Bronchoscopy[#]
Angiography and embolisation
Nonactive bleeding
Causal treatments
Gliadin-free diet, cow's milk protein exclusion or similar
Antimicrobial treatment
Foreign body removal
Surgery or vascular intervention for localised lesions
Biologicals for underlying rheumatological/immune diseases
Psychosocial treatment
Corticosteroids, other immunosuppressants

[#]: risky in small children, necessitating general anaesthesia; beware of rare air emboli to the brain in Osler–Weber–Rendu (hereditary haemorrhagic telangiectasia) airway disease.

Prognosis

The acute outcome is dependent on successful management of the respiratory compromise. Patients usually do not die from blood loss but suffocate from aspirated blood. Overall prognosis depends on the possibilities for treating the underlying condition and is generally good, although for idiopathic pulmonary haemosiderosis, 50% mortality rates have been reported previously. All diffuse cases should be collected in the chILD-EU Register of paediatric ILDs.

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Pleural effusion, chylothorax, haemothorax and mediastinitis

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Pleural effusion

The pleural space normally contains 0.3 mL of pleural fluid per kg of body weight. Lymphatic vessels can cope with several hundred millilitres of extra fluid over 24 h. An imbalance between pleural fluid formation and drainage will result in a pleural effusion. This can occur if there is an increase in capillary permeability (infectious, inflammatory or tumoural conditions) or hydrostatic pressure (congestive heart failure, volume overload), when oncotic pressure drops (in hypoproteinaemia as in nephrotic syndrome or malnutrition) or by transfer of fluid from the peritoneum.

Depending on the characteristics of the accumulated fluid, pleural effusions can be classified as transudates or exudates. Transudates are usually transparent, yellowish and serous in appearance and are typically produced by alterations in hydrostatic or oncotic pressure. In exudates, the fluid is more turbid and is generally related to inflammatory processes or problems with lymphatic drainage.

In a previously healthy child, a pleural effusion is usually secondary to acute bacterial pneumonia, and other causes are very uncommon. Therefore, this section will focus mainly on parapneumonic pleural effusion (PPE). The main features of other possible aetiologies are shown in table 1.

Key points

- All children with parapneumonic pleural effusion or empyema should be admitted to hospital and managed following local or national guidelines.
- Intravenous antibiotics and careful consideration of pleural drainage procedures are the most important aspects of parapneumonic effusion/empyema management.
- Chylothorax is a rare condition in children usually caused by injury to the thoracic duct; simple chest drainage and dietary modifications are the mainstay of treatment.
- When haemothorax is diagnosed, blood should be drained promptly from the pleural cavity with a chest tube.

Table 1. Aetiology of pleural effusion in children

Increased capillary permeability (exudate)
Pleuropulmonary infections
Connective tissue or collagen disorders
Granulomatous disease
Increased capillary hydrostatic pressure (transudate)
Volume overload
Congestive heart failure
Venous hypertension
Pericarditis
Decreased capillary oncotic pressure (transudate)
Nephrotic syndrome
Malnutrition
Hepatic cirrhosis
Other causes (exudate or transudate)
Pulmonary infarction
Inappropriate lymphatic flow
Mediastinal lymphadenopathy
Lymphoma
Superior vena cava syndrome
Thoracic duct anomalies
Thoracic trauma
Neoplasm
Haemorrhagic diseases
Pancreatitis

Clinical picture

There are two usual patterns of presentation of PPE. In the first, the child has classic symptoms of pneumonia (fever, cough, breathlessness, abdominal pain and malaise), but they are usually more affected than those with simple pneumonia alone, with pleuritic chest pain and even cyanosis. In the second, the child has the usual symptoms of pneumonia but does not respond to 48 h of an appropriate antibiotic treatment. On examination, a pleural effusion is suggested by unilateral signs of decreased chest expansion and dullness to percussion, reduced or absent breath sounds, and scoliosis.

Diagnosis

In contrast to community-acquired pneumonia, which may be diagnosed on clinical grounds only, the diagnosis of PPE requires an imaging technique to demonstrate the presence of fluid in the pleural space. The first imaging technique should be a posterior–anterior chest radiograph. The earliest sign of a pleural effusion is obliteration of the costophrenic angle. A rim of fluid may be seen ascending the lateral chest wall (meniscus sign). If the image is taken in a supine position, the appearance can be of a homogeneous increase in opacity over the whole lung field without blunting the costophrenic angle, or a classic pleural-based shadow. A lateral chest radiograph rarely adds anything extra and should not be obtained routinely.

Once a pleural effusion has been diagnosed or suspected by chest radiography, chest ultrasonography should be obtained to confirm the diagnosis, estimate the size of the effusion, differentiate between free and loculated pleural fluid, and determine its echogenicity (figure 1). It may also be used to guide chest drain insertion or thoracocentesis.

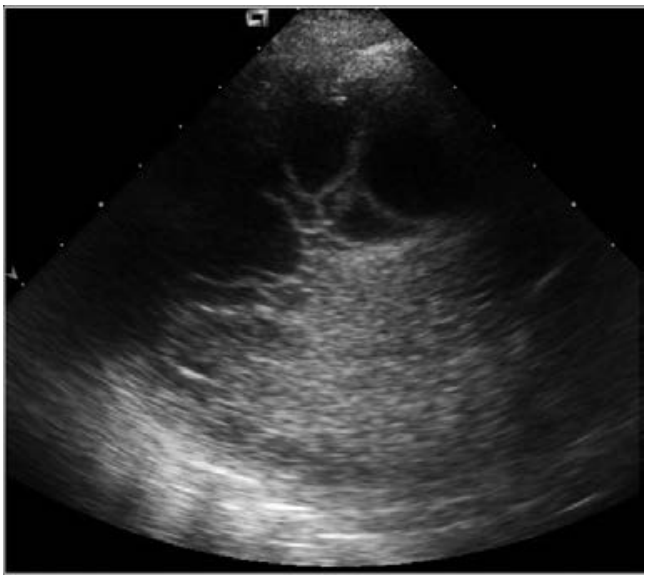

Figure 1. Chest ultrasound showing a loculated pleural effusion.

Chest CT scans involve radiation exposure that can be equivalent to 20–400 chest radiographs depending on technical factors and should not be performed routinely. Chest CT may have a role in complicated cases, including immunocompromised children where a CT scan can detect airway or parenchymal lung abnormalities, such as endobronchial obstruction or a lung abscess, or before surgery to delineate the anatomy.

Further diagnostic blood tests should be obtained after diagnosis and before starting antibiotic therapy:

- Full blood count (for anaemia, a white cell count with differential and platelet count)
- Electrolytes (to detect inappropriate antidiuretic hormone syndrome)
- C-reactive protein or other acute-phase reactants
- Blood culture, including anaerobic culture

Real-time PCR of both blood and pleural fluid for the detection of potential pathogen DNA should be added into the diagnostic tests. If available, sputum culture can also be useful.

Management

Once the diagnosis of PPE has been established, the decisions on additional diagnostic tests and therapeutic interventions should be conducted by following local guidelines. Several national scientific societies have published their own guidelines, and every paediatric centre treating children with pleural effusions should have their own protocol adapted to local circumstances.

All children with PPE should be admitted to hospital. Initial treatment should focus on general supportive measures and prompt intravenous antibiotic administration. General measures include assessing the need for supplemental oxygen (according to local guidelines, usually when S_{pO_2} is <92–94%), fluid therapy if the child is dehydrated or unable/unwilling to drink, pain control and antipyretics.

Empirical *i.v.* antibiotic treatment should begin as soon as possible. In the most common setting of a pleural effusion arising from community-acquired pneumonia, empirical treatment must cover *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Staphylococcus aureus*. In most cases, cefotaxime (150 mg·kg^{-1} per dose),

co-amoxiclav or cefuroxime are appropriate. Penicillin-allergic patients can be treated with clindamycin alone. If pneumatoceles are evident, antistaphylococcal cover is mandatory (cloxacillin or flucoxacillin). However, in cases of hospital-acquired pneumonia or following surgery, trauma or aspiration, broader-spectrum agents should be used to cover aerobic Gram-negative rods.

It is generally accepted that children with a small and uncomplicated PPE can be treated with antibiotic therapy without the insertion of a pleural drain. In these cases, isolated pleural taps for diagnostic purposes are not usually recommended, except when there are atypical features suggesting the presence of malignancy, such as the absence of acute fever or pneumonia and evidence of an underlying mediastinal mass or lymphadenopathy. In these uncommon situations, it is important to remember that large-volume aspiration and general anaesthesia pose a significant risk of sudden death in children with superior mediastinal obstruction due to malignancy; therefore, the volume of aspirated pleural fluid should be small (5 mL) and general anaesthesia should be avoided.

Specific indications for a pleural drain vary in different guidelines. As a general rule, there is significant evidence suggesting that a pleural drain is not always necessary and that antibiotics alone can be enough to provide excellent clinical outcomes when there is not a clear indication for chest drainage. Some guidelines consider fluid biochemical characteristics (pH <7.20, glucose <40 $mg \cdot dL^{-1}$ and lactate dehydrogenase >1000 $U \cdot L^{-1}$) as the criteria to decide when it is appropriate to drain a pleural effusion, although the evidence in paediatrics is scarce. Either way, drainage must be considered if the child is in respiratory distress due to lung compression by the pleural effusion, if there is a toxic appearance or if sepsis is suspected. It may also be considered if the effusion size is large (definitions vary from 10 mm thickness in ultrasonography or radiography to one-third of the hemithorax in radiography) or is enlarging, and the child is not responding after 48 h of antibiotic treatment.

Pleural drainage is rarely an emergency procedure and must be carefully planned and performed in the most appropriate setting by trained personnel, according to local guidelines. Two types of chest drain are generally used. Paediatric surgeons usually prefer large-bore chest tubes (~20 French) inserted surgically in the operating theatre with general anaesthesia and paravertebral block with local anaesthetics to provide post-operative pain relief. Respiratory paediatricians, paediatric intensivists and interventional paediatric radiologists usually prefer smaller drains (~10 French), including pigtail catheters, inserted by the Seldinger technique in paediatric intensive care units or interventional radiology rooms, with general anaesthesia or sedation. These two options are both appropriate and have similar outcomes, so the choice depends on local circumstances, although some studies suggest that small catheters (<14 French) are better tolerated. The chest tube should be inserted by well-trained personnel, or trainees under expert supervision, to minimise the risk of complications. Ultrasonographic guidance is mandatory, and the appropriate site for chest tube insertion should be marked with an "X" when this test is being performed. Pleural fluid must be obtained during the procedure and sent for microbiological and cytochemical tests, including Gram staining, culture for standard pathogens and mycobacteria, real-time PCR, glucose levels and pH.

All chest tubes should be connected to a unidirectional flow drainage system with an underwater seal, which must be kept below the level of the patient's chest at all times. The indications for suction are unclear in the management of pleural effusion, but it is commonly believed that it improves drainage. A low suction pressure (5–10 cmH_2O) is usually applied in the underwater seal, and it is acceptable to stop suction for short

periods (such as for radiographs or mobilisation). Regular flushing of small-bore drains to prevent blockage has been recommended. Patients with chest drains do not need to remain in the paediatric intensive care unit only for this reason and can be managed on a ward by staff trained in chest drain management.

Intrapleural fibrinolytics are considered a better option than simple chest drainage in most guidelines. Use of urokinase was shown to result in a significantly shorter hospital stay (7.4 *versus* 9.5 days) when given twice daily for 3 days (six doses in total) using 40 000 U in 40 mL 0.9% saline for children aged ≥1 year and 10 000 U in 10 mL 0.9% saline for children aged <1 year.

The drain should be removed when there is clinical resolution. An obstructed drain that cannot be unblocked should also be removed but replaced if significant pleural fluid remains. Pain control is extremely important during the time in which the chest drain remains in place.

Another pleural drainage method to be considered is surgery. Three surgical methods are available:

- Video-assisted thoracoscopic surgery (VATS), which achieves debridement of fibrinous pyogenic material, breakdown of loculations and drainage of pus from the pleural cavity under direct vision, leaving two or three small scars
- Mini-thoracotomy, which procures debridement and evacuation in a similar way to VATS but, as it is an open procedure, leaves a small linear scar
- Decortication, which involves an open posterolateral thoracotomy and excision of the thick fibrous pleural rind with evacuation of pyogenic material

Early VATS should be considered as an alternative to tube thoracostomy and fibrinolytics when a loculated effusion is present, and its use will depend largely on local availability and expertise. It seems to offer the same clinical outcomes as chest tube drainage and fibrinolytics, although with increased costs. Mini-thoracotomy should be reserved for more complex cases, and decortication should be performed only in symptomatic children with organised empyema not responding to previous treatment or in cases of lung entrapment.

Antibiotic *i.v.* treatment should continue until the child is afebrile or the chest drain is removed. Oral antibiotics, such as co-amoxiclav, are then administered for an additional 1–4 weeks after discharge, or for a longer period of time if there is residual disease.

Follow-up and long-term outcome

At discharge, most children will have abnormal chest radiographs and clinical examination (diminished breath sounds and some dullness on the affected area due to pleural thickening), which must not cause concern. Most affected children will return to having normal radiographs and clinical examination in 3–6 months, and after 12–18 months, they will have a full clinical recovery. In contrast to the situation in adults, long-term prognosis of PPE or empyema in children is excellent, and significant complications or sequelae are uncommon.

Chylothorax

Chylothorax is the accumulation of chyle in the pleural space and is an uncommon cause of pleural effusion in children. It is usually caused by an injury to the thoracic duct during surgery. The thoracic duct collects lymph from the abdomen, lower limbs, left thorax, head, neck and upper limbs. Disruption of the duct between the diaphragm

Table 2. Traumatic causes of chylothorax in children

Iatrogenic	Non-iatrogenic
Surgical	Forceful emesis or cough
Cardiothoracic surgery	Hyperextension of the neck or thoracic spine
Scoliosis or neck surgery	Mechanism of birth
Invasive procedures	Blunt trauma
Subclavian vein catheterisation	Penetrating chest trauma

and the T5 vertebra usually yields a chylothorax on the right side, while a left-sided chylothorax can be seen when damage occurs above T5.

Aetiology

The causes of chylothorax can be classified as traumatic and nontraumantic (tables 2 and 3). Most cases of chylothorax in children are acquired and of iatrogenic origin. According to some studies, cardiothoracic surgery accounts for 65–80% of all paediatric chylous effusions. Congenital presentation represents only a small percentage in the paediatric age group, although it is the most common type of pleural effusion in the neonatal period.

Diagnosis

Antenatal chylothorax can lead to restriction of normal lung development and cause lung hypoplasia. For this reason, severe respiratory distress can be present in some cases of congenital chylothorax. Respiratory symptoms depend on the size of the effusion, and most patients will show varying degrees of dyspnoea, cough or chest discomfort. Large volumes of chyle can lead to significant cardiorespiratory compromise.

Table 3. Nontraumatic causes of chylothorax in children

Congenital	Noncongenital
Abnormalities of the lymphatic system	Elevated venous pressure in the superior vena cava
Primary or secondary lymphangiectasias	Secondary to a Fontan procedure
Lymphangiomatosis	Venous thrombosis
Lymphatic dysplasia syndrome	Infectious
Genetic syndromes	TB
Noonan syndrome	Filariasis
Turner syndrome	Histoplasmosis
Down syndrome	Malignancy
Infectious	Lymphoma
TORCH infections	Teratoma
Thoracic duct atresia/agenesia	Sarcoma
Congenital diaphragmatic hernia	Neuroblastoma
Congenital cystic malformation of the lung	Other
Congenital heart disease	Transdiaphragmatic movement of chylous ascites
Congenital mediastinal/pleural tumours	Systemic disorders
Hydrops fetalis	Cardiac failure
Idiopathic	Benign tumours
Antenatal primary fetal hydrothorax	

TORCH: toxoplasmosis, rubella, cytomegalovirus and herpes simplex virus.

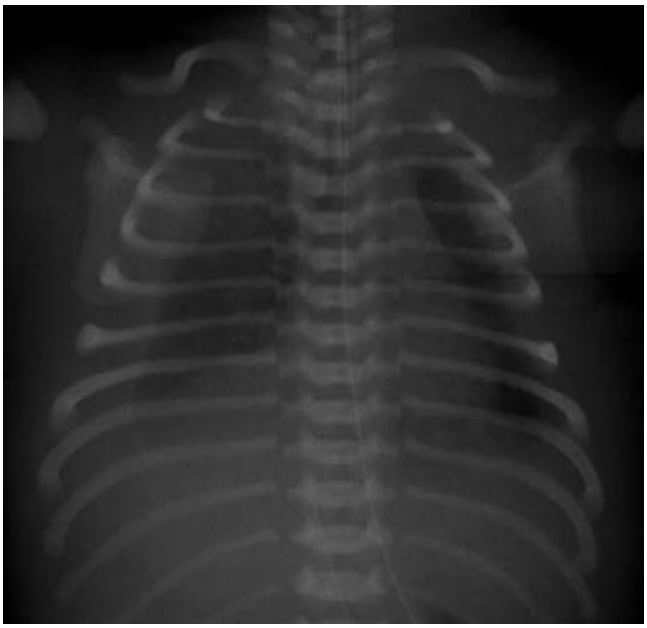

Figure 2. Chest radiograph of an infant with bilateral chylothorax.

A chest radiograph will demonstrate a unilateral or bilateral pleural effusion (figure 2). Chylothorax should be suspected when an extensive pleural effusion occurs in a neonate with a lymphatic malformation, some genetic syndromes, or after cardiothoracic surgery (tables 2 and 3).

Although pleural fluid from chylothorax is typically milky, it can appear completely clear when fasting. Definite diagnosis relies on biochemical analysis of the fluid drained from the pleural space, which will show an elevated level of triglycerides >110 $mg \cdot dL^{-1}$ and the presence of chylomicrons. A high lymphocyte count may also be present.

Differential diagnosis should be made with empyema and pseudochylothorax; the latter develops when an exudative effusion remains in the pleural space for a long period of time and gradually becomes enriched with cholesterol.

Management

If untreated, chylothorax can lead to nutritional compromise and immunological problems. Chest drainage with tube thoracostomy, together with nutritional modifications, has been the mainstay of treatment for many years. More recently, a dietary approach alone has been suggested as the initial treatment option.

Medical therapy

Nutrition

The use of medium-chain triglyceride milk formulas decreases overall lymphatic flow through the thoracic duct, while allowing spontaneous healing of the duct injury. Another option is total parenteral nutrition with bowel rest, although most reports indicate little difference in outcome compared with medium-chain triglyceride enteral nutrition. Chest drainage cessation with this dietary approach ranges from 1 to 4 weeks.

Medications

Somatostatin and synthetic analogues (octreotide) have been used in the treatment of chylothorax resistant to dietary modifications. Although their mechanism of action is not completely understood, they appear to reduce the intestinal blood flow

by vasoconstriction of the splanchnic circulation with reduction of lymphatic fluid output. In addition, they decrease gastrointestinal motility and gastric, pancreatic and biliary secretions, significantly diminishing the lymphatic flow. Dosage and method of delivery are not definitely established. Other medications such as nitric oxide, etilefrine and corticosteroids have been used in single case reports in adults.

Surgical therapy

The main indication for surgery is persistent chest drainage despite nutritional modifications and bowel rest. The most frequently used surgical techniques are pleurodesis, thoracic duct ligation and a pleuroperitoneal shunt.

Pleurodesis

Pleurodesis can be performed surgically or using chemical agents. Sclerosing substances (tetracycline, povidone iodine and talc) can be administered directly through the thoracostomy tube or with the assistance of VATS. Chemical pleurodesis with povidone iodine has shown good tolerance and relative success in congenital idiopathic chylothorax in neonates.

Thoracic duct ligation

Although direct surgical ligation of the thoracic duct at the rupture site would seem the most definitive treatment, it has yielded variable results with success rates between 25% and 100% in different series with a small number of patients.

Pleuroperitoneal shunt

Persistent chylothorax refractory to the standard medical or surgical therapies can be managed with pleuroperitoneal shunting. This involves communication between the pleural and peritoneal cavities *via* a valved subcutaneous catheter. Fluid is pumped from the chest into the abdomen where it is absorbed by peritoneal vessels. Possible complications include malfunction and infection.

Haemothorax

Aetiology

Haemothorax is a rare condition in children in which blood accumulates in the pleural space. It is usually caused by blunt or penetrating thoracic trauma and may be life threatening if a large-volume, rapidly developing haemothorax occurs. Bleeding from lacerated intercostal vessels or bone surfaces in rib fractures is the most common source of haemothorax in children. Other less frequent lesions such as pulmonary parenchymal lacerations or lung contusions may cause persistent and gradually increasing blood storage inside the chest. Massive haemothorax with hypovolaemic shock is indicative of injury to a great vessel or the heart, and has a mortality rate of >60%.

Diagnosis

Clinical symptoms depend on the severity of the haemothorax; tachypnoea, some degree of respiratory distress and decreased S_{pO_2} are usually observed. In those cases with massive bleeding, a diminished level of consciousness and clinical signs of haemodynamic instability are usually present. On auscultation, ventilation will be reduced or completely absent on the affected side. When two or more rib fractures are present, there is a high probability of multisystem injury including pulmonary contusion and haemothorax. As in adults, children with lung contusions have the same incidence of serious complications associated with this condition, such as pneumonia or acute respiratory distress syndrome.

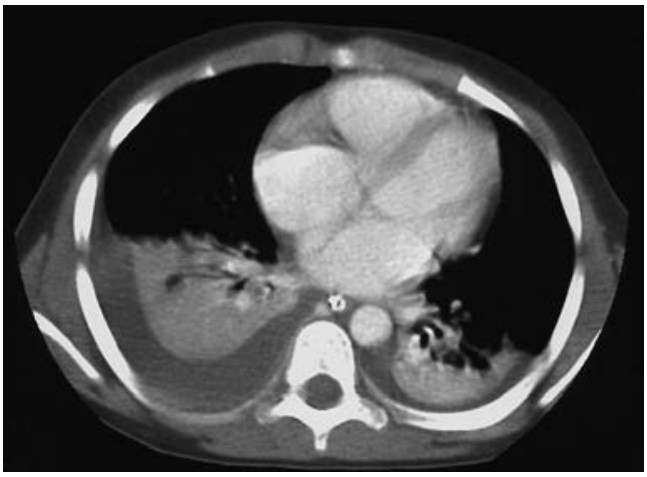

Figure 3. Chest CT showing bilateral haemothorax and lung contusion secondary to blunt trauma.

If haemothorax is suspected, a chest radiograph is the first imaging test to be performed. Due to the supine position, fluid present in the pleural space will be distributed diffusely across the lung field, giving an image of generalised increased opacity. Ultrasound is a quick and useful test to demonstrate cardiac or lung injuries and haemothorax, but a chest CT scan is the most valuable diagnostic tool, especially if a great vessel injury is suspected (figure 3).

Management

Management of significant haemothorax must deal with two crucial conditions:

- Increased intrapleural pressure with secondary lung collapse
- Reduced blood volume with possible haemodynamic instability

Both situations can be severe enough to seriously compromise oxygenation and cardiac output. Initial management measures must be directed to correct both conditions by ensuring an adequate airway and restoring the intravascular volume. When diagnosed, blood should be removed promptly from the pleural cavity by tube thoracostomy. Large catheters are preferable, although they should be matched to the patient's age and size. In some cases, haemodynamic collapse may occur with rapid evacuation of the blood inside the chest. This is because it may act as a tamponade reducing ongoing blood loss from the intravascular space. In this situation, intermittent clamping of the chest tube may be of some benefit in re-establishing the tamponade effect.

In most cases, bleeding will stop spontaneously within a short period of time without requiring any further surgical intervention. Drainage of the pleural cavity with effective lung expansion is all that is needed in this setting. Persistent bleeding in an unstable patient is an indication for urgent thoracotomy. Guidelines for operative intervention are: 1) a bleeding rate of 2–3 $mL \cdot kg^{-1} \cdot h^{-1}$ in a child over 4 h (200–300 $mL \cdot h^{-1}$ in an adolescent), or 2) a return of 20–30% of the blood volume in a child at chest tube placement (1000–1500 mL in an adolescent). As a general rule, the physiological response of the patient to volume resuscitation is the best guide in decision making, and a prompt and sustained answer precludes surgical exploration. In selected cases of ongoing haemothorax in an otherwise stable patient, thoracoscopy (VATS) may be considered instead of thoracotomy in order to identify and control the source of the bleeding.

Complications

Hypovolaemic shock is the most frequent complication when massive or persistent haemorrhage is present. Renal failure, severe acidosis or cardiac ischaemia may occur in this setting. When blood inside the pleural space is not drained promptly, it may become clotted and organised. Reabsorption may take place in the following weeks or months, but empyema or fibrothorax may develop in the meantime. In order to prevent these complications, a VATS procedure to evacuate the retained haemothorax is recommended within 1 week of injury.

Mediastinitis

Aetiology

Mediastinitis is an infection of the connective tissue of the mediastinum. Most cases of acute mediastinitis usually occur after sternotomy for cardiothoracic surgery, but it can also be caused by some oesophagogastric diseases or injuries and from adjacent spread of retropharyngeal or odontogenic infections. In children, oesophageal perforation due to a foreign body should be ruled out.

Diagnosis

Although mediastinitis is a rare post-operative complication of median sternotomy (0.1–5% of all paediatric patients undergoing this procedure), it represents a significant source of morbidity and mortality. Risk factors include young age, a high anaesthesiologist score and a long duration of the surgical procedure.

Mediastinitis most often presents days to weeks after cardiac surgery. Clinical signs are variable, usually in the setting of an unfavourable post-operative course. Sepsis, pleural effusion, pneumothorax, pneumomediastinum, thoracic pain, subcutaneous emphysema and odynophagia may be present in a patient with acute mediastinitis; less frequently, cardiac arrhythmias may occur.

The most common organisms isolated in children are *Staphylococcus* spp., but Gram-negative organisms account for up to one-third of cases in some series of post-operative mediastinitis. The microbiology of infection among heart and lung transplant patients may differ depending on the underlying condition as well as the use of post-transplant immunosuppression.

Management

Treatment for acute mediastinitis involves aggressive *i.v.* antibiotic therapy and surgical management. In post-operative mediastinitis, the standard surgical approach includes debridement followed by open wound care with delayed closure. Other surgical alternatives include closed suction with antimicrobial irrigation, vacuum-assisted closure and muscle flap closure. These strategies were developed initially for adults and later applied to children. Recently, some authors have suggested treating acute mediastinitis with debridement and concomitant primary closure without prolonged suction or irrigation.

Chronic mediastinitis is characterised by diffuse fibrosis of the soft tissues of the mediastinum. It is a very rare entity that can be seen in granulomatous diseases, such as histoplasmosis, or infections like TB, and after radiation therapy. Treatment remains controversial.

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Pneumothorax and pneumomediastinum

Nicolaus Schwerk, Julia Carlens and Hartmut Grasemann

Pneumothorax

Pneumothorax is defined as an accumulation of air in the pleural cavity. It can be classified as primary spontaneous pneumothorax (PSP), secondary spontaneous pneumothorax (SSP), or traumatic or iatrogenic pneumothorax. Whereas PSP occurs in the absence of an underlying pulmonary disease, SSP is the result of pre-existing lung affliction (table 1).

Epidemiology

Epidemiological data in children and adolescents are scarce. A recently published study of 42 595 patients aged ≥14 years who were hospitalised with a nontraumatic pneumothorax in France estimated an annual incidence of 22.7 cases per 100 000 inhabitants with a female/male ratio of 1/3.3. Of these cases, 85% were diagnosed as PSP. These findings are consistent with studies on PSP in adults, which show a male predominance with a reported annual incidence of 18–28 cases per 100 000 in males and 1.2–6 cases per 100 000 in females. In children, a male predominance is also consistently reported (65–80%), with a mean age at presentation of 14–16 years. While typically tall, thin boys with a below-average BMI are affected, it is important to note that pneumothorax can occur in any individual and age group. Smoking is a recognised risk factor for the development of pneumothorax in lung-healthy people

Key points

- The most common cause of pneumothorax in paediatric patients is the rupture of bullae or blebs in the apex of the lung without an underlying predisposing lung disease or history of trauma.
- When pneumothorax is suspected, the standard erect posterior–anterior chest radiograph in inspiration technique represents the diagnostic gold standard.
- Patients with pneumothorax who experience symptoms should be treated with needle aspiration or chest catheter insertion independent of the size of the pneumothorax.
- In the setting of recurrent pneumothorax or increased recurrence risk, surgical treatment is indicated. The preferred technique consists of resection of the causative blebs or bullae and a pleurodesis procedure.

Table 1. Causes of SSP and pneumomediastinum

Underlying disease
Asthma and allergic bronchopulmonary aspergillosis
Birt–Hogg–Dubé syndrome
BPD/chronic lung disease
Bronchiolitis obliterans
Congenital hyperlucent lobe/congenital emphysema
Congenital lung hypoplasia
Congenital pulmonary malformations (congenital cystic adenomatoid malformation)
Connective tissue diseases, *e.g.* Marfan syndrome, Ehlers–Danlos syndrome
CF
Diffuse parenchymal lung diseases/children's ILD (chILD)
Langerhans cell histiocytosis
Malignancies, *e.g.* lymphoma, pleuropulmonary blastoma, metastasis and penetrating tumours
Sarcoidosis
Sjögren syndrome
Systemic inflammatory diseases, *e.g.* rheumatoid arthritis, systemic lupus erythematosus, polymyositis and dermatomyositis
Infection
Bacterial (*e.g. Mycoplasma pneumoniae*), viral (*e.g.* influenza A/B virus), or fungal (*e.g. Pneumocystis jirovecii*, *Aspergillus fumigatus*)
Necrotising pneumonia or abscess
Parasitic (helminth) infections
Tuberculosis and nontuberculous mycobacteriosis
Trauma or iatrogenic
Barotrauma
Blunt or penetrating trauma of the chest wall
Complication of venepuncture of central veins or cardiac catheterisation
Endo- or transbronchial biopsy
Endoscopic lung volume reduction
Foreign body aspiration
Mechanical ventilation, ventilator-associated interstitial emphysema
Oesophageal perforation
Pleural effusion puncture (thoracentesis)
Post-surgical trauma

as well as in patients with pre-existing pulmonary diseases. Smoking is also known to be a risk factor for recurrence of pneumothorax.

Pathogenesis

Apical subpleural blebs and bullae are often found in patients with PSP (55–88% at the ipsilateral side and 15–66% at the contralateral side). Rupture of these lung bullae or blebs that develop without an underlying lung disease or history of trauma is generally considered to be the cause of PSP. In the upright posture, the gradient of negative pleural pressure increases from the lung base to the apex, so that alveoli at the lung apex, especially in tall individuals, are subject to significantly greater distending pressures than those at the lung base. Presumably, these pressure differences predispose to the development of apical subpleural blebs. Although apical subpleural blebs and bullae can also be found in healthy subjects, there is growing evidence that ipsilateral or contralateral bullae are risk factors for the recurrence of

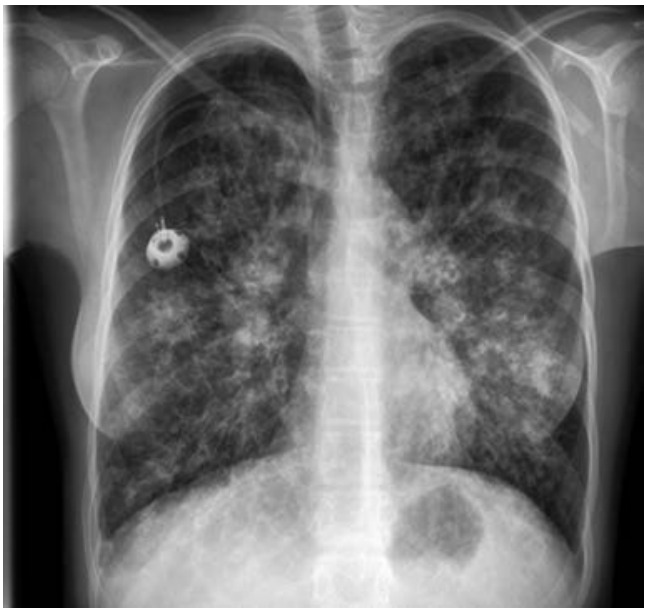

Figure 1. A right-sided apical pneumothorax in a patient with CF.

spontaneous pneumothorax. Although often assumed, there is no clear evidence of a relationship between physical exertion and the development of a pneumothorax. In children with PSP and basilar subpleural bullae or blebs and a positive family history for PSP, Birt–Hogg–Dubé syndrome should be considered. Blebs or bullae in the lower lobes can be detected in almost all patients with this autosomal-dominant disorder, which is caused by mutations in the folliculin gene, and 40% of affected individuals will develop PSP.

A special form of pneumothorax is ventilator-associated interstitial emphysema. Rupture of alveoli during mechanical ventilation, especially in neonates, can lead to air entry into perivascular connective tissue. Gas then migrates into the interstitium and gets trapped within the pulmonary perivascular sheaths, resulting in interstitial emphysema. Rarely, a pneumothorax results from infection with gas-producing micro-organisms, penetrating tumours or chest wall defects. Chest wall defects can be traumatic or iatrogenic. SSP constitutes a threat in patients with pre-existing underlying lung diseases, and the management in these individuals is potentially more challenging. SSP in patients with CF (figure 1) is associated with a significantly increased mortality risk. Treatment for SSP should be more aggressive than for PSP (*e.g.* broad indication for a chest drain insertion) and special consideration may need to be given to the treatment of the underlying disease. Therefore, following the initial treatment, patients with SSP should be transferred to a specialist centre whenever possible.

Symptoms

Typical symptoms are chest pain and dyspnoea. Symptoms can be relatively minor and self-limiting within 24 h so that a high index of initial diagnostic suspicion is required. In patients with SSP, clinical symptoms are usually more severe than those associated with PSP and may include severe breathlessness, even with small pneumothoraces. Severity of clinical symptoms is therefore an unreliable indicator of pneumothorax size. Characteristic signs on physical examination include the following:

- Diminished breath sounds on the affected side on auscultation
- Reduced lung expansion on the affected side
- Decreased vocal fremitus on the affected side
- Hyperresonance on percussion of the affected side

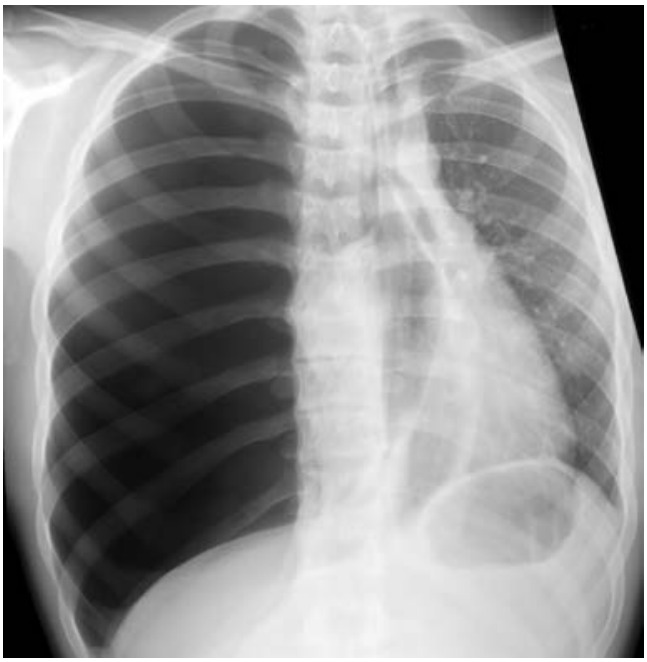

Figure 2. A large right-sided tension pneumothorax.

These signs can be subtle or even absent, especially in neonates and infants. As pneumothorax in this younger age group is potentially life threatening, a chest radiograph in any situation of unexplained cardiorespiratory symptoms is required to rule out pneumothorax. Diagnostic transillumination with cold light can be a useful alternative in neonates. At any age, in the case of cardiorespiratory distress with tachycardia, hypotension and/or cyanosis, a tension pneumothorax must be considered and rapid diagnosis and treatment is mandatory (figure 2).

Imaging

The standard erect posterior–anterior chest radiograph in inspiration technique remains the diagnostic gold standard, notwithstanding limitations including, for example, the problem of quantifying the size of a pneumothorax. Typical radiological signs are displacement of the pleural line and occasionally an air–fluid level (hydropneumothorax) visible in the costophrenic angle. Supine and lateral decubitus chest radiographs are alternative options for immobile patients, but these images are less sensitive for diagnosing pneumothorax than the posterior–anterior chest radiograph images in an upright position. In patients with cystic lung lesions, such as congenital pulmonary malformations or Langerhans cell histiocytosis (figure 3), lung lesions can lead to diagnostic errors, with potentially fatal consequences for the patient. Therefore, in uncertain cases, alternative techniques such as ultrasound or CT can be helpful. It is important to note that CT scans are only justified when confirming diagnosis is of clinical and therapeutic relevance. There is an increasing role of point-of-care thoracic sonography in the diagnosis of pneumothorax, especially in traumatology and intensive care medicine. The most important criterion for pneumothorax by ultrasound is the lack of respiratory mobility of the lung in dynamic examination. The extent of a pneumothorax cannot be assessed sonographically.

Although the size of a pneumothorax is less important for the acute treatment than the patient's symptoms, a large pneumothorax is a relevant risk factor for a bronchopleural fistula and an increased recurrence rate after conservative treatment.

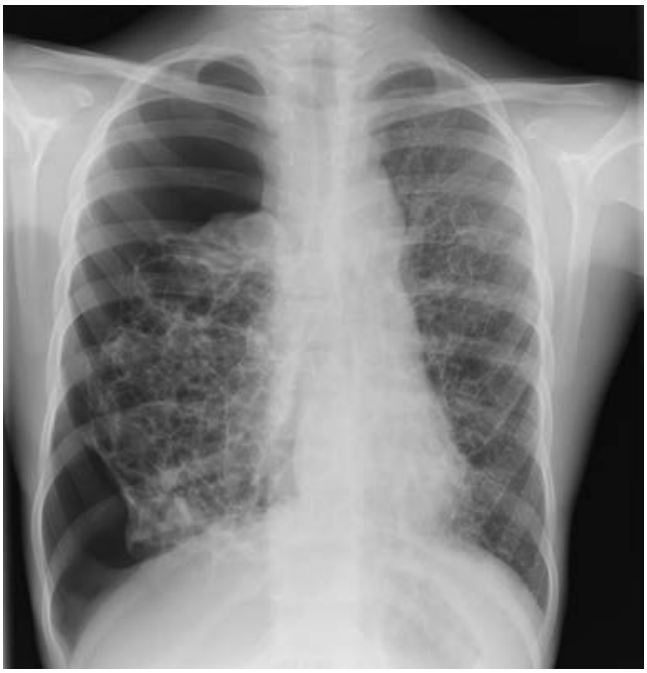

Figure 3. Pneumothorax in a patient with Langerhans cell histiocytosis.

Size should therefore be estimated for the primary assessment of a pneumothorax. There are numerous different approaches used to calculate the size of a pneumothorax. Commonly, an erect radiograph is used for these quantifications. According to the British Thoracic Society (BTS) guidelines, a large pneumothorax is defined as a 2-cm gap between the entire lateral lung edge and the chest wall. In the guidelines of the American College of Chest Physicians (ACCP), a large pneumothorax is defined as an apical distance of 3 cm. According to a recently published guideline of the German Society for Thoracic Surgery, the size of a pneumothorax should be determined in the initial chest radiograph by measurement of the interpleural distances in the apex area and laterally at the midpoints of the upper and lower halves of the collapsed lung, respectively. A large pneumothorax is assumed if the sum of the three measurements is ≥4 cm. However, as pneumothorax size does not correlate closely with its clinical manifestations and measures do not apply to small children, a thorough clinical evaluation is probably more important for determining the proper management strategy than the estimation of its actual size.

Therapy

There are no evidence-based guidelines for the treatment of pneumothorax in children, and recommendations of different national and international guidelines for adult patients are controversial. Therefore, treatment decisions are often made on the basis of institutional guidelines. After diagnosis of a PSP, possible therapeutic options and their advantages and disadvantages should be discussed in detail with the patient and/or the caregivers. It is generally agreed that patients experiencing respiratory symptoms should be treated independent of the size of the pneumothorax. Asymptomatic children should be observed and a repeat chest radiograph may be obtained during follow-up.

Observation only (watch and wait)

Conservative treatment with observation only in asymptomatic patients with small pneumothoraces has been shown to be safe. Up to 80% of patients are estimated

to have no active air leak, and recurrence in those managed by observation only is equal to or even less frequent than in those treated with chest drainage. Nevertheless, the potential daily reduction rate of spontaneous pneumothorax was estimated at 1.25–2.2% of the total volume of the hemithorax, and thus a long time to resolution of up to 30 days has to be considered.

Supplemental oxygen

Supplemental oxygen at high concentrations generates a partial pressure gradient between the pleural cavity and the capillary blood by decreasing the partial pressure contribution of nitrogen. This accelerates the absorption of gas from the pleural cavity. Application of oxygen at high flow rates of up to 16 $L \cdot min^{-1}$ has shown a four-fold increase in the rate of pneumothorax resolution compared with patients managed by observation only.

Needle aspiration and intercostal chest catheter insertion

There is an emerging body of evidence that, in adult patients with PSP, a single needle aspiration is not inferior to intercostal chest catheter (ICC) insertion with respect to efficacy and recurrence rates. Moreover, needle aspiration is less invasive, more cost-effective and associated with lower complication rates compared with an ICC. Unfortunately, no randomised controlled trials comparing needle aspiration and an ICC have been conducted in paediatric patients to date. Guidelines for adult patients recommend that aspiration of a maximum of 2.5 L should not be exceeded in order to avoid re-expansion oedema. Control radiographs are suggested after a single needle aspiration to assess the presence of an ongoing air leak. ICC insertion should be considered in the following situations:

- Age <1 year
- Bilateral pneumothorax
- Tension pneumothorax
- Evidence for a large or persistent air leak
- Pneumothorax recurrence within the first hours following aspiration
- Coexistence of a pleural effusion, especially in the case of haemothorax
- All children with iatrogenic and traumatic pneumothorax, SSP or coexisting pneumomediastinum

The success rates for small-bore ICCs are comparable to those for large-bore ICCs while being less painful; however, large-bore ICCs are indicated when the rate of air leak exceeds the capacity of a smaller ICC. Needle aspiration or ICC insertion should only be performed by or under the supervision of medical staff experienced in the procedure. Initial chest radiographic imaging should guide the site of placement. An appropriate approach in the majority of cases is the “triangle of safety”, which is bordered anteriorly by the lateral edge of the pectoralis major, laterally by the lateral edge of the latissimus dorsi, inferiorly by the line of the fifth intercostal space and superiorly by the base of the axilla (figure 4). An alternative approach is the second intercostal space in the midclavicular line. Proper sedation should be given in addition to local anaesthetic. After insertion, ICCs should be connected to a Heimlich valve or an underwater seal device. Digital systems with continuous monitoring of air drainage have been shown to shorten drainage time and length of hospital stay and to result in a reduction in treatment costs. The benefit of continuous suction is unclear. As initial suctioning might increase the risk of re-expansion pulmonary oedema, it is only recommended if lung re-expansion has not occurred after 48 h or for a persisting air leak, which may indicate a bronchopulmonary fistula. Optimal suction should entail pressures of −10 to −20 cmH_2O.

Figure 4. Schematic diagram of the triangle of safety.

Surgical management

The primary aim of a surgical intervention is to prevent recurrence of pneumothorax. Current indications for surgical intervention include:

- Second ipsilateral pneumothorax
- First contralateral pneumothorax
- Bilateral pneumothoraces
- Persistent air leak
- Associated haemothoraces
- Following a first episode in professionals at risk, including pilots and scuba divers

Surgical treatment consists of resection of the causative bullae or blebs associated with some type of pleurodesis procedure, either pleurectomy or pleural mechanical abrasion. Chemical pleurodesis is not used routinely in children because of the potential for severe side-effects. Autologous blood pleurodesis is a safe and effective alternative. The current gold standard in the adult literature is blebectomy and apical parietal pleurectomy. Video-assisted thoracoscopic surgery (VATS) is the primary recommended surgical intervention with a low morbidity of 2.4–9% and a low post-operative recurrence rate of 0–10%. Further advantages of VATS include decreased post-operative pain, a reduced length of hospital stay and improved lung function.

Recurrence

Whether children with PSP experience a higher rate of recurrence than adults remains unclear. Small case series have reported recurrence rates of 20–50% after the first PSP and 1–15% after surgical treatment. The recurrence risk in paediatric patients with SSP also depends on the underlying disease.

Pneumomediastinum and subcutaneous emphysema

Pneumomediastinum is defined as the presence of free air in the mediastinum.

Epidemiology

Currently, there are no epidemiological data in the paediatric literature, but undoubtedly pneumomediastinum is an exceedingly rare condition in this age group.

Pathogenesis

Rarely, pneumomediastinum can occur as spontaneous pneumomediastinum (*e.g.* Hamman syndrome) in the absence of a specific underlying disease. In these cases, it is thought to be the result of a sudden increase in intrathoracic pressure (*e.g.* emesis,

Figure 5. Pneumomediastinum in a 14-year-old girl with asthma. a) Posterior–anterior radiograph of the chest showing mediastinal air and subcutaneous emphysema in the neck and chest wall. b) CT scan of the chest confirming the diagnosis and illustrating the extent of the pneumomediastinum. Of note, there is also epidural emphysema (air in the spinal canal).

cough, physical activity or defaecation) and subsequent alveolar rupture. Further leakage of air throughout the interstitium and bronchovascular tissue follows a centripetal pattern towards the mediastinum. In most cases, however, pneumomediastinum is thought to be a complication of a specific underlying disease or the result of a specific pathological event leading to rupture of lung parenchyma or the bronchial tree (figure 5). Given the grave clinical consequences of pneumomediastinum and the necessity to institute specific treatment of an underlying cause, responsible predisposing conditions have to be excluded (table 1).

Symptoms

The severity of symptoms depends on the pneumomediastinum size and the underlying cause. While symptoms in children with spontaneous pneumomediastinum can be mild, pneumomediastinum as a complication of an underlying disease can be life threatening with reported mortality rates of up to 40%. Typical clinical signs are chest pain, dyspnoea and cough. In 30–40% of cases, pneumomediastinum is associated with subcutaneous emphysema with soft-tissue swelling of the neck, face and sometimes the whole chest wall in conjunction with characteristic subcutaneous crepitations.

Imaging

As for pneumothorax, the diagnosis of pneumomediastinum is made by radiography. However, up to 30% of cases of pneumomediastinum are missed on chest radiographs and therefore CT has become the gold standard for diagnosis, especially when the underlying predisposing condition is unknown.

Therapy

In the adult literature, several surgical techniques have been reported to treat pneumomediastinum and subcutaneous emphysema including mediastinal drain insertion and subcutaneous pigtail or large-bore drains with or without suction. All of these methods are invasive and bear a risk of infection. The most important therapeutic approach is treatment of the underlying cause. In addition, conservative treatment including analgesics, bed rest and avoidance of Valsalva manoeuvres may be beneficial. Symptoms generally improve within 3–15 days without sequelae. It is

not clear whether preventative antibiotic therapy can reduce the risk of secondary infections of the mediastinum. Nevertheless, antibiotic treatment should be initiated generously in patients with extended trauma of the bronchial tree or oesophagus or with a known infection as the underlying cause of pneumomediastinum.

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Drug- and radiation-induced lung disease

Nicolaus Schwerk, Julia Carlens and Matthias Griese

Drug-induced lung disease is an umbrella term for different acute or chronic lung diseases caused by medications. To date, more than 350 different drugs are known that potentially cause acute or chronic injury of the lungs, airways, pleura and pulmonary vessels. As any drug may induce toxicity, the number is continuously growing. Comprehensive and up-to-date information on all pneumotoxic drugs and corresponding disease patterns is available at Pneumotox Online (www.pneumotox.com).

Diffuse lung disease is the most common form of drug-induced lung disease. Drugs can cause nearly all histopathological patterns of interstitial pneumonia including diffuse alveolar damage, nonspecific interstitial pneumonia, eosinophilic pneumonia, pulmonary infiltrates and eosinophilia, organising pneumonia, bronchiolitis obliterans organising pneumonia, lymphocytic interstitial pneumonia, desquamative interstitial pneumonia, pulmonary granulomatosis-like reactions, usual interstitial pneumonia-like pattern, diffuse alveolar haemorrhage with or without capillaritis, and pulmonary alveolar proteinosis (table 1).

Neither clinical symptoms nor radiological or histological findings are pathognomonic for drug-induced lung disease. Unfortunately, clinical findings often mimic pulmonary involvement of a pre-existing disease or complications such as opportunistic infections. Furthermore, one drug can often produce more than one pattern of histopathological involvement, even in one patient. Thus, confirmation of drug-induced lung disease is often a challenge for the treating physician and in most cases diagnosis is by exclusion.

Key points

- Drug- and radiation-induced lung disease is a potentially life-threatening condition. Symptoms are nonspecific and therefore diagnosis is by exclusion in most cases.
- Drugs can cause nearly all histopathological patterns of interstitial pneumonia.
- Patients with malignancies are at increased risk for drug-induced lung injury.
- Drug withdrawal is the treatment of choice. Corticosteroids are recommended in severe cases or where there is no clinical improvement after drug withdrawal.

Table 1. Different forms of drug-induced lung disease with examples of causative drugs, corresponding symptoms, radiological and histological findings, and treatment options

Pattern	Drugs	Symptoms and signs	Radiological findings	BAL findings	Histology (lung biopsy)	Treatment options/ outcome
Acute drug-induced lung disease with respiratory failure						
Acute methotrexate lung	Methotrexate	Dry cough, dyspnoea, tachypnoea, hypoxaemia, respiratory failure, fever	Ground-glass opacities, diffuse alveolar opacities, mosaic attenuation	Elevated $CD4^+$ or $CD8^+$ lymphocytes	Granulomas, cellular interstitial pneumonia, type 2 cell hyperplasia, interstitial inflammation/ oedema, fibrosis, DAD and DAH (hyperacute disease)	Drug withdrawal, high-dose corticosteroids
Acute cellular interstitial pneumonia	Gold, interferon-α, nitrofurantoin	Dry cough, dyspnoea, tachypnoea, hypoxaemia, respiratory failure, fever	Ground-glass opacities, diffuse alveolar opacities, mosaic attenuation	Elevated $CD4^+$ or $CD8^+$ lymphocytes	Cellular interstitial pneumonia, NSIP pattern, type 2 cell hyperplasia, interstitial inflammation	Drug withdrawal, high-dose corticosteroids
Acute eosinophilic pneumonia	Amitriptyline, chloroquine, fludarabine, infliximab, interleukin, minocycline, sertraline, troleandomycin, tryptophan	Dry cough, dyspnoea, tachypnoea, hypoxaemia, respiratory failure, fever	Interlobular thickening, alveolar opacities, migratory opacities, pleural effusion, enlarged lymph nodes, inverse bat-wing pattern, localised consolidation	Eosinophilia	Alveolar and interstitial eosinophilic inflammation	Drug withdrawal, high-dose corticosteroids

(*Continued*)

Table 1. Continued

Pattern	Drugs	Symptoms and signs	Radiological findings	BAL findings	Histology (lung biopsy)	Treatment options/ outcome
Acute chemotherapy lung	All-*trans* retinoic acid, anti-TNF-α antibody, arabinoside, aspirin, azathioprine, bleomycin, busulfan, chlorambucil, cyclophosphamide, cytosine, docetaxel, etoposide, fludarabine, gefitinib, gemcitabine, imatinib, interferon-γ, interleukin-2, irinotecan, melphalan, 6-mercaptopurine methotrexate, mitomycin C, nitrofurantoin, nitrosourea, paclitaxel	Dry cough, dyspnoea, tachypnoea, hypoxaemia, respiratory failure	Diffuse pulmonary infiltrate, white lung, ground-glass pattern, linear opacities, interlobular thickening	No distinct pattern	DAD, type 2 pneumocyte dysplasia, interstitial/alveolar oedema, early fibrosis	Drug withdrawal, high-dose corticosteroids
Acute amiodarone pneumonitis	Amiodarone	Dry cough, dyspnoea, tachypnoea, hypoxaemia, respiratory failure, ARDS-like picture	Patchy or diffuse opacities with increased attenuation, intralobular thickening, interlobular thickening, diffuse ground-glass opacities	No distinct pattern	DAD, type 2 pneumocyte dysplasia, interstitial/ alveolar oedema, dyslipidosis, foamy alveolar and interstitial cells, early fibrosis	Drug withdrawal, high-dose corticosteroids; poor outcome, high mortality

(*Continued*)

Table 1. Continued

Pattern	Drugs	Symptoms and signs	Radiological findings	BAL findings	Histology (lung biopsy)	Treatment options/ outcome
Drug-induced acute pulmonary oedema	Blood transfusion, colchicine, contrast material, cyclophosphamide, epinephrine, high-dose intravenous β_2-agonists, hydrochlorothiazide, methotrexate, nitrofurantoin, noramidopyrine, NSAIDs, opiates, vasopressin	Acute dyspnoea, tachypnoea, hypoxaemia, respiratory failure, ARDS-like picture	Intralobular thickening, smooth interlobular thickening, diffuse alveolar opacities with or without "bat-wing pattern"	No distinct pattern	Interstitial and alveolar oedema	Drug withdrawal, positive-pressure breathing, role of corticosteroids unclear
Drug-induced DAH	Abciximab, allopurinol, all-*trans* retinoic acid, anticoagulants, aspirin, azathioprine, clopidogrel, fibrinolytics, gold, hydralazine, leflunomide, methotrexate, nitrofurantoin, phenytoin, penicillamine, propylthiouracil, sirolimus, tirofiban	Acute dyspnoea, tachypnoea, hypoxaemia, respiratory failure, ARDS-like picture, arthralgias, extrapulmonary manifestations	Diffuse or patchy alveolar opacities	Increased bleeding in serial aliquots, haemosiderin-laden macrophages (diagnostic)	DAH pattern, capillaritis in some cases	Drug withdrawal, high-dose corticosteroids

(*Continued*)

Table 1. Continued

Pattern	Drugs	Symptoms and signs	Radiological findings	BAL findings	Histology (lung biopsy)	Treatment options/ outcome
Subacute/chronic drug-induced lung disease						
Drug-induced nonspecific interstitial pneumonia (syn. cellular interstitial pneumonia)	ACE inhibitors, β-blockers, chlorambucil, flecainide, fludarabine, fluoxetine, maprotiline, methotrexate, nilutamide, nitrofurantoin, procainamide, simvastatin, sulfasalazine	Dry cough, progressive dyspnoea, hypoxaemia, fever	Ground-glass opacities, mosaic attenuation, alveolar infiltrates, alveolar consolidation, pleural effusion, mediastinal lymphadenopathy, interlobular thickening, crazy-paving pattern	Lymphocytic inflammation, elevated $CD4^+$ or $CD8^+$ lymphocytes, neutrophilic inflammation, mixed lymphocytic/ neutrophilic inflammation	Cellular interstitial pneumonia, interstitial oedema, moderate fibrosis	Drug withdrawal, corticosteroids in severe cases
Desquamative interstitial pneumonia	Interferon-α, nitrofurantoin	Dry cough, progressive dyspnoea, hypoxaemia, fever	Sharply demarcated mosaic with low lung attenuation	No distinct pattern	Massive accumulation of intra-alveolar macrophages	Drug withdrawal, corticosteroids in severe cases
Pulmonary infiltrates and eosinophilia	ACE inhibitors, amitriptyline, carbamazepine, chloroquine, clomipramine, contrast material, interferon, maprotiline, mesalazine, methotrexate, minocycline, montelukast, myrimethamine, NSAIDs, pentamidine, phenytoin, radiation therapy, sertraline, sulfamethoxazole, sulfamides, sulfasalazine, trazodone, tryptophan, venlafaxine	Dry cough, dyspnoea, hypoxaemia, wheeze, fever, chest pain, skin rash, heart involvement	Inverse bat-wing pattern, interlobar thickening, localised consolidation, migratory opacities, Kerley B lines, lymph node enlargement, pleural effusion	Eosinophilic inflammation	Alveolar and interstitial eosinophilic infiltration, Charcot–Leyden crystals, variable angiitis, fibrosis, mucus plugging, bronchiolitis with necrosis	Drug withdrawal, corticosteroids in severe cases

(*Continued*)

Table 1. Continued

Pattern	Drugs	Symptoms and signs	Radiological findings	BAL findings	Histology (lung biopsy)	Treatment options/ outcome
Amiodarone pneumonitis	Amiodarone	Dyspnoea, dry cough, hypoxaemia, weight loss, malaise, fever, chest pain (pleuritic), crackles, wheeze, fever, chest pain	Bilateral often asymmetric interstitial or alveolar infiltrates, opacities (alveolar, interstitial or mixed), pleural thickening, lone or multiple masses abutting the pleura, large apical nodules with a centre of decreased attenuation	Neutrophilic and/ or lymphocytic inflammation, eosinophilic inflammation (rare), foamy macrophages, haemosiderin-laden macrophages	Interstitial oedema, nonspecific inflammation, interstitial fibrosis, large number of foamy macrophages	Drug withdrawal, corticosteroids in severe cases
Organising pneumonia/ bronchiolitis obliterans organising pneumonia	ACE inhibitors, amiodarone, bleomycin, β-blocking agents, carbamazepine, gold, interferons, mesalazine, methotrexate, minocycline, nitrofurantoin, NSAIDs, penicillamine, radiation therapy, statins, sulfasalazine	Dyspnoea, low-grade fever, pleuritic chest pain	Migratory opacities, patchy opacities along bronchovascular bundles, localised consolidation, macronodular opacities	No distinct pattern	Alveolar and ductal fibrosis, type II pneumocyte hyperplasia, interstitial inflammation, intra-alveolar fibrin, interstitial eosinophilia, interstitial oedema	Drug withdrawal, corticosteroids in severe cases

(*Continued*)

Table 1. Continued

Pattern	Drugs	Symptoms and signs	Radiological findings	BAL findings	Histology (lung biopsy)	Treatment options/ outcome
Drug-induced pulmonary fibrosis	Amiodarone, carmustin, chlorambucil, cyclophosphamide, gold, lomustine, methotrexate, sulfasalazine	Dyspnoea, hypoxaemia, clubbing, repeated episodes of pneumothorax	Predominantly basilar streaky opacities, regional volume loss, honeycombing, coarse interstitial reticular and perilobular opacities, traction bronchiectasis	No distinct pattern	Interstitial fibrosis, thickened alveolar septa, type II cell dysplasia, honeycombing, UIP pattern	Drug withdrawal (rarely followed by improvement), corticosteroids (response often limited), lung transplantation; poor outcome
Drug-induced granulomatosis	Bleomycin, etanercept, methotrexate, phenylbutazone, phenytoin, sirolimus	Dyspnoea, dry cough, hypoxaemia, ARDS (rare)	Micronodular opacities	No distinct pattern	Diffuse granuloma	Drug withdrawal, corticosteroids
Radiation-induced lung disease	Ionising radiation	Dry cough, dyspnoea, hypoxaemia, moderate fever, ARDS (rare)	Changes predominate in the irradiated area, hazy ill-defined patchy nodules, area of condensation with volume loss	Lymphocytic inflammation	Type II cell dysplasia, hyaline membranes, interstitial and alveolar oedema, alveolar haemorrhage, fibrosis, traction bronchiectasis	Drug withdrawal, corticosteroids in severe cases

DAH: diffuse alveolar haemorrhage; DAD: diffuse alveolar damage; NSIP: nonspecific interstitial pneumonia; TNF: tumour necrosis factor; ARDS: acute respiratory distress syndrome; NSAID: nonsteroidal anti-inflammatory drug; ACE: angiotensin-converting enzyme; UIP: usual interstitial pneumonia-like.

Depending on the pathogenic mechanisms (*e.g.* direct toxicity, immune-mediated), the toxicity of a drug, exposure time and dose, comedications, additional lung injuries (*e.g.* radiation, surgery, infection), the underlying condition and patient age, the time of onset and the severity of symptoms are variable. In the majority of cases, drug-induced lung disease occurs concurrent with treatment, but rarely it may also develop months or years after the drug has been discontinued.

Children with malignancies are at increased risk of developing drug-induced lung disease, with an incidence of up to 60%. This is because they frequently receive several pneumotoxic drugs at the same time and often have additional risk factors for lung injury, such as transfusion of blood products, radiation therapy to the thorax, volume overload and haematopoietic stem-cell transplantation. Similarly, children with connective tissue diseases also have an increased risk for drug-induced lung disease. Often, the underlying disease may have diffuse interstitial lung involvement, and exposure to pneumotoxic drugs such as methotrexate or biologicals is quite frequent in these patients. This can lead to difficulties in treatment decisions because drug withdrawal is the treatment of choice in drug-induced lung disease, whereas escalation of treatment would be necessary in cases of pulmonary manifestation of the underlying condition.

Although there are known conditions with increased risk for drug-induced lung disease, it can potentially develop in any child under treatment with a drug, independent of age or underlying disease. Early recognition, exclusion of other causes, withdrawal of the drug and possible further treatment are necessary to avoid severe pulmonary damage or even death.

Epidemiology

There are no systematic studies on the incidence of drug-induced lung disease in children. Therefore, most information about the rate of this disease is from adult populations. The incidence ranges from about one in 100 000 patients for nitrofurantoin up to 60% for bleomycin in combination with other chemotherapeutic agents. Other drugs that are most often reported to cause drug-induced lung disease include chemotherapeutic agents such as busulfan, chlorambucil, cyclophosphamide, methotrexate, mitomycin, all-*trans* retinoic acid and nitrosourea. Other drugs that quite frequently cause drug-induced lung disease include amiodarone, antibiotics, nonsteroidal anti-inflammatory drugs and nitrofurantoin. There is growing evidence that biologicals such as interferon-γ, cytokines, intravenous immunoglobulins, antithymocyte globulin and granulocyte colony-stimulating factor might also induce lung injury.

Symptoms and signs

Dry cough, shortness of breath, dyspnoea and, in more severe cases, hypoxaemia, respiratory failure and an acute respiratory distress syndrome-like picture are most frequently reported. Additional complaints include chest pain, fever, malaise, skin rash and weight loss.

These symptoms and signs may develop either rapidly, yielding acute drug-induced lung disease and often severely ill patients, or insidiously. In these latter patients, even if asymptomatic, impaired lung function (mostly with a restrictive pattern) or reduced diffusion capacity might be detected. Subacute or chronic forms of drug-induced lung disease can evolve after weeks, months or years under treatment with a drug that has previously been well tolerated, or even after treatment cessation. Therefore, regular

Table 2. Diagnostic criteria for drug- or radiation-induced lung disease

1)	**Drug and radiation history** A detailed history is mandatory and should include any drugs, even if taken for a long time or discontinued before the onset of symptoms. This should include over-the-corner medications, dietary compounds, herbs, illicit substances and radiation therapy to the chest.
2)	**Drug singularity: correct identification of the drug** In patients exposed to several drugs, the symptoms and signs should be matched to all drugs received. It should be identified which drug is potentially causing the clinical picture of the patient. This can be done by reviewing the literature or with the support of the Pneumotox website.
3)	**Consistent timing of exposure and onset of symptoms** Onset of signs and symptoms before exposure to the suspected drug rules out causality. Patients can become symptomatic even months to years after termination of treatment with the drug, while other patients develop symptoms even after tolerating a drug for years.
4)	**Clinical, imaging, BAL and pathological patterns consistent with the specific drug** After diagnostic work-up, it should be checked whether clinical, radiological and histopathological findings (if available) are congruent with the reported lung injuries caused by the drug. This can be done by reviewing the literature or with the support of the Pneumotox website.
5)	**Careful exclusion of another cause** As drug-induced lung injuries often resemble diffuse lung diseases of other origin with respect to symptoms, signs and radiographic and histopathological findings, other causes for diffuse lung diseases have to be ruled out carefully (*e.g.* infections including opportunistic infections, exposure to other drugs, chemicals, street or illicit substances and environmental agents, independent onset of an ILD not related to drug toxicity).
6)	**Remission of symptoms with removal of drug** This is a very important diagnostic criterion. Depending on the kind of injury and time to diagnosis, withdrawal of the drug does not lead to clinical improvement in some cases. Steroids are therefore often used in severe cases and in patients who do not improve after cessation of a therapy.
7)	**Recurrence with re-challenge** Although this is a useful approach for confirmation of diagnosis, it cannot be recommended in general and is only justified when the suspected drug is essential for treatment of the underlying disease.

Adapted from Pneumotox Online (www.pneumotox.com/diagnosing-dird).

clinical follow-ups including PFTs and diffusion capacity (where possible) in patients at increased risk for drug-induced lung disease are strongly recommended.

Diagnosis

A clear systematic and stepwise approach should be adopted in each patient (table 2):

1) There must be an initial high degree of suspicion for the potential presence of drug-induced lung disease, based on a detailed history.
2) It is unlikely that several drugs are responsible for drug-induced lung disease at the same time, so the most likely compound should be identified, based on details of the individual case.

3) A temporal association must be recognised between exposure to the agent and the development of respiratory symptoms and signs. The onset of symptoms should follow (not pre-date) the onset of treatment with the specific drug. The time span between the onset of treatment with a specific drug and manifestation of drug-induced lung disease may be as short as a few seconds in patients with drug-induced anaphylaxis or acute bronchospasm, a few hours in transfusion-related acute lung injury or drug-induced noncardiac pulmonary oedema, or weeks to years into treatment with chemotherapeutic agents.
4) The lung injury pattern must be determined precisely, as well as whether it is consistent with the pattern that the suspected drug may induce. To this end, BAL is a useful procedure. Infections can be excluded and BAL cytology, even if not specific, can help to categorise injury type. BAL lymphocytosis, eosinophilic inflammation and dysplastic type II pneumocytes can be indicative of drug-induced hypersensitivity pneumonitis, eosinophilic pneumonia and chemotherapy-induced lung disease. Sanguineous BAL fluid with increasing discoloration from fraction to fraction is diagnostic for diffuse alveolar haemorrhage. Milky-appearing BAL fluid with diffuse periodic acid–Schiff-positive staining is suggestive of pulmonary alveolar proteinosis. In selected cases, lung biopsy is required to confirm the diagnosis of drug-induced lung disease. These drugs may include novel drugs applied with little experience in pulmonary toxicity, when there is no alternative to treatment with a certain drug, or when contradictory test results, signs or symptoms are present. Histopathological examination of lung tissue can rule out involvement of the underlying disease or an infection and help diagnose a drug-induced condition if a pattern consistent with the particular drug is found. Transbronchial biopsies are not recommended because the risk (pneumothorax)/benefit (representative sample) ratio is too high. If lung biopsy is intended, minimal invasive thoracosopy is the procedure of choice.
5) Using the procedures in step 4), other conditions that can cause the same symptoms and signs should be excluded.
6) Treatment with the suspected drug should then be stopped immediately. Diagnosis of drug-induced lung disease is very likely when withdrawal is quickly followed by clinical and radiological improvement. However, recovery of lung disease may often be slow.
7) Whether a re-exposure is necessary to confirm the diagnosis in such cases is a matter of ongoing debate but is often declined for ethical issues, especially in children. However, this decision has to be made on an individual basis and with respect to the need for the suspected drug for treatment of the underlying disease.

Often, the diagnosis of drug-induced lung disease must remain speculative and this should be stated, based on the number of supporting steps obtained during diagnostic work-up.

Treatment

The most important "treatment" is immediate withdrawal of the drug. In severe cases or when withdrawal of the drug does not lead to clinical improvement, corticosteroids are commonly used, even if the efficacy has not been evaluated in controlled clinical trials (table 1). In severe cases, patients may have to be ventilated or treated with extracorporeal lung assistance. In the case of continuous disease progression despite withdrawal of the causative drug and without a response to high-dose corticosteroids, lung transplantation should be considered carefully as a treatment option.

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Neuromuscular disorders

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While some neuromuscular diseases are very rare, neuromuscular disorders as a group are quite common in childhood, with an overall prevalence of about one in 3000 children. Most are inherited in origin, the most common being Duchenne muscular dystrophy, spinal muscular atrophy, congenital muscular dystrophies and myopathies. Neuromuscular disorders in infants comprise a spectrum, ranging from profound floppiness and respiratory compromise at birth, such as in patients affected by type 1 spinal muscular atrophy, to disorders at the opposite end, where the patients are able to sit and walk but have later-onset respiratory problems.

The probability of respiratory complications varies according to diagnosis, genotype and age. For details, see the British Thoracic Society guideline for respiratory management of children with neuromuscular weakness. Over the past 20 years, an increasing amount has been learned about genotype–phenotype correlations and respiratory management strategies. In some conditions, the natural history has changed significantly with the introduction of ventilatory support, and the course of numerous neuromuscular disorders will change with the introduction of innovative therapies.

Respiratory assessment

Children with neuromuscular weakness have a restrictive pattern of spirometry in PFTs. This is caused by variable combinations of reduced inspiratory muscle strength, the presence of a thoracic scoliosis, and reduced chest wall and pulmonary compliance, the latter caused by micro- or macroatelectasis. Inspiratory and expiratory muscle strength mostly decrease in parallel, but when diaphragm strength is preserved, expiratory muscle weakness may predominate (*e.g.* in spinal muscular atrophy). Expiratory muscle weakness combined with inspiratory muscle weakness leads to poor cough efficacy and secretion

Key points

- Neuromuscular disorders are relatively common in children, with a prevalence of one in 3000.
- Sleep disordered breathing is likely when vital capacity falls to <60% predicted.
- NIV is indicated to control symptomatic sleep disordered breathing.
- Use of NIV in Duchenne muscular dystrophy may double life expectancy.

clearance and can be measured by cough peak flow: values <270 L·min^{-1} in children aged ~10 years and above suggest reduced cough power, while values <160 L·min^{-1} are associated with increased frequency of chest infections. In patients with congenital myopathies and muscular dystrophies, a vital capacity of ≤60% predicted is predictive of the presence of sleep disordered breathing, which initially occurs in rapid-eye-movement (REM) sleep and then spreads to all sleep stages. Usually, this appears as nocturnal hypoventilation, but obstructive hypoventilation may be seen in some conditions such as Duchenne muscular dystrophy. Sleep studies should be carried out routinely in these children, and in any with sleep-related symptoms or recurrent chest infections, in those requiring hospitalisation and in cases of failure to thrive.

Scoliosis is common and will occur in children with spinal muscular atrophy types 1 and 2 and in 70–90% of those with Duchenne muscular dystrophy. Scoliosis progresses with the adolescent growth spurt and transition to permanent wheelchair use. Use of steroid therapy in patients with Duchenne muscular dystrophy and preservation of standing using frames may reduce scoliosis severity. Moreover, treatment with nusinersen for spinal muscular atrophy may improve peripheral and respiratory muscle function, resulting in delayed onset and progression of scoliosis and hypoventilation. Scoliosis surgery is carried out to prevent progression of the curvature and achieve comfort, rather than to increase lung volumes.

Bulbar involvement is inevitable in type 1 spinal muscular atrophy and some conditions such as myotubular myopathy and myotonic dystrophy, but in others, such as Duchenne muscular dystrophy, it is a late-stage phenomenon. Assessment of swallowing function is a key part of respiratory management in any child with neuromuscular disease; weakness is suggested by slow feeding, choking, aspiration and recurrent chest infections. Nutritional assessment is also crucial, and if adequate nutrition cannot safely be achieved orally, then percutaneous gastrostomy placement may significantly improve quality of life and reduce respiratory complications.

Sleep studies

Overnight oximetry is often used to screen for sleep disordered breathing in children with neuromuscular disease. While a normal trace in a child who has slept well usually excludes a significant problem, values of S_{aO_2} within the normal range can occasionally be seen in children with mild OSA/hypopnea and can be accompanied by hypercapnia in children using CPAP or NIV. If there is a high suspicion of sleep disordered breathing, multichannel monitoring including a measure of overnight carbon dioxide tension (*e.g.* P_{tcCO_2}) is preferred.

Long-term assisted ventilation

Measurement of carbon dioxide control is also required to assess ventilator efficiency in children started on NIV. Patients with neuromuscular disease with nocturnal hypoventilation are likely to deteriorate with the development of daytime hypercapnia and/or progressive symptoms within 2 years and may benefit from the introduction of nocturnal NIV before daytime hypercapnia ensues. Noninvasive approaches are preferable, providing bulbar function is adequate. Pressure-preset ventilators are usually used. Care should be taken to ensure ventilator performance meets the child's ventilatory needs; for example, if the inspiratory trigger is insensitive, the work of breathing increases, but if it is too sensitive, autotriggering resulting in asynchrony may occur. In addition, mask rotation and avoidance of tight-fitting interfaces should be employed to reduce the risk of pressure over facial structures resulting in midfacial

hypoplasia and pressure sores. Customised masks reduce the occurrence of mask-related problems in children.

Research has shown that NIV in Duchenne muscular dystrophy extends survival. Before ventilatory support, the median survival was ~18 years; in contrast, about a third of patients with the disease now live into their 30s and 40s. Similarly, in type 1 and 2 spinal muscular atrophy and the congenital muscular dystrophies, NIV is associated with a reduction in respiratory tract infections, with improved school attendance and quality of life. A nuanced response to ventilatory support is required; in some instances, this may be lifesaving and extend life by many years, while in others with more severe disease, NIV may palliate symptoms or respiratory distress and allow hospital discharge but is not intended to extend life expectancy. Goalsetting and an anticipatory care plan are an important part of the care of any child with neuromuscular weakness.

Chest physiotherapy and cough augmentation

Standard chest physiotherapy is vital for successful management and may be complemented by manual cough augmentation and breath stacking to improve lung recruitment, using an Ambu bag. Use of NIV alone may help with secretion clearance, and physiotherapy should be performed while the child uses the ventilator. However, in those with a cough peak flow of <270 $L \cdot min^{-1}$ and/or poor cough in whom these simpler techniques are not sufficient, a cough insufflator–exsufflator device may improve cough peak flow and reduce pulmonary morbidity. A randomised controlled trial in children and adults has shown that insufflation–exsufflation can increase cough peak flow and is well tolerated (Chatwin *et al.*, 2003). Although there are no randomised controlled trials of long-term use, the combination of NIV and cough insufflation–exsufflation with or without enteral feeding may reduce the need for a tracheostomy in children with mild-to-moderate bulbar/swallowing dysfunction.

Tracheostomy ventilation

NIV is usually preferable to tracheostomy as it is simpler for the child and family, but invasive ventilation is indicated in the situations listed in table 1. The risk management of a tracheostomy ventilator-dependent child clearly differs from that of a child using NIV.

Other systems/complications

Cardiomyopathy is seen in all Duchenne muscular dystrophy patients by the mid- to late-teenage years and should be treated with angiotensin-converting enzyme (ACE) inhibitor and a β-blocker. Cardiac involvement is also highly prevalent in Becker muscular dystrophy, myotonic dystrophy and the lamininopathies such as Emery–Dreifuss muscular dystrophy. The limb-girdle muscular dystrophies (LGMDs) are a very heterogeneous group, and cardiac surveillance should be adapted to the underlying

Table 1. Indications for tracheostomy ventilation

Severe bulbar weakness leading to aspiration
Upper airway problems limiting delivery of NIV
Failure to control ventilation with noninvasive mode
Intractable interface problems
Near 24-h ventilator dependency, especially in early infancy
Patient/family preference

disorder; for example, cardiac disease is common in the sarcoglycanopathies (LGMD types 2C–F), but less frequent in the dysferlinopathies (*e.g.* LGMD type 2B) and calpainopathies (*e.g.* LGMD type 2A).

GOR and feeding problems are common and may require supplemental feeding. In young adults with Duchenne muscular dystrophy and in patients managed on ventilator support for many years, a new set of problems is emerging, such as renal and bladder calculi, and intermittent episodes of bowel pseudo-obstruction probably caused by a combination of autonomic dysfunction and reduced abdominal muscle tone.

Palliative care

Many children with neuromuscular disorders experience muscle, back and joint pain; in fact, 40% of older Duchenne muscular dystrophy patients report daily pain and fatigue. Good supportive care and symptom palliation are vital and do not equate to end-of-life care, as symptom relief may be required for many months or years before death. Analgesia should not be stinted for fear of respiratory failure. Careful uptitration of opioids usually avoids this problem, and ventilatory support can always be added if respiratory insufficiency ensues.

In all children receiving NIV, an anticipatory care plan should be drawn up by joint consultation between the care team, the patient and the family. This covers escalation of therapy during acute exacerbations and the agreed limits to intervention in the face of long-term irreversible decline.

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Chest wall disorders

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Paediatric pathologies that affect the shape and function of the chest wall include congenital structural anomalies of the rib cage, spine and thoracic musculature, as well as acquired diseases such as costal Ewing sarcoma and neurogenic scoliosis. Congenital chest wall disorders may be apparent at birth or become symptomatic with time, usually as a result of disturbed growth and development. Here, the most important features of congenital thoracovertebral disorders will be highlighted; a discussion of acquired chest wall diseases is beyond the scope of this chapter.

Pathophysiology of respiratory compromise in chest wall disorders and scoliosis

Long-term respiratory stability requires that ventilation and gas-exchange reserves keep up with the increasing demands of the growing body and that expectoration of accumulating airway secretions remains effective. While infants with thoracovertebral deformities are compromised in their respiratory stability by the increased chest wall compliance and collapsibility of the airways, older children are more limited by the abnormal stiffness of the chest. The recruitment of inspiratory reserve to full expansion of the thoracic cage depends on the free mobility of the costovertebral and

Key points

- Despite obvious deformations, lung function remains surprisingly preserved in most individuals with adolescent idiopathic scoliosis, pectus excavatum and pectus carinatum.
- In contrast, severe thoracic restriction conveys a high risk of pulmonary morbidity and respiratory failure in early-onset scoliosis and complex syndromal thoracovertebral malformations.
- Surgical correction rarely improves lung function but is expected to halt further deterioration by stabilising the underlying thoracovertebral pathology.
- Recent developments in orthopaedic techniques allow timely intervention in early-onset scoliosis, promoting spinal and chest wall growth, but the potential for improving lung function remains unclear.

costosternal articulations, and on a slanting position of the ribs at rest, which, by lifting the ribs into a horizontal position, allows widening of the chest diameter in the lateral dimension (bucket-handle movement) and the anterior–posterior dimension (pump-handle movement). For this to be accomplished with minimal effort, alignment of the respiratory muscles, particularly of the intercostal musculature, must have optimal leverage angles.

The severity of a thoracovertebral malformation often correlates with the degree at which these structural requisites for respiratory stability are lost. Stiffness of the chest and disadvantageous positioning of the respiratory muscles render these children disproportionally dependent on diaphragmatic breathing, which, in turn, may be negatively affected by distortion and flattening of the diaphragm. Equally, when the chest gets stiffer, cough efficiency becomes increasingly dependent on abdominal muscle strength.

Congenital chest wall and sternal defects

Poland syndrome

Poland syndrome (also known as Poland sequence) is a constellation of anomalies whose hallmark is unilateral hypoplasia or aplasia of the pectoral muscle, which may or may not be associated with a malformation of the ipsilateral upper extremity, typically a symbrachydactyly. There can be hypo- or aplasia of the breast and nipple and occasionally deformities of the ribs, sternum and vertebrae. The right side is affected in 58–75% of cases, and there is a male preponderance with a male/female ratio of 2–3/1. Concomitant Moebius syndrome, a syndrome of congenital facial and ocular nerve palsy, may be present. Poland syndrome does not usually affect respiratory function but may have a significant psychosocial impact. Surgical treatment options include fat grafts/implants and tissue flaps, and reconstruction of the ribs and sternum may be needed.

Pectus excavatum

The pectus excavatum deformity has a prevalence of one in 400 people with a male/female ratio of 3–5/1. Occurrence is sporadic, familial or syndromic (*e.g.* Marfan sydrome, Noonan syndrome); in addition, it may be seen in survivors of congenital diaphragmatic hernia, or secondary to long-standing significant upper airway obstruction. Pectus excavatum can become apparent at any age during growth and is not spontaneously reversible except for the secondary form.

Significant pectus excavatum is associated with mild restrictive lung function with a decrease in median vital capacity (VC) to ~80–85% predicted. The probability of significant restriction is four times higher if the Haller index is >7, which is defined as the ratio between the transverse thoracic diameter and the narrowest distance between the sternum and vertebra. Significant airway obstruction is rare. Although measureable lung function abnormalities are usually mild, many affected individuals complain about shortness of breath and reduced exercise tolerance. Reduced exercise capacity may be caused by a limitation of venous return and right cardiac filling but remains unexplained in the majority of cases.

Available data report no benefit of corrective surgery for lung function but a possible favourable effect on exercise capacity, independent of the therapeutic approach (*i.e.* treatment with a vacuum bell, an open surgical procedure or MIRPE (minimally invasive repair of pectus excavatum), also known as the Nuss procedure). The majority of patients, however, seek correction for aesthetic reasons. In MIRPE, the sternum is

pushed into the correct position by a convex steel bar, which is introduced with only two small incisions on each side of the chest. The bar remains in place for 2–4 years.

Pectus carinatum

The pectus carinatum deformity is three times rarer than pectus excavatum, occurring sporadically, with a familial predisposition in 25% of cases, or as part of a genetic syndrome such as Marfan syndrome, Noonan syndrome or homocystinuria. In most affected individuals, cardiopulmonary function is not impaired, but many suffer from the psychosocial impact, which may justify treatment. The most common non-operative method is bracing, especially with a dynamic compression system (*e.g.* the FMF Dynamic Compressor System). Surgical treatment options are sternochondroplasty (Ravitch procedure) or, gaining in popularity, minimally invasive repair.

Flaring of the costal arch

Flaring of the costal arch is seen in combination with pectus excavatum and pectus carinatum. It does not usually affect respiratory function but can be aesthetically disturbing, especially after correction of the pectus deformation. Treatment with an elastic brace is often performed, but its effectiveness is not proven. Operatively, a minimal subperichondral partial resection can be performed.

Sternal clefts

Congenital sternal clefts can be complete or partial. Partial superior clefts prevail; partial lower clefts are often associated with ectopia cordis or pentalogy of Cantrell. Other concurrent malformations, such as midline defects, are found in up to three-quarters of cases, but many individuals with sternal clefts are asymptomatic. Reported complaints include exercise intolerance, cough and vulnerability to lower respiratory tract infections. Early surgical repair is often recommended, the more theoretical rationale being concerns about chest instability and risk of trauma.

Pentalogy of Cantrell

This is a rare, combined midline defect including the pentade of a supra-umbilical abdominal wall defect with or without evisceration, an inferior sternal cleft, a pericardial defect or ectopia cordis, a median diaphragmatic defect, and a congenital heart defect such as a ventricular septal defect or tetralogy of Fallot. The outcome depends on the extent of the malformation and the complexity of the congenital heart defect. Mortality in children with the complete pentalogy is high.

Thoracovertebral deformities

Isolated congenital scoliosis and adolescent idiopathic scoliosis

The period of fastest spine growth is from birth to 5 years (T1–L5 2.2 cm·year^{-1}) when spinal length gain is almost 50%. Growth then transiently slows to 1.1 cm·year^{-1} and reaccelerates for the pubertal growth spurt to 1.8 cm·year^{-1}, starting at 10–11 years in girls and 2 years later in boys. The thoracic volume makes up around 6% of its adult size at birth, 30% at 5 years of age and 50% at 10 years.

Early-onset scoliosis (EOS) is defined as any spinal deformity diagnosed before 10 years of age, independent of aetiology. Over time, 70% of EOS cases worsen and require treatment, approximately half by surgical intervention. In isolated EOS, chest growth is impaired mainly in patients with severe EOS, defined as a Cobb angle of >65º, conveying an increased risk of progressive respiratory failure and mortality.

*Figure 1. The risk of progression in EOS can be estimated by the rib–vertebra angle difference (RVAD). The rib–vertebra angle on the convex side (*b*) of the apical vertebra is subtracted from the angle of the concave side (*a*). If the difference is >20º, there is a high risk of an increase in deformity, while with a difference of <20º, spontaneous improvement can often be observed, especially with idiopathic EOS.*

The overall prognosis is worse in the presence of primary thoracic cage malformations or in neurogenic EOS. The best outcome may be expected in cases of idiopathic EOS with little rotational deviation (a rib–vertebra angle difference of <20º, according to Mehta, 1972) (figure 1).

Survival improves significantly if idiopathic scoliosis is diagnosed at ≥5 years and is normal in adolescent idiopathic scoliosis (AIS), which, as per the definition, is diagnosed at ≥10 years of age.

Most individuals with AIS have normal lung function. When scoliosis progresses, however, lung function decreases due to a reduction in both the volume and compliance of the chest, and to a change of the lever arm vectors of the respiratory muscles. TLC is preserved longer than VC, resulting in an extrinsic (asymmetrical) overinflation with an increased RV/TLC ratio. Ventilation becomes increasingly inhomogeneous, but bronchial obstruction is found in <20% of cases. The degree of pulmonary restriction is underestimated if height-based reference values of normal lung function are used. In order to avoid misclassification of lung function results in patients with scoliosis, taking the arm span as a surrogate for standing height may be a practicable solution in children. Other alternative anthropometric references such as ulnar length require the implementation of specific reference equations.

The Cobb angle cannot reliably depict the three-dimensionality of scoliosis, and it correlates only moderately with the degree of pulmonary limitation. A decrease in FVC to <80% pred may be expected in AIS from Cobb angles of 70–100º onwards, but the variability of pulmonary restriction remains significant. Rotation in the transverse plane is an important feature of scoliosis, clinically manifesting as a rib hump or lumbar hump, depending on the apex of the scoliosis, and additionally impairs lung function in patients with advanced scoliosis or concomitant thoracic hypokyphosis (*i.e.* a reduced physiological thoracic kyphosis). It is estimated that the height and

length of the scoliotic curvature and the presence of hypokyphosis (<10º sagittal angulation) account for up to 20% of FVC reduction.

AIS patients often complain about reduced exercise tolerance. Average maximum inspiratory and expiratory pressures are ~70% pred, which is in part attributable to the disadvantaged leverage vectors of the respiratory muscles. Exercise limitation probably also reflects a reduced range of motion of the thorax, as well as a generalised muscle weakness that has repeatedly been found in AIS patients and that might contribute to the pathogenesis of scoliosis.

AIS requires clinical and radiographic monitoring at regular time intervals, the risk of progression being determined by the severity of the scoliosis (*i.e.* the Cobb angle) and the pubertal stage. Children with EOS, especially those with complex thoracovertebral syndromes, need a multidisciplinary tailored approach with emphasis on growth and nutrition, sleep quality and sleep disordered breathing, and cardiac function. Ventilatory support is generally offered early if symptoms and signs of failure to thrive, sleep disordered breathing or pulmonary arterial hypertension arise, and if intervention is ethically desirable.

Complex syndromal thoracovertebral malformations

Complex syndromal thoracovertebral malformations comprise a heterogeneous group of combined malformations of the spine and thoracic cage that lead to severe kyphoscoliosis and/or narrowing and stiffening of the thoracic cage. The respiratory function of affected children is impaired by the thoracic restriction, reduced respiratory muscle efficiency, weak cough and impaired airway clearance. Additional symptoms may arise from associated malformations, GOR and heart failure. Asymmetrical ventilation and perfusion is detectable in many affected children. These malformations not only cause physical suffering but also result in enormous psychosocial stress from social marginalisation, school absenteeism, and concerns about the future and partnership. Medical care therefore requires a multidisciplinary approach. Numerous syndromes may manifest with complex thoracovertebral malformations, including diastrophic dysplasia, infantile Marfan syndrome, Klippel–Feil syndrome, Jeune syndrome (asphyxiating thoracic dystrophy), Jarcho–Levin syndrome and VACTERL (vertebral defects, anal atresia, cardiac defects, tracheo-oesophageal fistula, renal anomalies and limb abnormalities) associations.

Thoracic insufficiency syndrome

The severe thoracic restriction is associated with lung hypoplasia and respiratory failure. This common feature led Campbell *et al.* (2003) to propose the concept of thoracic insufficiency syndrome (TIS), defined as the inability of the thorax to allow normal respiration and lung growth. TIS is divided into four different types of volume-depletion deformities (table 1).

Table 1. Types of volume-depletion deformities causing TIS

Type	Characteristics
I	Unilaterally absent ribs with scoliosis and hemihypoplasia of the thorax
II	Unilaterally fused ribs with scoliosis and hemihypoplasia of the thorax
IIIa	Vertebral malformation with loss of thoracic height and kyphosis causing bilateral longitudinal restriction of the lungs (*e.g.* Jarcho–Levin syndrome)
IIIb	Global thoracic hypoplasia with windswept deformity and lateral lung constriction on both sides (*e.g.* Jeune syndrome)

Patients with unilaterally absent ribs and an associated flail chest have a high mortality in the first years of life. Death is usually caused by respiratory failure and/or right heart failure. The unilaterally fused ribs type is the most common form and typically leads to worsening of scoliosis and pulmonary function with growth. The differentiation into the four types of TIS guides surgical management. For the paediatric pulmonologist, it is important to recognise that both chest radiography and PFTs do not reliably reflect the degree of respiratory morbidity. Studies suggest that sleep studies may be more sensitive in detecting respiratory limitation.

Jeune syndrome (asphyxiating thoracic dystrophy)

Jeune syndrome is a rare osteochondrodysplasia with autosomal-recessive inheritance and variable expression that occurs in all ethnicities with an estimated incidence of one in 130 000. The syndrome belongs to the skeletal ciliopathies, and a number of genes have been implicated. Cilia are well-conserved structures present in almost all cells, and mutations have been associated with various syndromes, including various short-rib syndromes. A narrow, bell-shaped and very stiff thorax with an almost normal-sized vertebral column is the hallmark of Jeune syndrome (TIS type IIIb). Chest width is reduced in both the sagittal and coronal plane with shortened ribs typically bowed inwards at the bony tips, resulting in a clover-leaf appearance of the thoracic cage in the transverse plane. Other skeletal features of the pelvis and extremities are common and are associated with short stature, and vertebral malformations of the neck need special attention for their potential to damage the cervical medulla. One-third of affected individuals have renal disease including cysts, tubular atrophy and renal failure. Other organ manifestations involve the liver, the pancreas, intestinal malrotation and the eyes. There is no apparent correlation between the severity of thoracic dystrophy and the extent of parenchymal involvement.

Numerous cases have been described in the literature. Mortality is as high as 50%, with up to 80% dying within the first 2 years due to respiratory failure and cor pulmonale. Most survivors need some sort of ventilatory support. Thorax expansion surgery increases the transverse cross-sectional area, but its effect on ventilation, lung growth and function remains uncertain. Jeune patients surviving into adolescence are at risk of developing end-stage renal disease.

Spondylocostal and spondylothoracic dysostosis (Jarcho–Levin syndrome/ Lavy–Moseley syndrome)

Jarcho–Levin syndrome encompasses individuals with a very short spine and malformed vertebral bodies, and a malformed rib cage with fused, dysplastic or absent ribs. Various gene mutations have been found and underlie the phenotypic variations. Spondylocostal dysostosis (Jarcho–Levin syndrome *sensu stricto*) may be distinguished from spondylothoracic dysostosis (Lavy–Moseley syndrome). Severe pulmonary restriction leads to chronic respiratory failure, recurrent pneumonias and right heart failure.

Spondylocostal dysostosis occurs as both an autosomal-recessive and an autosomal-dominant trait, and is characterised mainly by the following:

- Abnormal segmentation of at least 10 consecutive vertebral bodies
- Costal malalignment, fused ribs and costal bifurcations, or occasionally absent ribs
- Mild scoliosis with variable potential for progression, depending on the asymmetry of the costal malformations (TIS type II or IIIa)

Multiple associated malformations are known. Progression of scoliosis occurs in 75% of cases without early thoracic expansion. Mean survival has improved significantly, but long-term prognosis is as yet unknown.

Spondylothoracic dysostosis is an autosomal-recessive syndrome that occurs mostly in individuals of Puerto Rican descent, characterised by an extremely short spine with posteriorly fused ribs giving a crab-like appearance on a chest radiograph (TIS type IIIa). Among other malformations, it may be associated with congenital diaphragmatic hernia, which further worsens the prognosis of these children who are almost exclusively dependent on diaphragmatic breathing. Mortality is very high and is generally attributable to respiratory failure, pulmonary arterial hypertension and heart failure.

Orthopaedic treatment of scoliosis and thoracovertebral malformations, and impact on lung function

Crucial to the success of surgical treatment is definition of the appropriate method and the time point of the intervention.

Early multilevel spinal fusion surgery, especially in the thoracic part of the vertebral column, has been completely abandoned because it results in a shortened and stiffened spine with reduced growth of the rib cage, leading to respiratory compromise as well as back and chest pain. Up to 50% or 10 cm of spinal length can be lost by spinal fusion before 5 years of age, with a corresponding significant loss of thoracic volume. According to Karol *et al*. (2008), an 18 cm length of the thoracic spine is deemed necessary as a prerequisite for satisfactory lung function.

Distraction-based growth-sparing implants, such as spine-based growing rods, can improve the deformity of the spine and stimulate the growth of the vertebral column, and can be implanted at an early age. However, they have no beneficial impact on chest growth and are therefore standard treatment for EOS without vertebral or costal malformations.

EOS that is associated with rib cage malformations tends to progress rapidly and to end in TIS. The primary goal of treatment is to partially correct the deformity and stabilise the achieved correction, usually beginning at the age of 1.5–2 years. The current surgical approach is expansion thoracoplasty using rib-based implants such as the vertical expandable prosthetic titanium rib (VEPTR). These devices focus primarily on improving the space available for the lungs, thereby allowing lung expansion and, hopefully, stimulating lung growth.

New magnetically controlled, expandable rods obviate the need for repeated surgical interventions required to expand traditional growing rod or VEPTR devices, and allow outpatient lengthening of the rods in frequent small steps, reducing anaesthetic and infectious risks.

Whether these interventions stimulate pulmonary catch-up growth is not yet clear. CT scans revealed a 25–90% increase in thoracic cage volume after VEPTR treatment, which is probably the consequence of enlargement of the coronal chest diameter and stimulation of spinal growth. Reported clinical benefits of expansion thoracoplasty include improved exercise tolerance, reduced ventilatory support, increased body weight and reduction of polyglobulia. Whether the improvement of these surrogate markers results from improved breathing mechanics, a larger chest volume or even alveolar catch-up growth is a matter of debate. Preliminary longitudinal lung function studies have failed to document any significant catch-up growth in children with TIS after repeated thoracic expansion. It is unknown whether an age limit exists for possible pulmonary catch-up growth, or whether VEPTR treatment halts the progression of scoliosis and thoracic deformation in children with complex thoracovertebral malformations.

Spinal fusion rarely leads to improved lung function, either in AIS or in patients with neuromuscular disease. A rib hump resection is even accompanied by a 15–20% decrease in FVC in the first post-operative months that slowly recovers to the pre-operative level within 2 years. In contrast, in patients with neuromuscular disease, specifically in those with Duchenne muscular dystrophy, timely spinal fusion seems to reduce the rate of pulmonary function decline.

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Plastic bronchitis

Bruce K. Rubin and Maxim Itkin

Plastic bronchitis is an uncommon disease characterised by the presence of cohesive branching casts filling the airways. This disease was first described by Galen, who believed that patients were expectorating pulmonary veins (*venae arteriosae expectoranti*). Plastic bronchitis has had many names over the years, but the terms plastic bronchitis and cast bronchitis are most commonly used.

Diagnosis

Plastic bronchitis is part of the secretory hyperresponsiveness disease spectrum. The diagnosis of plastic bronchitis is confirmed by identifying the cohesive, branching airways casts that are expectorated by the patient or removed bronchoscopically (figure 1). Bronchoscopic removal is most common in young children with severe, life-threatening respiratory distress due both to the cast and to the underlying cardiac disease. These casts contain lymph and mucin, but unlike normal mucin polymers that are joined linearly, there is significant cross-linking between adjacent mucin strands. The casts contain variable amounts of fibrin, with most patients having only small amounts of fibrin in expectorated casts.

In patients with bronchiectasis and CF, there are large amounts of polymeric DNA and F-actin as the principal polymer gel substance. These mucus (sputum) plugs have low cohesivity and rarely, if ever, develop into solid cohesive complex branching casts

Key points

- Plastic bronchitis in children is usually associated with congenital heart disease and Fontan single-ventricle physiology. This is called classic or lymphatic plastic bronchitis.
- Cast formation appears to be related to poor cardiac output, lymphatic abnormalities and inflammation, and can be dramatically ameliorated by lymphatic imaging and ablation of aberrant lymphatics.
- There is no proven therapeutic value in using hypertonic saline, salbutamol, corticosteroids, *N*-acetylcysteine, dornase alfa, antibiotics or expectorants.
- Nonlymphatic or eosinophilic plastic bronchitis appears to be distinct from asthma and is similar to chronic desquamative eosinophilic bronchitis.

Figure 1. Typical expectorated branching casts of lymphatic plastic bronchitis.

diagnostic of plastic bronchitis. There is also no polymeric DNA or F-actin in plastic bronchitis casts, further distinguishing them from mucus plugging. Plastic bronchitis also appears to be different from the mucus plugging associated with fungal inflammation of the airway, as noted in allergic bronchopulmonary aspergillosis. The eosinophilic (nonlymphatic) form of plastic bronchitis is distinct from asthma and usually responds poorly to asthma medications. It is a form of secretory hyperresponsiveness similar to chronic desquamative eosinophilic bronchitis. These patients are said to have nonlymphatic or eosinophilic plastic bronchitis.

We have examined plastic bronchitis casts from more than 70 adults and children with a variety of associated conditions and all showed the presence of inflammatory cells. Although plastic bronchitis was once classified as type 1 or type 2 (cellular and acellular), the consistent appearance of inflammatory cells, predominantly lymphocytes with a minor component of macrophages, makes this classification of limited therapeutic or prognostic value. Inflammatory cells are seen more commonly in noncardiac or eosinophilic plastic bronchitis, but inflammatory cells are also prominent in casts from patients with classic or eosinophilic plastic bronchitis.

Plastic bronchitis is probably underdiagnosed. The diagnosis is often made at autopsy after death from respiratory failure. Identified patients probably represent the most severe cases, with dramatic branching casts, airway obstruction and extensive atelectasis.

Recently, dynamic contrast-enhanced magnetic resonance lymphangiography (DCMRL), described more fully in the next section, has demonstrated abnormal

Table 1. Conditions associated with plastic bronchitis

Proven
Congenital heart disease with Fontan physiology
Sickle cell acute chest syndrome
Pulmonary lymphatic abnormalities
Influenza A virus pulmonary infection
Toxic inhalation
Possible
Other congenital cyanotic cardiac disease
Nonpulmonary lymphatic abnormalities
Hypersecretory and near-fatal asthma ("eosinophilic casts")
Allergic bronchopulmonary aspergillosis
Unlikely
CF
COPD
Bronchiectasis
Bacterial pneumonia

pulmonary lymphatic anatomy and flow in patients with plastic bronchitis in association with single-ventricle and Fontan physiology, as well as some patients with idiopathic plastic bronchitis. This is now known as lymphatic or typical plastic bronchitis.

Disease associations

Plastic bronchitis in young children is associated primarily with congenital heart disease, particularly in children with single-ventricle, Fontan physiology (table 1). The occurrence, severity and frequency of exacerbations of plastic bronchitis vary markedly among patients with congenital heart disease, sometimes first appearing years after surgery.

The lymphatic aetiology of this disorder was defined using DCMRL. DCMRL is performed by injecting gadolinium contrast into the groin lymph nodes while monitoring the progression of the contrast cranially using magnetic resonance angiography sequences. DCMRL can demonstrate the abnormal lymphatic flow from the thoracic duct into the airways and pulmonary parenchyma, termed "pulmonary lymphatic perfusion". In most of these patients, a congenital lymphatic variant is present, and with increased flow in the lymphatic system due to chronic right-sided heart failure, there is associated congestion of the abnormal lymphatic vessels and seeping of the fluid into the bronchial lumen. This abnormal perfusion can be demonstrated by injecting the blue dye lymphazurin into the thoracic duct while performing bronchoscopy (figure 2). Abnormal pulmonary lymphatic flow similar to this was also seen in adults with idiopathic plastic bronchitis. The precipitating cause of "lymphatic plastic bronchitis" is unknown; however, most adults with idiopathic disease are obese (unpublished Registry data).

Plastic bronchitis is also associated with sickle cell disease acute chest syndrome. It is not known whether development of casts in sickle cell disease leads to areas of hypoxaemic sickling within the lung, producing the symptoms of acute chest syndrome, or whether the acute chest syndrome itself predisposes to cast formation. Plastic bronchitis is not associated with pulmonary bacterial infection, and in general, antibiotics are not recommended as part of therapy. However, plastic bronchitis has

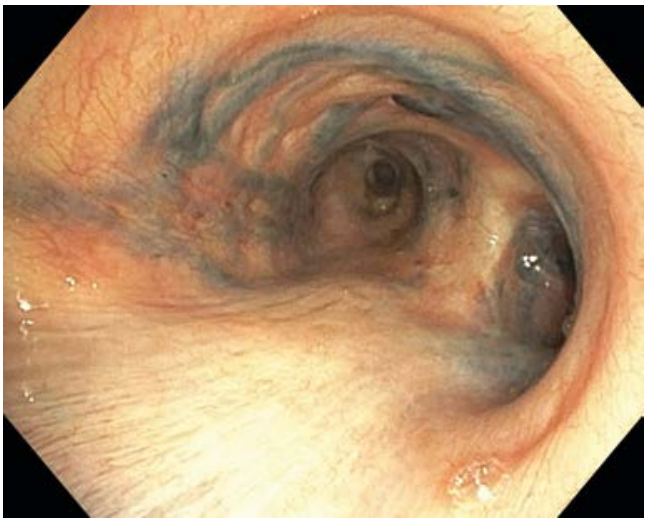

Figure 2. Blue dye injected into the pulmonary lymphatics seeping into the airway of a patient with congenital heart disease and typical lymphatic plastic bronchitis.

been shown to be associated with influenza A infection in children, and similar cast formation has been described in birds who have been experimentally infected with avian influenza.

Far less is known about eosinophilic casts with no lymphatic involvement. In some respects, this appears to be more like eosinophilic oesophagitis or chronic desquamative eosinophilic bronchitis than asthma. It is controversial whether severe asthma and airway plugging should be considered a plastic bronchitis-like disease. Fatal asthma secretions are extremely cohesive and when extracted from the airway may have similar branching casts with cellular debris and Charcot–Leiden crystals. In this respect, they more closely resemble plastic bronchitis than mucus plugging. Our limited experience of about 15 patients with the eosinophilic form of plastic bronchitis suggests that corticosteroids are not very effective (with the exception of allergic bronchopulmonary aspergillosis). We have seen some benefit from inhaled heparin as therapy.

Therapy

Because plastic bronchitis is an uncommonly reported condition, most reports of "effective" therapy are isolated case reports or small case series. Furthermore, most patients reported in these case studies have received many different medications, making it difficult to ascertain which of these therapies, if any, are effective (table 2). Evaluation of data from the International Plastic Bronchitis Registry suggests no benefit from the use of asthma medications such as short-acting β-agonists (*e.g.* salbutamol) or inhaled corticosteroids. There is no therapeutic benefit from using inhaled dornase alfa (Pulmozyme; Roche), as plastic bronchitis casts do not contain polymeric DNA. There is no benefit in using expectorants such as guaifenesin or hypertonic saline, or mucolytics such as *N*-acetylcysteine. These medications should only be used with caution as some can induce mucus secretion or increase airway inflammation.

There have been several case reports that the inhalation of tissue plasminogen activator (tPA) can improve plastic bronchitis, most likely through fibrin depolymerisation. tPA is extremely expensive and can be irritating to the airway, with haemoptysis or dyspnoea being reported after inhalation. In patients with acute airway obstruction due to plastic bronchitis, a trial of aerosol tPA should be considered at a dose of 0.7–1.0 $mg \cdot kg^{-1}$ every 4 h. Inhaled heparin has also been effective in patients with plastic

Table 2. Recommendations for therapy

Good evidence
Airway clearance including physical therapy and devices such as a high-frequency chest compression vest
Aerosol heparin
Aerosol tissue plasminogen activator
Cardiac transplantation
Anecdotal or case report evidence
Hyperosmolar saline
Low-dose oral macrolides (clarithromycin or azithromycin)
Oral or inhaled corticosteroids (only for eosinophilic casts)
Thoracic duct ligation
Modifications of Fontan (fenestration or take down)
No evidence and not recommended
β-agonist aerosol
Dornase alfa (Pulmozyme)
Mucolytics such as *N*-acetylcysteine
Expectorants such as guaifenesin
Nonmacrolide antibiotics

bronchitis. Heparin has no effect on preformed fibrin but has been shown both to reduce mucin secretion and to prevent tissue factor activation of the fibrin pathway. Heparin also has anti-inflammatory properties and is far less irritating to the airway, and is less expensive than some of the other agents. A trial of aerosolised heparin at a dose of 5000 units every 4 h should be considered.

Isolated reports suggest that inhaled anticholinergics may reduce cast formation. Although there has been a concern that inhaled anticholinergics may "thicken" secretions, this has not been the case when these have been used to treat asthma, CF or COPD. There is no role for the use of antibiotics to treat bacterial infection in plastic bronchitis. However, low-dose macrolides can decrease mucin production by inhibiting extracellular regulated kinase (ERK1/2). There are case reports suggesting that low-dose macrolides can attenuate the severity of plastic bronchitis, similar to their use in CF or diffuse panbronchiolitis.

In patients with documented abnormal pulmonary lymphatic flow, lymphangiography and percutaneous access of the thoracic duct, followed by embolisation with *N*-butyl cyanoacrylate glue and coils, resolves casting in most patients.

Airway clearance appears to be among the safest of therapies (table 2). Once plastic bronchitis has been diagnosed, starting the daily use of a high-frequency chest compression vest for those with an effective cough, or the Cough Assist device (Philips Respironics) for those with impaired cough, can prevent cast reaccumulation. We also recommend exercise as an effective form of airway clearance if possible, as well as good nutrition, which can consist of protein repletion in children with protein-losing enteropathy, and sometimes weight loss, especially in obese adults with plastic bronchitis.

The future

It is not clear what percentage of patients with plastic bronchitis have lymphatic abnormalities. However, owing to the impressive therapeutic benefit of thoracic duct embolisation in these patients, it is recommended that all patients with this

condition undergo DCMRL imaging. In cases of abnormal pulmonary lymphatic flow, embolisation of the thoracic duct is recommended as a first-line therapy.

Through the US National Institutes of Health, Office of Rare Diseases, we have established an International Plastic Bronchitis Registry to collect data on patients throughout the world (ClinicalTrials.gov identifier NCT01663948). This will help us to generate hypotheses that can be tested clinically, and potentially will allow us to use genome or inflammasome screening to interrogate potential causes for this devastating disease. We have also set up a tissue repository of expectorated bronchial casts, and with an approved protocol, we will make these available to investigators interested in studying this devastating disease. Information can be accessed through the ClinicalTrials.gov website or by contacting the authors of this chapter.

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Haemangiomas, lymphangiomas and papillomatosis

Thomas Nicolai

Haemangiomas

Airway haemangiomas are benign capillary tumours. Between 4% and 5% of infants will have cutaneous haemangiomas (more commonly females), and of these, 1–2% will have airway haemangiomas. Those with haemangiomas with a "beard distribution" are more likely to have airway haemangiomas. About 25% of airway haemangioma cases also have involvement of the skin.

Haemangiomas have a predictable time course of proliferation over the first few months of life, followed by involution between 9 and 12 months of age. Management is predicated on this known time course.

The most common benign capillary tumours in the paediatric airway are subglottic and glottic haemangiomas, which may be present at birth and usually grow for the next 4–6 months. Haemangiomas of the lower airways have been described but are rare. Laryngeal haemangiomas can also be part of larger haemangiomas that may extend into the intrathoracic cavity.

Clinical signs

Sometimes, the haemangioma may be present at birth, leading to neonatal inspiratory stridor. This early presentation is rare, however. In a typical case, inspiratory stridor develops over the first 4–12 weeks of life, depending on the size of the haemangioma and its rate of growth. Clinical symptoms may include feeding problems as well as failure to thrive. Often, an acute viral airway infection will acutely increase the pre-existing airway obstruction caused by a haemangioma.

Key points

- Haemangiomas are benign and respond to propranolol.
- Lymphangiomas may need to be resected if they obstruct the airway; the clinical course is less predictable.
- Papillomatosis of the larynx may require repeated surgical resection and often responds to cidofovir.
- Newer therapies are currently being explored for lymphangiomas and papillomas.

The most common differential diagnosis is croup or laryngomalacia. In contrast to croup, the symptoms caused by a laryngeal or tracheal haemangioma exacerbated by a viral infection will not fully disappear after the acute phase of the respiratory infection and may actually progress to overt respiratory insufficiency. Often, an expiratory component of the stridor becomes apparent with critical obstruction, and the voice or cry is changed in quality and loudness. The resulting biphasic stridor is an alarm sign, indicating critical airway narrowing.

In neonates and infants with stridor, all other possible causes of upper airway narrowing such as congenital malformations or acquired stenoses of the larynx and trachea must be included in the differential diagnoses.

Diagnosis

The diagnosis is suspected by a typical history and an inspiratory but sometimes also expiratory noise. Laryngotracheoscopy (usually performed with a flexible endoscope) is often the easiest way to diagnosis whether a subglottic haemangioma is suspected based on clinical signs and history. Subglottic haemangiomas have a quite typical appearance (figure 1a) and may form a rounded unilateral or bilateral structure in the subglottic area. The surface is smooth and often has a reddish colour. In very rare cases, a biopsy may be needed, and histology and staining for glucose transporter 1 (GLUT1) protein will establish the diagnosis.

A very useful instrument for diagnosis is ultrasound, which can delimit the typical subglottic tumour structures. In theory, an MRI scan can show the typical blood-filled glottic or subglottic rounded structure. However, care must be taken as children may need sedation for MRI scans, and when these children are intubated for this purpose, the haemangioma will be compressed by the endotracheal tube and may then be missed. The intubation procedure itself can also be quite dangerous with damage to the subglottic area or even bleeding. Therefore, airway endoscopy is recommended as the diagnostic procedure.

Figure 1. a) Subglottic haemangioma almost totally obstructing the airway. b) The same subglottic haemangioma much reduced in size after 1 week of treatment with propranolol (2 mg·kg^{-1}·day^{-1}).

Therapy

Mortality without treatment has been reported to be 50%. Therapy used to rely on long-term systemic steroids with all their known side-effects. Intralesional local application of steroids was also tried but with limited success. Almost two-thirds of the children were eventually tracheotomised. Various methods of removing the haemangioma surgically have been described. Careful endoscopic laser resection has been reported to be quite successful in avoiding tracheotomy in almost all cases and is likely to remain a good option in nonresponders to propranolol.

Before these therapeutic options became available, many children had to remain tracheotomised for 2–3 years until the size of the malformation had become small enough to allow decannulation. However, recently it was found by a serendipitous discovery that propranolol will shrink haemangiomas and arrest further growth (figure 1b). Propranolol targets vascular tone, angiogenesis and apoptosis, and inhibits the proliferation, migration and tube formation of haemangioma cells through hypoxia inducible factor-1α (HIF-1α)-dependent mechanisms.

Currently, therapy consists of the administration of propranolol (1–2 $mg \cdot kg^{-1} \cdot day^{-1}$ or in some cases up to 3 $mg \cdot kg^{-1} \cdot day^{-1}$), sometimes (in severely dyspnoeic children) accompanied by initial short-term (several days) steroid therapy (*e.g.* prednisolone 1–2 $mg \cdot kg^{-1} \cdot day^{-1}$). If effective, propranolol is usually administered over the growth period of the haemangioma and often until the child has reached 1 year of age, and is tapered before discontinuation. However, there are no current generally accepted guidelines regarding the dosage or duration of propranolol therapy for airway haemangiomas.

Using this strategy, it is usually possible to avoid tracheostomy, as only ~14% of infants with an airway haemangioma are nonresponders. Catch-up growth of airway haemangiomas in infants after cessation of propranolol has been reported in ~7% of children and may need extended therapy. Refractoriness of the regrowth to propranolol has been described. The long-term prognosis of this tumour is excellent.

Lymphangiomas

Lymphangiomas are not neoplastic growing lesions but malformations of the lymphoid tissues affecting the upper airways and lungs in a complex fashion. It is assumed that these malformations originate from primitive lymphatic sacs, formed of mesenchymal or epithelial embryonic tissue. Dysplastic lymph capillaries do not allow normal drainage of interstitial fluid and lead to tissue swelling and cystic transformation of the affected structures. This malformation is not usually confined to specific organs and may involve larger regions of the body. This explains the changeable course of the size of the lymphangioma with, for example, sudden increases in size of pharyngeal masses during viral infections or following bleeding into the lymphangioma. It also explains why therapeutic options are sometimes limited: total resection of the affected tissue is not always possible, and remaining (often clinically unapparent) malformed regions may later expand in size when drainage of the lymphatic fluid is obstructed. Other manifestations of lymphatic malformations (lymphangiectasis, lymphangiomatosis and lymphatic dysplasia syndrome) may concern the whole lung and/or mediastinum and lead to chylothorax and respiratory failure.

Clinical signs

Lymphangiomas can involve the pharynx and larynx and lead to severe airway compromise. In ~50% of cases, the lymphangioma may be present at birth,

Figure 2. Lymphangioma of the larynx infiltrating the right dorsal aspect.

being visible as a cranial, pharyngeal or neck mass, and/or leading to neonatal inspiratory stridor. In 90% of cases, symptoms are present by 2 years of age. Clinical manifestations may also occur later in life, for example with swelling due to an acute viral infection or when bleeding into the lymphangioma leads to an abrupt increase in lesion size. Other rare disease entities from the spectrum of lymphatic dysplasia will lead to different clinical presentations, such as respiratory failure due to chylothorax in pulmonary lymphangiectasis.

Diagnosis

Antenatal diagnosis on MRI is sometimes possible. The organ-specific involvement and results of imaging studies (usually MRI) will allow the classification of primary lymphatic dysplasias. In the case of lymphangiomas involving the airways, an endoscopy shows an obstructing mass, which may have a typical multicystic appearance, and allows a biopsy (figure 2). The individual findings obviously depend on the exact location and nature of the malformation. MRI scans will delineate the extension of the lymphangioma into adjacent tissues (figure 3).

Figure 3. MRI showing lymphangioma of the larynx.

Therapy

Therapeutic options include surgical resection, infiltration with sclerosing agents, interferon-α2b and laser resection, but the optimal selection of therapy requires considerable experience. The natural history of lymphangiomas is less benign than that of haemangiomas, as involution is not seen regularly.

Future developments

Recently, the use of sildenafil seems to be a promising new therapeutic approach as described in case reports, but controlled studies are only currently under way (*e.g.* ClinicalTrials.gov identifier NCT02335242). Another promising therapeutic agent in complicated refractory lymphangioma is sirolimus.

Papillomatosis

Recurrent respiratory papillomatosis of the larynx in children is the most common tumour of the paediatric larynx, and involvement of the lower airways can occur. Clinically, most cases in children are due to infection by human papillomavirus (HPV) types 6 and 11. The annual incidence of recurrent respiratory papillomatosis has been estimated to be two to four per 100 000 of the population. The risk is increased in HIV-infected children.

There is a high-risk triad comprising teenaged primigravid mothers, vaginal delivery and first-born children. The risk is related to prolonged contact of the newborn's upper airways with the genital tract of the HPV-infected mother during delivery. The infection is caused by transmission during birth from the mother's genital lesions to the child's airways. A caesarean section can reduce but not totally eliminate the infection risk. However, very few children born to mothers with genital HPV infections later develop airway papillomatosis and therefore individual risk factors must also play a role in disease manifestation. Subtle complex abnormalities of the immune response to HPV have been found in these patients.

Clinical signs

The usual time point of clinical manifestation in children is 3–4 years of age. Clinical signs include progressive dyspnoea, hoarseness and stridor. A later presentation in adults is also seen. Papillomas can grow quite large and obstruct the laryngeal opening completely, and they may extend into the lower airways.

Diagnosis

A persistent hoarse voice or voice change with stridor warrants laryngoscopy. Laryngotracheoscopy will show the typical cauliflower-like appearance of growth, usually above the vocal folds (figure 4), and a biopsy will allow identification of the HPV type. The lesion may also involve the glottis and subglottic region.

Manifestation at <3 years of age and more than four surgical procedures to remove airway-obstructing papillomas are associated with a more aggressive clinical form, which will need more frequent interventions and may not resolve spontaneously.

Therapy

Therapy may include resection of the papillomas, either surgically or with a microdebrider or laser. However, utmost care must be taken not to cause secondary airway stenosis. It must be kept in mind that papillomatosis itself does not lead to

Figure 4. Papillomatosis of the larynx with obscured vocal folds.

scarring and once overcome will leave a normal larynx. However, surgery sometimes leads to highly dangerous laryngeal scarring at the level of the vocal fold, in particular if the resection of the papillomas has either been too aggressive including more than one vocal cord during one session, or if resection was close to the anterior commissure of the vocal folds. The use of laser surgery may lead to heating of structures below the level of the papillomas such as the vocal fold, thereby causing damage with scar formation. These scars can lead to complete airway obstruction and tracheostomy. Children with airway papillomatosis and tracheostomy are at risk of generalisation of the papillomatosis to the lower airways (trachea and bronchi) where eradication of the papillomas is usually impossible.

A therapeutic modality that is widely used is the virustatic drug cidofovir. This antiviral has shown clinical effectiveness in treating adults with AIDS and systemic HPV infection, and is also used widely to infiltrate papillomas locally. There are no good randomised studies, but well-documented case series in children and adults with aggressive papillomatosis show that ~60–80% of patients will respond, with the therapy leading to less frequent interventions for papilloma resection or even disappearance of the lesions.

From experiments in cell cultures and marker expression studies, some concern has been voiced that cidofovir may increase laryngeal cancer risk. However, this cancer has never been clearly attributed to cidofovir use, and papillomatosis itself can lead to airway cancer when it is present for many years. A recent study assessing its safety in a large number of patients found no increase in laryngeal malignancies (Tjon Pian Gi *et al.*, 2013). Therefore, in cases with aggressive disease, cidofovir may be useful and is sometimes the only option available. However, parents must be informed about their choices and the possible side-effects of the drug and the infection itself. In HIV-infected children, antiretroviral therapy must be added to the treatment.

Case series have shown a partial response of papillomatosis to high-dose (25 $mg \cdot mL^{-1}$, 5–45 mg total per treatment) intralesional injections of bevacizumab, without clinical side-effects. In extremely severe treatment-resistant papillomatosis in adults, systemic administration (5–10 $mg \cdot kg^{-1}$ every 2–4 weeks) showed improvement with no clinical complications. Possible side-effects of systemic therapy in adults with malignancies include hypertension, gastrointestinal perforation and thromboembolism.

The therapeutic use of quadrivalent vaccines against HPV including types 6 and 11 has shown promise, reducing the frequency of required interventions in established

disease. The effect is believed to be linked to decreased local re-infection at surgical resection sites due to increased antiviral antibodies. Vaccination has been recommended in recent reviews. However, controlled studies are currently lacking.

In rare cases, a generalised HPV infection of the lung follows tracheobronchial dissemination, resulting in cavitation. This is typically seen on CT scans of the lung. It is more frequent in adult patients, and it may be difficult to differentiate this from carcinoma formation.

Future developments

Recent research has elucidated that in many people HPV is present in the airway mucosa without overt papillomatosis and that the oncogene Rac1 (Ras-related C3 botulinum toxin substrate 1) is overexpressed in the epithelium of these individuals. The downstream product of Rac1, cyclo-oxygenase-2 (COX-2), can be blocked with a COX-2 inhibitor, which leads to diminished HPV transcription in cell culture. An initial study treated three patients with the COX-2 inhibitor celecoxib and achieved disease remission in all of the patients (Lucs *et al.*, 2012). A prospective study has been initiated (ClinicalTrials.gov identifier NCT00571701), but the initial unpublished data seem to show no proof of general efficacy. Other agents that have been tried for papillomatosis but for which no clear benefit has as yet been demonstrated convincingly include artemisinin and propranolol, while interferon seems effective but has had unacceptable side-effects in some children.

Vaccination programmes against HPV will hopefully reduce the frequency of this worrisome disease. The pre-vaccination prevalence of HPV in Australia was estimated as one in 100 000 of the population and has decreased to almost one-tenth of this value after the introduction of HPV vaccination programmes.

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Lung and mediastinal tumours

Amalia Schiavetti and Giulia Varrasso

Lung tumours

Primary tumours

Primary pulmonary neoplasms are rare in children, while metastatic disease or inflammatory/congenital diseases are recognised more frequently.

Clinical picture

Primary pulmonary tumours in children present with nonspecific symptoms. Some lesions are found incidentally on radiological studies requested for unrelated medical diseases. Common presenting symptoms include cough, chest pain, haemoptysis and shortness of breath, and may mimic common entities. Most patients are initially diagnosed as having pneumonia, which contributes to a delay in diagnosis.

Diagnosis

The initial work-up consists of baseline laboratory tests and chest radiography. Persistent symptoms or persistent radiological findings despite therapy require a CT scan and/or chest MRI as well as evaluation by a pulmonologist. CT is most useful for parenchyma lesions, whereas MRI provides better visualisation of soft-tissue lesions, vascular anatomy and masses of the mediastinum. The presence of a suspicious mass lesion can require biopsy procedures by bronchoscopy for endobronchial lesions or

Key points

- Primary pulmonary neoplasms are rare in childhood; metastatic disease or inflammatory/congenital diseases are recognised more frequently.
- The most common primary lung malignancies in children are pleuropulmonary blastoma and carcinoid tumour; bronchogenic carcinomas are exceptionally rare.
- Symptoms of primary lung tumours in childhood are nonspecific (cough, haemoptysis, chest pain or shortness of breath); persistent symptoms or persistent radiographic findings despite therapy require a CT scan and/or chest MRI.
- Tumours arising in the anterior mediastinum are most commonly due to lymphoma followed by germ cell tumours; large masses present life-threatening airway compromise, especially during anaesthesia.

thoracoscopy/mediastinoscopy for peripheral or mediastinal lesions. Bronchoscopic evaluation should consist of gross inspection. Tracheal and endobronchial tumours are most likely to be carcinoid tumours or mucoepidermoid carcinomas, both malignant processes. Tissue biopsy of endobronchial lesions can be performed, although this procedure is opposed by some authors because of the risk of fatal haemorrhage. If attempted, endobronchial biopsy should be done in a setting where thoracic surgery is immediately available. Recently, minimally invasive image-guided biopsy has been performed.

A history of a congenital cystic malformation of the lung has been reported to increase the risk of lung malignancy. It is thought that these malformations may undergo malignant degeneration over time.

Prognosis and treatment

In adults, ~80% of lung tumours are carcinomas. In children, pleuropulmonary blastoma (PPB), inflammatory myofibroblastic tumour and carcinoid tumour are frequently recognised. The prognosis and treatment are dependent on the histology and stage.

Malignant tumours

Pleuropulmonary blastoma

PPB is a rare malignant embryonal mesenchymal neoplasm of the lung and pleura, first described in 1988. This tumour occurs almost exclusively in children <6 years of age. Three subtypes of PPB have been described:

- Type I is cystic and lacks a solid component
- Type III is solid without a cystic component
- Type II consists of a mixture of solid and cystic components

PPB has a propensity to metastasise to the brain. The differential diagnosis for type I PPB includes more common benign cystic lung malformations. Chemotherapy and complete surgical resection can improve survival. Radiotherapy is rarely applied. The overall 2-year survival is 63% (type I 80%, type II 73%, type III 48%). PPB is a strikingly familial cancer with genetic implications for others in the immediate and extended family. In fact, in ~25% of cases, PPB is associated with other extrapulmonary lesions in the same patient or family members. PPB has been linked to a mutation in the *DICER1* gene in ~66% of cases as part of a predisposition syndrome for different types of tumours.

Carcinoid tumour

Carcinoid tumour is considered a low-grade neuroendocrine carcinoma due to its potential for locally aggressive growth and low potential for metastasis. These lesions are typically obstructive endobronchial masses in older children and adolescents and tend to be endobronchial, which probably explains the presentation with haemoptysis. A carcinoid tumour can secrete serotonin and kallikrein and can cause carcinoid syndrome characterised by flushing and diarrhoea. This tumour has somatostatin receptors and is positive on an octreotide scan. The outcome is related to the extent of disease and to the tumour resection.

Mucoepidermoid carcinoma

Mucoepidermoid carcinoma is typically an exophytic polypoid mass that causes bronchial obstruction. CT can show calcifications in 50% of cases.

Inflammatory myofibroblastic tumour

Inflammatory myofibroblastic tumour has traditionally been considered benign and is known by many names including plasma cell granuloma and inflammatory

pseudotumour. In 2006, the World Health Organization defined inflammatory myofibroblastic tumour as an intermediary lesion with clinical relapse and malignant potential. It appears as a nodular lesion, more frequently intraparenchymal. Surgical resection is the treatment of choice, although chemotherapy has been proposed as an adjuvant therapy.

Benign tumours

Among benign lung tumours, hamartoma may present as a large parenchymal mass located peripherally. Chest CT classically shows fat and "popcorn" calcifications. The lesion should be removed surgically.

Metastatic tumours

Metastatic lung tumours are more common than primary lung malignancies in children, and may be excised for diagnosis, staging or therapeutic purposes. Metastatic tumours account for ~80% of all lung tumours in children. Wilms tumour, lymphoma, hepatoblastoma, rhabdomyosarcoma, Ewing sarcoma, osteosarcoma and gonadal tumours can produce metastases in the lungs, both isolated and multiple (figure 1).

Secondary involvement of the lung in systemic diseases

Langerhans cell histiocytosis

In multisystem Langerhans cell histiocytosis, the disease presents in multiple organs including the lungs. The lung is considered a high-risk organ. Chest radiography may show a nonspecific interstitial infiltrate. A chest CT is needed to visualise the cystic/nodular pattern of Langerhans cell histiocytosis, which leads to the destruction of lung tissue. Medical treatment following the Histiocyte Society clinical trials is recommended (Aricò, 2016).

Leukaemia and lymphoma

Leukaemic infiltration of the lung may cause a pattern radiographically similar to primary infections. Lung involvement by leukaemia usually manifests as patchy interstitial, septal or pleural infiltrates in contrast to non-Hodgkin and Hodgkin lymphomas, which tend to form larger, well-circumscribed nodules. An associated mediastinal mass or hilar adenopathy is a variable feature.

Figure 1. Metastatic Wilms tumour in a 9-year-old girl. a) Axial chest CT showing bilateral, large hilar nodes and multiple round lung lesions with right pleural thickening. b) Chest axial CT performed after chemotherapy showing a dramatic decrease in parenchyma lesions and hilar nodes. There is no pleural involvement.

Mediastinal tumours

Tumours in the mediastinum are best characterised by the compartment in which they arise. Malignant tumours arising in the anterior mediastinum are most commonly due to lymphoma followed by germ cell tumours, while carcinoid tumours and thymoma are more rarely recognised. Tumours of the posterior mediastinum are usually of neurogenic origin, with neuroblastoma being the most common.

Benign tumours are typically teratomas localised in the anterior mediastinum.

Anterior mediastinum

Thoracic lymphoma

Around 60% of all lymphomas in children are non-Hodgkin lymphoma, with Hodgkin lymphoma making up the remainder (figure 2).

Chest radiographs demonstrate a mediastinal mass. MRI is more accurate than CT. Positron emission tomography (PET)/CT imaging is a very sensitive tool in staging patients with lymphoma; recently, PET/MRI has shown comparable sensitivity with reduced radiation exposure. The growth rate in non-Hodgkin lymphoma is often rapid and can cause life-threatening complications. In particular, children with anterior mediastinal masses are at high risk of life-threatening airway compromise during anaesthesia. Large mediastinal masses can cause compression of surrounding mediastinal structures, and patients may have symptoms of airway obstruction or cardiovascular compromise. The additive effects of an anaesthetic with paralysis and positioning during biopsy can lead to acute airway obstruction and death. Lymph nodes in areas outside the mediastinum provide access for tissue diagnosis; in the other cases, a diagnostic and management challenge arises for paediatric surgeons. Some patients at greatest risk require pretreatment of the mass before tissue diagnosis. Biopsy may be obtained by transthoracic puncture under CT or ultrasound guidance. If a patient requires general anaesthesia for diagnosis, the surgeon should have a well-defined and preoperatively established contingency plan. Of the many criteria used to identify children at greatest risk for anaesthetic complications, the peak expiratory

Figure 2. Hodgkin lymphoma in 7-year-old boy. a) Anteroposterior and b) chest lateral radiographs demonstrate a large anterior mediastinal mass lesion.

flow rate (PEFR) and the tracheal cross-section area seem to be the most reliable. General anaesthesia should not be administered to children if the PEFR and a tracheal cross-section area are both <50% predicted.

Chemotherapy is the main component of treatment for childhood non-Hodgkin and Hodgkin lymphomas. Radiotherapy is added in high-risk cases of Hodgkin lymphoma.

Germ cell tumours/teratomas

Mediastinal malignant germ cell tumours include seminomas and nonseminomatous tumours such as teratocarcinoma, yolk sac tumour, embryonal carcinoma, choriocarcinoma and mixed types. Benign tumours are teratomas. A malignant germ cell tumour is generally a complex tumour often containing coexisting benign components. Seminomas lack serological markers, whereas nonseminomatous tumours are often associated with increased serum β-human chorionic gonadotropin or α-fetoprotein levels. CT and/or MRI demonstrate different components such as fat, calcifications and soft tissue. Surgical excision is the therapy of choice in benign tumours such as teratomas. Malignant germ cell tumours are chemosensitive.

Posterior mediastinum

Approximately 90% of posterior mediastinal masses in children are of neurogenic origin. Most are ganglion cell tumours that arise from sympathetic chain ganglia and form a spectrum of disease ranging from highly aggressive (neuroblastoma) to less aggressive (ganglioneuroblastoma and benign ganglioneuroma). About 30% of these contain calcifications on radiological imaging. MRI is the best diagnostic tool. Meta-iodobenzylguanidine scintigraphy is useful for diagnosis of primary tumours as well as of metastasis.

Chest wall tumours

The most common malignant primary tumours of the chest wall arise from bone or soft tissue. They are mostly commonly of the Ewing types (Askin or primitive neuroectodermal tumour). Imaging findings that suggest a malignant chest wall mass include rib destruction, pleural extension and a large size.

Mesenchymal hamartomas of the chest wall are unusual rib lesions most commonly affecting infants. Although the imaging features suggest an aggressive process, mesenchymal hamartomas are benign lesions.

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Sickle cell disease

Tobias Ankermann

The term sickle cell disease (SCD) is used to refer to a haemoglobinopathy that results from a genetic variant giving rise to sickle haemoglobin (HbS). This includes homozygous SCD (HbSS, also known as sickle cell anaemia) and compound heterozygous haemoglobinopathies (*e.g.* HbS-β-thalassaemias, HbSC disease). In Europe, the birth prevalence of homozygous SCD is estimated at 43.12 per 100 000.

HbS haemoglobinopathies cause a chronic haemolytic anaemia and a disease of the blood vessels. HbS is caused by a mutation in the β-globin locus on chromosome 11; HbSS leads to polymerisation and a loss of solubility of the haemoglobin during deoxygenation. The subsequent change in the rheological properties of the erythrocyte leads to dysfunction in the microcirculation with vaso-occlusive crises. Vascular occlusions can occur in almost all organs (*e.g.* skin, lung, liver, spleen, bone, kidney and brain). The clinical consequences of this are acute and chronic pain, hyposplenism (or functional asplenia in older children following splenic sequestration) with secondary immunodeficiency, osteonecrosis, nephropathy and cerebral infarction. The most common causative organisms of infectious complications following secondary immunodeficiency are *Streptococcus pneumoniae*, *Salmonella* spp., *Haemophilus influenzae* type b, *Neisseria meningitidis* and *Mycoplasma* spp. In acute chest syndrome (ACS) of infectious origin, the most commonly identified agents are atypical bacteria and viruses.

The chronic disease of the vessels results in priapism, cerebrovascular disease, hypercoagulability and inflammation of endothelial structures.

Key points

- Sickle cell disease (SCD) includes sickle haemoglobin haemoglobinopathies, which lead to haemoglobin polymerisation with subsequent vaso-occlusion, a chronic haemolytic anaemia and endothelial damage in blood vessels, with consequent chronic organ failure.
- In the lungs and airways, SCD induces acute pulmonary vascular occlusions, acute chest syndrome, lower respiratory tract infections and chronic lung disease with lung fibrosis and pulmonary hypertension.
- Important pulmonary comorbidities of children with SCD are bronchial hyperresponsiveness, atopy and asthma.

In the lungs and airways, SCD leads to acute manifestations (acute pulmonary vascular occlusions, ACS and acute lower respiratory tract infections) and a chronic lung disease with lung fibrosis and secondary pulmonary hypertension with cor pulmonale. Children with SCD often exhibit frequent wheezing, bronchial hyperresponsiveness and bronchial asthma. The comorbidity of SCD and asthma is associated with a higher incidence of vaso-occlusive crisis and episodes of ACS and consequently an increased mortality. The role of OSAS is not yet clearly defined. Chronic pulmonary complications are major contributors to morbidity and mortality in adults.

The keystones of care for SCD are:

- Protection against infections by vaccination against pneumococci, *H. influenzae* type b, *Neisseria* spp. and influenza A virus, and use of antibiotics (prophylactic penicillin in small children, continued until the immunisation series is complete, with pneumococcal polysaccharide vaccine for HbSS and HbS-β^0-thalassaemia)
- Early intervention to prevent disease progression if pain or fever occurs
- Optimal asthma therapy
- Working with haematologists to assess hydroxyurea, folic acid and occasionally a transfusion regime
- Screening for arterial hypertension, retinopathy (beginning at 10 years of age) and risk of stroke using transcranial Doppler in children with HbS-β^0-thalassaemia aged 2–16 years

In ACS, oxygen, hydration, analgesia, antibiotics and incentive spirometry (in ACS and in vaso-occlusive crises to prevent ACS) are required.

Acute chest syndrome

ACS is an acute lung injury and is caused by infection, fat embolism, venous thromboembolism, vaso-occlusion or a combination of these factors. It is defined as respiratory signs and/or symptoms (cough, tachypnoea, chest pain, retractions, rales, crackles, wheezing and hypoxaemia) and/or new infiltrates on chest radiography and fever (>38.5ºC) (table 1). One-third of children with ACS complain of abdominal pain and pain in their extremities. Figure 1 shows a practical approach to the diagnosis of ACS. The discrimination of ACS from pneumonia or other lower respiratory tract infections is often difficult but not essential for treatment. Children with suspected or manifest ACS should be admitted to hospital for close observation of their clinical and respiratory status. Treatment should be initiated early and is based on the administration of oxygen to counter the polymerisation of HbS.

Table 1. Clinical criteria for the diagnosis of ACS in children with SCD

A new pulmonary infiltrate detected by chest radiography involving at least one complete lung segment that is not consistent with the appearance of atelectasis
and
One or more of the following signs or symptoms:
Cough
Signs of increased work of breathing (retractions, tachypnoea)
Chest pain
Wheezing
Rales
Body temperature >38.5ºC
Hypoxaemia relative to baseline measurement

Figure 1. Outline of a practical approach if the criteria for ACS are met in children with SCD. Adapted from Miller (2011).

The keystones of ACS therapy are:

- Antibiotic treatment (third-generation cephalosporin or amoxicillin/β-lactamase inhibitor plus a macrolide; consider vancomycin if methicillin-resistant *Staphylococcus aureus* is suspected)
- Inhalation of β_2-sympathomimetics
- Intravenous hydration
- Analgesia
- Incentive spirometry

If the haemoglobin concentration decreases (≥2 $g \cdot dL^{-1}$ below individual baseline) or P_{aO_2} decreases to <70 mmHg (*i.e.* below the normal range during oxygen therapy), then blood transfusion is indicated. One small trial (DeNOVO) suggested that patients with ACS and early transfusion had an improved outcome when compared with historical data (Vichinsky *et al.*, 2000). In very severe cases, an exchange transfusion should be considered. Extracorporeal membrane oxygenation and nitric oxide are therapy options in very severe cases but are not standard therapies.

The use of glucocorticoids is controversial. In mild ACS, positive effects have been described, but there are reports that administration of glucocorticoids in ACS leads to relapse after sudden termination, reactive vaso-occlusive disease and longer hospitalisation. In children with ACS on artificial ventilation, it may be necessary to perform bronchoscopy and to apply DNase to remove mucus and/or bronchial casts. Figure 2 outlines the procedure and therapy for ACS.

Figure 2. Procedure and therapy if the criteria for ACS are met in children with SCD. CRP: C-reactive protein; LDH: lactate dehydrogenase; BUN: blood urea nitrogen; PEP: positive expiratory pressure; Hb: haemoglobin; ECMO: extracorporeal membrane oxygenation. Adapted from Miller (2011).

Chronic lung disease in SCD

Fibrotic remodelling of the lung occurs due to changes in the structure and function of the endothelium and the metabolism of nitric oxide. ACS and asthma are important risk factors for this process. PFTs in preschool children are mostly unaffected but sometimes demonstrate an obstructive pattern. A restrictive pattern occurs, beginning in the second decade. In the third decade, there can be a progressive decline in TLC and diffusion capacity. CT may show ILD.

Atopy, asthma and bronchial hyperresponsiveness are important comorbidities in children with SCD. The prevalence of asthma in children with SCD is between 20% and 48%. Children with SCD and asthma and/or specific sensitisation suffer more frequent and earlier episodes of ACS. Wheezing in SCD may also be related to the inflammation induced by the disease itself. The paediatric pulmonologist should examine children with SCD when they are well on an individual basis (every 4 months in young children with SCD and respiratory comorbidities; every 6–12 months in older children with HbSS and HbS-β^0-thalassaemia). Integral parts of the consultation are:

- History
- Recording of S_{aO_2} in room air
- PFTs, only in symptomatic children (according to age, including diffusion capacity in older children)
- Echocardiography to rule out pulmonary hypertension, only in children with symptoms suggestive of pulmonary hypertension (*e.g.* exertional dyspnoea, fatigue, syncope)

- Allergy tests (skin-prick test or specific IgE)
- Checking for signs and symptoms of OSA

If a decline in lung function or a specific sensitisation is detected in a patient with asthma, lung function should be tested every 6 months.

Children with abnormal overnight S_{aO_2} levels (<95%) and/or abnormal PFTs should be screened for OSA and obstruction of the upper airways, ILD and pulmonary hypertension. At present, there is no specific therapy for chronic lung disease in SCD. Asthma in SCD is associated with ACS, a faster decline in lung function and increased mortality, and should therefore be managed based on established asthma guidelines. In childhood, pulmonary hypertension is less common. Therefore, evidence-based recommendations for the treatment of pulmonary hypertension in children with SCD are lacking. The use of sildenafil, bosentan and prostacyclins has been reported.

Course of lung disease in SCD

Children with SCD demonstrate a decline in lung function with increasing age, accompanied by decreasing exercise tolerance. The incidence of ACS and comorbidity with asthma are important risk factors for the development of chronic lung disease and mortality later in life. With optimal care, children with SCD are able to reach the sixth decade of life. Without structured care, many children will not reach adulthood.

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Physiology and pathophysiology of sleep

Frederic Proulx, Valeria Caldarelli and Refika Ersu

Sleep is an active neurophysiological process and primary activity of the developing brain. Sleep is part of the daily routine for humans and operates in a 24-h cycle. Research demonstrates that adequate sleep in children is essential for normal growth and development; moreover, it is a predictor of adult health. Physiological parameters including brain activity, muscle tone and cardiorespiratory control differ in sleep *versus* wakefulness. The homeostatic process regulates the moment in which we fall asleep and the moment in which we wake up. More precisely, the two-process model of sleep and wakefulness predicts the day-to-day synchronisation of an organism with its environment by the interaction of a circadian (process C) and a homeostatic process (process S). During sleep, an ultradian rhythm determines the timing and duration of sleep states. The ultradian rhythm refers to the alternation of two distinct types of sleep throughout the sleep period: non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. Each type is associated with distinctive levels of arousal, autonomic response, brain activity and muscle tone. Sleep duration, quality and architecture change over the lifespan, particularly in the first 5 years of life.

Neural mechanisms of sleep from newborn to adolescent

Maturation of sleep depends on and reflects the maturation of the central nervous system (CNS), so there is a different sleep structure in newborns, children and adolescents. Sleep stages can be determined only by overnight PSG, which includes

Key points

- Sleep is an active neurophysiological process essential to normal growth and development, and physiological changes from newborn age to adulthood.
- Newborn and infant sleep stages are characterised differently to those of older children and adolescents.
- A two-process model of sleep regulation, describing process S (sleep homeostasis) and process C (circadian timing of sleep and waking), is used to define the interaction between sleep and wakefulness.
- Insomnia is the most common sleep disorder in children.

an electroencephalogram (EEG), electro-oculogram (EOG) and chin electromyogram (EMG) monitoring, with standardised methods used to score the sleep stages. During sleep, all humans cycle between different sleep stages, and this is called the sleep cycle.

Newborn to 6 months of age

The American Academy of Sleep Medicine (AASM) guidelines suggest using the newborn criteria in infants aged <2 months:

- Active sleep is characterised by low-voltage irregular or mixed EEG activity, rapid eye movements, movement and irregular heart rate
- EMG activity may be decreased or absent, consistent with REM sleep in adults
- Quiet sleep is characterised by high-amplitude, mixed-frequency EEG and trace-alternant EEG activity, few body movements, and regular respiration and heart rate
- Indeterminate sleep is scored when features of both active sleep and quiet sleep are present in the same epoch

Children and adolescents

Children and adolescents have two sleep states:

- REM sleep
- NREM sleep with further subdivisions into stages 1–2 (N1, N2), based on the predominant EEG frequency pattern, and stage N3 denoting slow-wave sleep

Development of the structure of sleep from the newborn to the adolescent

Sleep changes physiologically from the neonatal to adolescent age. After birth, features of adult sleep emerge following the development of the CNS. For each age, there is an EEG aspect and different qualities and quantities of sleep.

- Spindles are a transient EEG phenomenon with waves of 12–14 Hz lasting ≥0.5 s. They appear as early as 3–4 weeks post-natal age, but are typically seen by 6–8 weeks post-natal age and reflect the development of thalamocortical structures as well as neural maturation. A nadir occurs at ~2 years, before reaching a maximum at ~11 years of age. Sleep spindles are characteristic features of stage 2 (N2).
- Dominant posterior rhythm (DPR): at 3–4 months of life, infants show irregular 50–100 µV, 3.5–4.4 Hz background activity over the occipital area. It is similar to an alpha-rhythm in older children and adults.
- K complexes: these appear from 5 to 6 months post-term. K complexes consist of a sharp negative (up to 200 mV) deflection followed by a lower positive deflection; the complex lasts >0.5 s, and is maximal over the frontal scalp region. From their first appearance, K complexes increase in amplitude to reach a maximum at ~3–5 years of age. K complexes are characteristic features of stage 2 (N2).
- Delta activity appears at ~2–3 months of age.
- NREM sleep stages are differentiated between 3 and 6 months of age, with the majority of infants demonstrating clear differentiation of NREM sleep stages by the age of 6 months.

Sleep cycle length

Sleep cycles lengthen throughout childhood, and sleep duration becomes shorter. In infants, sleep cycles last ~50 min. They reach maturity around middle childhood,

lasting between 90 and 110 min. It is important to understand that each sleep cycle usually ends with brief arousal with a rapid return to sleep. Spontaneous arousals during sleep, especially at the end of a sleep cycle, are normal. Arousal threshold is at its lowest during N1 sleep and is highest during N3 sleep, meaning it is easier to wake from N1 than N3 sleep.

At term, infants spend up to 50% of their sleep time in active sleep. From birth, the proportion of quiet sleep increases while active sleep decreases, such that slow-wave sleep occupies more sleep time than REM sleep by 1 year of age. Throughout development, the amount of REM sleep decreases, accounting for approximately 25–30% of the night in children and 20–25% of the night in adolescents. Early childhood is a time of predominant N3 sleep, with a rapid decrease in slow-wave sleep during adolescence (a decline of ~50%).

Sleep duration

At birth, the circadian rhythm is not fully developed, so sleep can occur as easily during the daytime hours as during the night. The normal full-term newborn sleeps ~16–18 h per day. This sleep time gradually decreases over the years. In the first year of life, night-time sleep gradually becomes a single continuous block, and daytime sleep gradually decreases over the first 3 years. By the age of 4 years, most children no longer require a daytime nap. Night-time sleep needs gradually decrease to become similar to the needs of an adult by adolescence. The National Sleep Foundation has published ranges of sleep duration in 24 h for each developmental stage. This can provide some guidance for parents, who often wonder if their child sleeps enough. Although most children's sleep duration will fall within the recommended time ranges, some children may need more or less sleep. It is important to understand that multiple studies have shown that sleep looks more like a growth curve, with significant variability at each age. The variability in total sleep time is greater in infancy than at any other developmental period, with a range of 12–18 h in 24 h.

Circadian rhythms and sleep and waking homeostasis

Sleep is regulated by two overlapping systems: the circadian system and sleep–wake homeostasis. The circadian system endogenously synchronises biological rhythms, including sleep, cyclically with the 24-h day. The circadian system is adjusted through the influence of a separate system driven by exogenous factors. Sleep–wake homeostasis describes the body's internal neurophysiological drive toward a balance between sleep and wakefulness. Sleep–wake rhythms are linked to the rhythm of other functions, including endocrine hormone secretion, core body temperature and sensory processing.

The biological two-process model of sleep regulation is used to define the interaction between sleep and wakefulness. These two processes refer to process S (sleep homeostasis) and process C (circadian timing of sleep and waking).

Process S (the pressure to sleep, or sleep need) is very high during the first part of the night and decreases as sleep duration increases. Therefore, process S increases as the duration of wakefulness increases and decreases as sleep occurs during the night. Sleep pressure/sleep needs change during development: newborns have a low tolerance to sleep loss; as children get older, their daytime sleep need (naps) will taper off around 3–5 years; middle childhood and adolescence display a further increase in sleep loss tolerance, resulting in later bedtimes.

Process C represents the endogenous circadian pacemaker, which is located in the suprachiasmatic nucleus and creates a sleep–wake rhythm that is independent of sleep and wake duration. The human circadian rhythm functions on a cycle slightly longer than 24 h, and zeitgebers (time givers), which are external cues, are crucial to maintaining an effective circadian rhythm. The light–dark cycle is the most prominent regulator of the circadian rhythm. Melatonin is the most critical hormone in sleep–wake cycle regulation. It is secreted by the pineal gland and triggered by dim light; bright light suppresses it. Melatonin release occurs typically 2 h before sleep onset and leads to feeling sleepy.

During waking hours, substances called somnogens are accumulated in the CNS, driving the urge to sleep after long periods. One of the most important somnogen substances is adenosine, which is a byproduct of biological activity in the brain. It accumulates with activity, increasing sleep propensity, and then dissipates with rest and sleep. Adenosine promotes sleep by inhibiting arousal; it activates the hypothalamic ventrolateral preoptic (VLPO) nucleus neurons, which inhibit arousal-promoting centres.

Processes S and C work together to provide wakefulness during the day and consolidate sleep during the night. During the day, as the duration of wakefulness increases, the sleep pressure builds up, and the circadian rhythm maintains wakefulness. During the night, the sleep pressure rapidly decreases, and the circadian rhythm helps maintain sleep. During the early morning, the high level of sleepiness that results from circadian rhythm is counterbalanced by the lack of homeostatic sleep pressure. There are normal individual differences and developmental changes in this process.

In newborns, the sleep–wake rhythm is organised in periods of ~4 h, which are more important than the circadian component of 24 h. The development of the 24-h rhythm during the post-natal period depends mainly on brain maturation and becomes evident ~4 weeks after birth. The circadian rhythms of temperature and melatonin could play a role in the establishment of rhythms at 4 weeks of age. The sleep–wake cycle of the infant is driven by the need to eat frequently. As babies grow, their sleep becomes better consolidated. In young children, as in adolescents, non-respect of time clues can lead to important consequences on the sleep cycle up to a complete inversion of day–night rhythm.

Ultradian rhythms

Sleep has a cyclic organisation that alternates between NREM and REM sleep, with each cycle lasting on average from 90 to 110 min.

NREM sleep makes up the majority of the night and is divided into three stages.

- Stage 1: in this stage, there is an intense sleepiness and sometimes hallucinations and/or brief involuntary muscle contractions. The EEG pattern transitions from alpha-waves, which have a frequency of 8–13 Hz, to theta-waves with a slower frequency (4–8 Hz) (figure 1).
- Stage 2: initiation of true sleep. There is a decreased awareness of outside stimulus and decreased muscle activity. The EEG findings are characterised by sleep spindles and K complexes (figure 2). A sleep spindle represents a phasic burst of 11–16-Hz activity, typically lasting for 0.5–1.5 s. A K complex is an EEG event consisting of a well-delineated negative sharp wave immediately followed by a positive component standing out from the background EEG with total duration ≥0.5 s.

- Stage 3: deep, slow-wave sleep. In this stage, an individual is the least responsive to external stimuli. Parasomnias, night terrors, sleepwalking and nocturnal enuresis can occur in this sleep stage. The EEG pattern is characterised by high-amplitude and low-frequency delta-waves of <3 Hz (figure 3).

REM sleep has a role in memory integration and consolidation and in CNS development. Dreaming and nightmares occur during REM sleep. It is characterised by a burst of rapid eye movements; there is a high brain metabolic rate, a variable heart rate, an active suppression of peripheral muscle tone and a lack of normal thermoregulation. The EEG pattern is characterised by desynchronised cortical activity with low-voltage and high-frequency EEG (figure 4). The first REM period typically occurs between 70 and 100 min after sleep onset and is brief. REM periods increase in length in the last third of the night.

Figure 1. Stage NREM 1 in a 30-s epoch. The EEG presents low-amplitude mixed frequency (<50% alpha-activity) with no spindles or K complexes; sharp waves appear near the transition to stage N2. The EOG shows slow rolling eye movements. EMG activity may be lower than when awake.

Figure 2. Stage NREM 2 in a 30-s epoch. At least one sleep spindle or K complex is seen on the EEG, with <20% slow-wave activity. EMG activity may be lower than when awake.

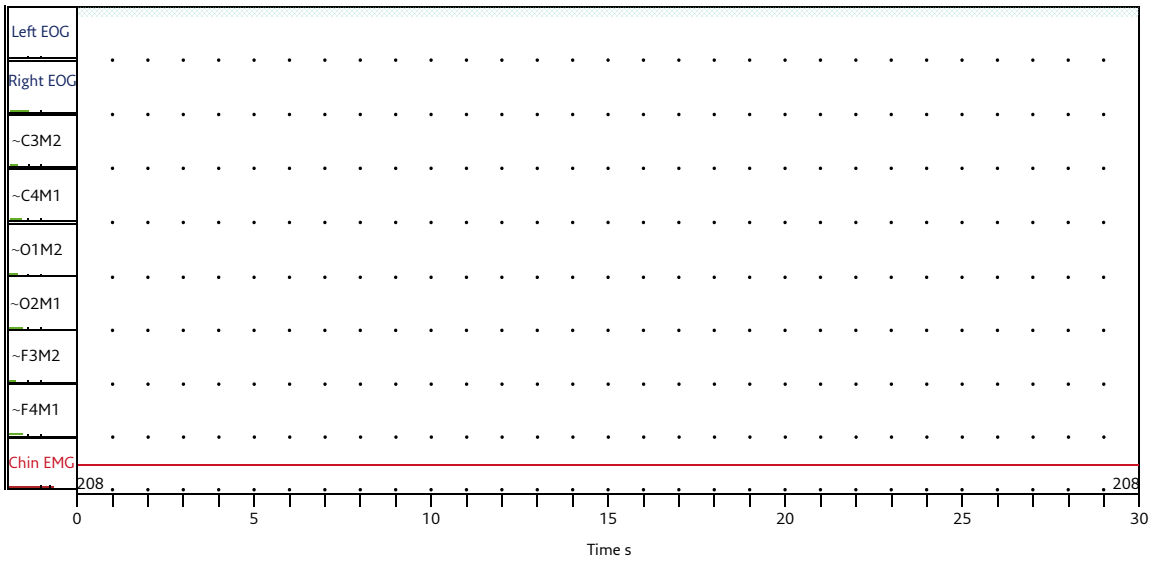

Figure 3. Stage NREM 3 in a 30-s epoch. On EEG, high-amplitude delta-waves occupy >20% of the epoch. EMG activity is usually low.

Figure 4. REM sleep stage in a 30-s epoch. This displays a low-voltage, mixed-frequency EEG, episodic rapid eye movements on EOG, and a relatively reduced EMG (equal to or lower than the lowest seen in NREM sleep).

Neurophysiology of sleep

Ascending arousal system

The sequence of states of alertness (wakefulness, NREM and REM sleep) is mediated by a complex of neuronal networks and neurotransmitters ensuring the transmission of nerve impulses from neuron to neuron ascending from the brainstem and hypothalamus to the cerebral cortex.

There are two anatomical branches of the ascending arousal system: the first branch travels through the thalamus and the second through the hypothalamus and basal forebrain.

- The thalamic branch is primarily composed of cholinergic neurons providing input to the thalamic-relay nuclei and the reticular nuclei of the thalamus, resulting in thalamocortical activation.

- The hypothalamic/basal forebrain branch originates in the brainstem and posterior hypothalamus in the locus coeruleus, dorsal raphe nucleus and tuberomammillary nucleus (TMN) and results in cortical and subcortical activation.

The sleep–wake system

Falling asleep requires the activation of sleep-promoting pathways and deactivation of the arousal pathways. The neurons of the VLPO area and medial preoptic (MNPO) area innervate the nuclei of the ascending arousal system (laterodorsal tegmental and pedunculopontine tegmental nuclei, locus coeruleus, dorsal raphe nucleus, TMN and the orexin/hypocretin neurons) and secrete inhibitory neurotransmitters/neuropeptides (γ-aminobutyric acid and galanin), thus inhibiting arousal.

During sleep, VLPO neurons block cortical activation by inhibiting the neurons of the ascending arousal system. Inhibition of the arousal system leads to a decrease in local monoamine levels, leading to VLPO disinhibition, thus further reinforcing VLPO activity, and therefore further suppression of the arousal system.

Waking is the result of the action of a complex network of monoaminergic neurons distributed from the hypothalamus to the spinal bulb, determining arousal. Information flows from one neuron to another through alternating neurotransmitters such as acetylcholine, glutamate, serotonin (5-hydroxytryptamine), dopamine, noradrenaline or histamine.

In addition, the waking system includes a small group of hypocretin neurons (also known as orexins) located in the lateral hypothalamus. These peptides act as excitatory neurotransmitters of almost all neural networks of awakening.

The sleep and awake states are discrete behaviour states and require a regulatory system that ensures the prompt transition between each state. This is achieved physiologically through mutually inhibitory feedback loops between the sleep-promoting pathways and the arousal pathways.

Pathophysiology of sleep

Sleep disorders are classified by the AASM in the International Classification of Sleep Disorders (ICSD)-3 into six major categories (table 1).

Insomnia

Insomnia is the most common sleep disorder in children and is defined in ICSD-3 as requiring one of the following symptoms to be reported by patient or caregivers: difficulty initiating sleep, difficulty in maintaining sleep, waking earlier than desired, bedtime resistance or difficulty sleeping without an intervention from parent or caregiver. The presence of daytime consequence is also required for the diagnosis.

Table 1. ICSD-3 diagnostic sections

Insomnia
Sleep-related breathing disorders
Central disorders of hypersomnolence
Circadian rhythm sleep–wake disorders
Parasomnias
Sleep-related movement disorders

The pathophysiology of insomnia is unknown. A theory postulates that autonomic, somatic and cortical arousals associated with factors such as stress or predisposing conditions increase sensory processing and results in insomnia.

Sleep disordered breathing

Sleep disordered breathing in children is discussed in chapters "Polysomnography" and "OSAS and upper airway resistance syndrome".

Hypersomnolence

Sleep quantity and sleep quality are two separate sleep domains. Conditions leading to poor sleep quality or quantity may cause excessive daytime sleepiness. Insufficient sleep duration, pain, insomnia, periodic limb movement and sleep disordered breathing can all induce sleep fragmentation, which further decreases sleep quality/quantity, leading to sleepiness. The most common disorder leading to excessive daytime sleepiness among children and teenagers is insufficient nocturnal sleep.

Evaluation of sleepiness starts with a complete sleep history and physical examination. The Multiple Sleep Latency Test (MSLT) is a useful test to measure the degree of sleepiness. It consists of five 20-min periods spaced at 2-h intervals during which subjects are asked to fall asleep while lying in bed in a quiet, dark room during daytime. This test assesses the presence of sleep-onset REM periods (SOREMPs). Nocturnal PSG is performed the night before to rule out other sleep disorders and ensure that subjects are not sleep deprived.

Hypersomnias of central origin

Central disorders of hypersomnolence include narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), idiopathic hypersomnia, Kleine–Levin syndrome, hypersomnia due to a medical disorder, medication or substance, or associated with a psychiatric disorder.

Narcolepsy is classified within CNS hypersomnia and is subdivided into NT1, characterised by cataplexy and low levels of cerebrospinal (CSF) hypocretin (hcrt)-1, and NT2, with normal CSF hcrt-1 and without cataplexy. Narcolepsy is a chronic and lifelong neurological sleep disorder characterised by difficulty maintaining wakefulness and sleep for long periods. The primary symptoms are excessive daytime sleepiness and cataplexy (sudden loss of muscle tone with preservation of consciousness in response to strong emotion) which is considered as the most specific symptom of NT1. Along with excessive daytime sleepiness, the clinical picture of narcolepsy includes hallucinations at sleep onset or offset (hypnagogic or hypnopompic, respectively), sleep paralysis, disrupted night sleep continuity and both REM and NREM sleep-related parasomnia comorbidities. NT1 is caused by a marked reduction in neurons in the lateral hypothalamus that produces a wakefulness-associated neuropeptide (hcrt). Loss of hcrt may lead to abnormal function in sleep and wake regulation systems, resulting in excessive daytime sleepiness and REM sleep-related symptoms. The mechanism underlying the loss of hcrt is unknown, but both genetic and environmental factors play a major role in narcolepsy susceptibility, and autoimmune-mediated mechanisms are hypothesised as underlying factors. >98% of people with type 1 narcolepsy carry HLA-DQB1*0602, a finding that makes this the strongest association between HLA and a disease state. Diagnosing narcolepsy can be challenging in children. Although >50% of patients report symptom onset before the age of 18 years, delayed diagnosis among narcolepsy patients is well described. Increasing paediatric narcolepsy awareness starts with understanding the potential contributing factors to this delay. Children who have excessive daytime sleepiness

may exhibit other symptoms, such as hyperactivity, distractibility, impulsiveness or irritability in an attempt to cope with or counteract their sleepiness. These symptoms can be attributed to attention deficit hyperactivity disorder. Recognition of cataplexy imposes a diagnostic challenge in the paediatric population. The onset of cataplexy can be delayed for years after the onset of excessive daytime sleepiness. Close to disease onset, children may have a distinct presentation of cataplexy. Complex movement disorders with negative or active motor features (head drop, tongue protrusion, raising eyebrows, lip licking/biting) can be seen. In addition, cataplectic facies are described, characterised by facial muscle weakness with manifestations such as drooping eyelids, facial slackening, mouth opening and/or tongue protrusion without any clear emotional triggers.

Presence of two or more SOREMPs on the MSLT is diagnostic for narcolepsy. Although serologic testing for the HLA-DQB1*0602 haplotype is not diagnostic, it is sometimes used as an adjunctive test. CSF hcrt analysis can help in establishing the diagnosis and make the distinction between NT1 and NT2; however, it is not easily accessible in all care facilities.

The treatment of narcolepsy is beyond the scope of this chapter; readers are referred to the further reading list.

Idiopathic hypersomnia is a diagnosis of exclusion. It is defined as a disorder associated with nonimperative sleepiness, long unrefreshing naps and difficulty reaching full awakening. An important difference between idiopathic hypersomnia and narcolepsy is the absence of SOREMPs during the MSLT.

Kleine–Levin syndrome is characterised by recurrent episodes of hypersomnolence, frequently associated with hyperphagia and hypersexual behaviours. Each period can last 1–2 weeks, and sometimes persists for longer. It is seen more commonly in adolescent males. It is a rare condition, and no specific aetiology has been found.

Other medical disorders should be considered in the differential diagnosis. Neurological disorders such as epilepsy or CNS lesions producing increased intracranial pressure can lead to hypersomnia. Sleepiness can be caused by several medications or drug abuse. Psychiatric disorders can also present with an increase in sleep needs.

Circadian rhythm sleep–wake disorders

ICSD-3 classifies circadian rhythm sleep–wake disorders (CRSWDs) as dyssomnias, and they are further divided into six subtypes: advanced sleep–wake phase disorder (ASWPD), delayed sleep–wake phase disorder (DSWPD), irregular sleep–wake rhythm disorder (ISWRD), non-24 h sleep–wake rhythm disorder (N24SWD), jet lag disorder and shift work disorder. These conditions are the result of a problem with the internal biological clock known as the circadian timing system and/or a misalignment between the circadian timing system and the external 24-h environment (school, work, social activities). The major clinical characteristic shared by all these conditions is an inability to fall asleep and wake at the desired time. The advance of the major sleep episode with respect to the patient's desired or required sleep–wake times characterises ASWPD, which implies difficulty staying awake during evening hours and frequently presents with falling asleep before the completion of pertinent work, social and family obligations. DSWPD manifests as a delay of the major sleep episode with respect to the patient's desired timing or the timing required to attend social, educational and/or occupational demands. N24SWD is diagnosed when patients fail to entrain to the 24-h light–dark cycle and clock times. Most patients affected by N24SWD are totally

blind, but it can also occur among sighted persons. Lack of a clear circadian pattern of sleep–wake behaviour characterises ISWRD. Thus, prolonged periods of wakefulness during the typical nocturnal sleep episode in addition to excessive sleepiness and prolonged sleep bouts during daytime hours are experienced by afflicted individuals. The AASM recommends that clinicians use actigraphy, a procedure that records and integrates the occurrence and degree of limb movement activity over time, in the assessment of CRSWD.

Parasomnias

Parasomnias are undesirable physical events or experiences that occur during entry into sleep, within sleep or during arousal from sleep. ICSD-3 classifies parasomnias as occurring in NREM sleep (disorders of arousal) or REM sleep. Several forms of NREM parasomnias exist. They include confusional arousals, sleep terrors and sleepwalking and represent a dissociated state between NREM sleep and full awakenings. The definitive pathophysiology is unknown. They typically occur within the first few hours of sleep, when slow-wave sleep predominates. Potential triggers are conditions that increase the depth of NREM sleep or increase cortical arousals from sleep. Nocturnal seizures should always be considered in the differential diagnosis of parasomnias, which can have overlapping manifestations. Parasomnias typically start with arousal-like behaviours, such as eye-opening, head elevation, staring, face rubbing, yawning and stretching. They typically occur within the first 3 h of sleep, whereas seizures can occur at any time of the night. Parasomnias have variable patterns and gradual offset, whereas seizures tend to be <2 min long and are stereotyped motor patterns with abrupt onset and offset. Triggering stimuli are present in about half of NREM parasomnias, but precede epileptic events less commonly.

Sleep-related movement disorders

Sleep-related movement disorders include several conditions characterised by relatively simple, nonpurposeful and usually stereotyped movements, thus making a distinction with complex movements usually found in parasomnias. These movements occur in sleep, primarily during sleep–wake transitions, and which disturb sleep or its onset. They include restless leg syndrome (RLS), periodic limb movements disorder, bruxism, sleep-related rhythmic movement disorder and benign sleep myoclonus of infancy. Only RLS will be reviewed briefly here. RLS is characterised by unpleasant dysaesthesia, primarily in the legs, and an irresistible urge to move the limbs to relieve sensations. A worsening of symptoms with rest or inactivity and a circadian component (peak in the evening hours) could also be found. The pathophysiology of RLS is related to dopamine dysfunction, which results in increased sympathetic activity. Iron is a cofactor in the rate-limiting step in dopamine synthesis; therefore, iron deficiency indirectly leads to dopamine dysfunction, resulting in RLS. A serum ferritin level <50 $ng \cdot mL^{-1}$ appears to increase the risk of RLS and is typically the threshold used to determine treatment with iron supplementation.

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Polysomnography

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Clinical evaluation alone does not have sufficient sensitivity or specificity to establish a diagnosis of OSAS in children. Following recognition of the child who is at risk of OSAS based on the presence of relevant symptoms and physical findings (such as habitual snoring, witnessed apnoeas, adenotonsillar hypertrophy), an objective tool should be used to diagnose OSAS, to determine severity and the response to treatment. According to the American Academy of Pediatrics clinical practice guideline on childhood OSAS, as well as the European Respiratory Society (ERS) task force statement on OSAS in children (Kaditis *et al*., 2016), attended, in-laboratory, overnight video-PSG is considered the gold-standard diagnostic method. PSG is also used to diagnose and to follow-up children with sleep disordered breathing conditions other than OSAS. Because PSG is a relatively expensive procedure, requiring significant time and healthcare resources, understanding the indications, strengths, limitations and clinical utility of PSG is necessary to ensure optimal utilisation.

Respiratory indications for PSG in children

Diagnosis of sleep-related breathing disorders

PSG is indicated when:

- The clinical assessment suggests a diagnosis of OSAS in children
- The clinical assessment suggests a diagnosis of congenital central alveolar hypoventilation syndrome or sleep-related hypoventilation due to neuromuscular

Key points

- Polysomnography is the gold standard for the diagnosis of sleep disordered breathing in children.
- Paediatric polysomnography should be performed in a sleep laboratory equipped for children and staffed by qualified personnel following the American Academy of Sleep Medicine standards for testing.
- Age-adjusted rules for the scoring and interpretation of polysomnography should be used for children.

disorders or chest wall deformities (it is indicated in selected cases of primary sleep apnoea in infancy)
- There is clinical evidence of a sleep-related breathing disorder in infants who have experienced an apparent life-threatening event

Assessment of response to treatment

Children with mild OSAS pre-operatively should undergo clinical evaluation following adenotonsillectomy to assess for residual symptoms. If there are residual symptoms of OSAS then PSG should be performed.

PSG is indicated following adenotonsillectomy to assess for residual sleep-related breathing disorders in children with pre-operative evidence for moderate-to-severe OSAS, obesity, craniofacial anomalies that obstruct the upper airway and neurological disorders (*e.g.* Down syndrome, Prader–Willi syndrome, myelomeningocele). It is also indicated in children after treatment of OSAS by rapid maxillary expansion to assess for the level of residual disease and to determine whether additional treatment is necessary. Children with OSAS treated with an oral appliance should have clinical follow-up and PSG to assess response to treatment.

PSG is indicated for positive airway pressure titration in children with OSAS and for noninvasive positive pressure ventilation titration in children with other sleep-related breathing disorders.

Follow-up PSG in children on CPAP support is indicated to determine whether pressure requirements have changed as a result of the child's growth and development; if symptoms recur while on positive airway pressure; or if additional or alternative treatment is required.

Children treated with mechanical ventilation may benefit from periodic evaluation with PSG to adjust ventilator settings. PSG for the management of oxygen therapy is not routinely required in children treated with supplemental oxygen. Children treated with tracheostomy for sleep-related breathing disorders benefit from PSG as part of the evaluation prior to decannulation. These children should be followed clinically after decannulation to assess for recurrence of symptoms of sleep-related breathing disorders.

Respiratory diseases

PSG is indicated in the following respiratory disorders, if there is clinical suspicion of an accompanying sleep-related breathing disorder:

- Chronic asthma
- CF
- Pulmonary hypertension
- BPD
- Chest wall abnormalities, such as kyphoscoliosis

Polysomnography methods

PSG in children should be performed in a child-friendly laboratory. Since the sleep requirement varies during childhood, the expected circadian timing of the child's natural sleep period should match the staffing and timing of the PSG. The study must be attended all night by a trained technician to ensure the quality of the study. It is equally important to note that none of the current polysomnographic systems can generate accurate automated reports on paediatric PSG studies. An automated report can both underestimate and overestimate the clinical condition. For this reason,

paediatric PSG studies should be reviewed manually using the raw data by trained physicians with knowledge of paediatric PSG studies.

In general, the result from a single-night study is sufficient for the purpose of diagnosis of children with suspected OSAS. Two studies assessing the "first-night" effect in children have shown that the parameters are not significantly different between the first and second nights of PSG.

Technique

Standard PSG components are summarised in table 1 and figure 1. Each child is continuously observed by a technician trained in paediatric PSG, who also records sleep behaviour and respiratory events (table 1 and figure 1).

Electroencephalogram

The international 10–20 system of electrode placement is used to determine surface electrode placement. Electrodes placed on an imaginary grid points in the frontal, central or occipital regions (F, C or O, respectively) and the reference electrodes are placed on either mastoid (M). By convention, left-sided leads are odd-numbered and right-sided leads are even-numbered. The American Academy of Sleep Medicine (AASM) recommends F4-M1, C4-M1 and O2-M1. Since children frequently displace leads during sleep, contralateral leads are typically applied as well (F3-M2, C3-M2 and O1-M2). Children have high amplitude brain waves; thus, electroencephalogram (EEG) recordings may need a sensitivity of 10–15 $\mu V \cdot mm^{-1}$, compared to 5 $\mu V \cdot mm^{-1}$ in adults.

Electro-oculogram

Eye movements are detected by placing surface electrodes near the outer canthus of each eye. The electro-oculogram (EOG) electrodes should be offset from horizontal,

Table 1. Components of PSG in children

EEG: current AASM recommendations are F4-M1, C4-M1 and O2-M1 with backup (F3-M2, C3-M2 and O1-M2)
Eye movements (EOG) from electrodes placed near the outer canthus of each eye
Submental EMG activity from electrodes placed over the mentalis, submentalis muscle and/or masseter regions
Rhythm ECG with one lead II electrode or more chest leads at the discretion of the provider
Respiratory effort by chest wall and abdominal movement *via* inductance plethysmography or oesophageal pressure (the AASM does not recommend strain gauges or piezoelectric belts)
Nasal–oral airflow *via* oronasal thermal sensor and nasal pressure transducer
S_{pO_2} including waveform measured with a pulse oximeter with a maximum acceptable signal averaging time of ≤3 s at a heart rate of 80 beats·min^{-1}
P_{ETCO_2} numerical and waveform or P_{tcCO_2} numerical
Body position *via* sensor and direct observation
Limb movements (right and left legs) *via* electromyogram
Snoring recording or vibration (frequency and/or volume)
Audio/video recording using infrared or low-light equipment

Data from the American Academy of Sleep Medicine (AASM), 2018. EEG: electroencephalogram; EOG: electro-oculogram; EMG: electromyogram; P_{ETCO_2}: end-tidal carbon dioxide tension.

Figure 1. Components of paediatric PSG.

one slightly above and one slightly below the horizontal plane, to detect both horizontal and vertical eye movements. As infants and young children have smaller heads than adults, EOG leads may need to be placed 0.5 cm from the outer canthi. These electrodes are important in identifying eye movements associated with wakefulness and rapid eye movement (REM) sleep.

Electromyogram

Two surface electrodes are placed either on the mentalis or submentalis to detect muscle activity. As infants and young children have smaller heads than adults, chin electromyogram electrodes may need to be placed 1 cm apart, rather than 2 cm apart as in adults.

Electrocardiogram

A simple single-lead ECG should be used to monitor cardiac rate and rhythm to enable to detect cardiac arrhythmias and changes resulting from respiratory disturbances to be assessed.

Respiratory effort

Chest and abdominal wall motion can be measured in a number of ways. Respiratory inductance plethysmography (RIP) is the preferred method. Oesophageal pressure monitoring is rarely used, as it is invasive, and the nasal pressure flow signal is often used as a surrogate when the upper airway resistance syndrome is suspected.

Nasal–oral airflow

Airflow is measured by the oronasal thermal air sensor and nasal pressure cannula. The thermistor is the recommended sensor for apnoea detection. Nasal pressure cannula, sum of the thorax and abdomen belt signals (RIP_{sum}), the time derivative of the RIP_{sum}

signal (RIP_{flow}) or end-tidal carbon dioxide tension (P_{ETCO_2}) can be used as alternative apnoea sensors. Nasal pressure cannula is a reasonable alternative to oesophageal pressure monitoring. It captures airflow and is connected to a pressure transducer to generate a signal, which correlates with the size of breath and airflow resistance. It is the recommended signal for hypopnoea detection. An oronasal thermal air sensor, RIP_{sum}, RIP_{flow} or dual thoracoabdominal RIP belts can be used as alternatives.

Oxygen saturation

The sensor is incorporated into a soft cuff that fits around a finger or toe or clips to an ear lobe. Children tend to move frequently during sleep, so the monitoring of the pulse waveform in addition to the saturation value is helpful in distinguishing motion artefacts from true desaturation.

Carbon dioxide

Measurements of carbon dioxide have been used in two contexts during PSG:

- P_{ETCO_2} waveform as an indicator of airflow obstruction and, hence, apnoea
- Measurement of P_{ETCO_2} or P_{tcCO_2} as a quantitative measure of hypoventilation during sleep

Monitoring carbon dioxide has been considered of potential value in diagnosing obstructive hypoventilation syndrome. Furthermore, the measurement of carbon dioxide is useful in children with chronic lung disease or those receiving ventilatory support. It is especially important to measure carbon dioxide when supplemental oxygen is initiated in the sleep laboratory, as some patients may be dependent on their hypoxic drive to breathe. Adding oxygen without monitoring carbon dioxide may lead to worsening hypoventilation and the clinical deterioration of the patient.

P_{ETCO_2} can be measured directly from a tracheostomy or endotracheal tube, or as a side-stream measure from a nasal cannula. P_{ETCO_2} values may be inaccurate in patients with obstructive lung disease with long time constants, such as in patients with advanced CF.

An alternative measurement option for evaluating hypoventilation is P_{tcCO_2}. Transcutaneous measurements may be preferable to end-tidal measurements in children with advanced obstructive lung disease, infants with rapid respiratory rates, children who breathe through their mouth and children receiving CPAP, in whom the CPAP airflow may interfere with end-tidal measurements. Although most studies comparing P_{ETCO_2} and P_{tcCO_2} to arterial samples have been performed in the intensive care unit or during anaesthesia, these studies show a good correlation.

Body position

Body position is frequently measured during PSG, although the measurement of body position is less important in young children than in adults, as OSAS is less positional.

Oesophageal pH

Oesophageal pH is occasionally measured to determine whether gastro-oesophageal reflux is contributing to night wakenings, apnoea or desaturation. pH probe insertion is more invasive than the rest of the leads on a polysomnogram and takes specialised skill; placement must be confirmed using radiography. The percentage of total sleep time (TST) with pH <4 and the number and length of pH drops to <4 can be quantified, and reviewed for an association with respiratory disturbances.

Video and sound recording

Good-quality video recordings are an important component of a sleep study, and can be made using infra-red or low-light cameras and appropriate microphones. Video and sound recordings can provide useful information on sleep behaviour, snoring, sleep disturbance and breathing patterns.

Limb movements

Gross body movements and limb movements may be assessed from direct observation, a video recording or from recordings of a peripheral electromyogram recording. These may be of use in detecting the extent of sleep disturbance or arousal frequency, and are necessary for assessment of sleep state in infants. Monitoring the electromyogram from a leg muscle (conventionally, tibialis anterior) is a useful measure of peripheral skeletal muscle tone and allows assessments of gross body movements and arousals during sleep.

Interpretation of the polysomnogram in children

Standard duration of the study

A study of the whole night is the recommended investigation to assess sleep disordered breathing. A minimum of 6 h sleep is desirable. The timing of the studies is also important. The study timing should be set to mimic the child's bedtime as closely as possible.

Sleep stage analysis

It is helpful to quickly review the patient's sleep architecture by viewing the hypnogram. A hypnogram is a graphical summary of the different sleep stages achieved. It is important to review the sleep architecture in terms of what is to be expected for the patient's age. Paediatric sleep staging rules are used in children aged ≥2 months post-term. Sleep is analysed in 30-s epochs.

Components of sleep architecture

Sleep is divided into stages: wake (W), non-REM (NREM; stages N1, N2 and N3) and REM (R). In infants aged <2 months (conceptional age 37–48 weeks), sleep is scored as stages W, N, R and transitional (T). Scoring of sleep and wakefulness in infants at 38–48 weeks conceptional age is based on behavioural observation, regularity or irregularity of respiration, and EEG, EOG and electromyogram patterns specific to infants. If an epoch contains either three NREM and two REM characteristics or two NREM and three REM characteristics, it is scored as stage T. In infants and young children, a posterior dominant rhythm predominates in wakefulness. In older children it is referred as to alpha rhythm, which has a frequency of 8–13 Hz (table 2).

Stage W is also associated with rapid eye movements with normal or high chin muscle tone and eye blinks. In stage 1, low-amplitude activity (predominantly 4–7 Hz) and vertex sharp waves with slow eye movements and reductions in muscle activity are observed; stage 2 is characterised by sleep spindles and K complexes with a low muscle tone compared to wakefulness; stage 3 is scored if there are high-amplitude delta waves for >20% of the epoch. REM is defined as low-voltage, fast-frequency brain waves with episodic eye movements and inactivity in muscle tone.

Table 2. Initial age of waveform onset

	Age of onset
Sleep spindles	6 weeks to 3 months post-term
K complexes	3–6 months post-term
Slow-wave activity	2–5 months post-term
Posterior dominant rhythm	
3.5–4.5 Hz	3–4 months post-term
5–6 Hz	5–6 months post-term
7.5–9.5 Hz	3 years
Vertex sharp waves	4–6 months post-term
Hypnagogic hypersynchrony	3–6 months post-term

NREM stage 1 sleep occupies 4–7.7% of TST, and stage 2 occupies 36–49% of TST, with the combination of stage 1 and 2 in each study ranging from 41% to 53% of the TST. Slow-wave sleep occupies 14–32% of the TST, whereas REM sleep occupies 17.4–21.1% of the TST. Children usually have a short period of stage 1/2 after sleep onset, and then enter stage 3. Stage 3 sleep predominates early in the night, with regular cycling between stages 1/2, 3 and REM. A night of normal sleep usually consists of between four and six NREM/REM sleep cycles. The first REM sleep period usually occurs ~70–90 min after sleep onset. The first cycle begins by moving from wakefulness to NREM sleep. The first REM period follows the first period of NREM sleep. The two sleep states continue to alternate throughout the night with an average period of ~90–120-min intervals. Length of time spent in REM is short earlier in the night, with lengthening of REM episodes as the night progresses.

Components of sleep architecture should be assessed including percentage of TST spent in stages 1/2, 3, REM and wakefulness. These percentages should be compared with age-appropriate normal values.

Sleep latency, the time after lights out until sleep is achieved, should also be noted. Sleep latency is generally <25 min in children. It may be prolonged if the child has recently had a nap, and it may be shortened in certain sleep disorders.

Sleep efficiency is a measurement of the amount of the total time in bed that the patient spends asleep, and should be noted. Sleep efficiency in children is usually >89%.

Arousal summary

An arousal is scored when there is an abrupt change in the EEG frequencies >16 Hz (but not spindles) lasting 3 s, following ≥10 s of continuous sleep. Arousals can be attributed to preceding events, including respiratory events, leg movements, snore events or technician presence in the room, or may occur without an obvious trigger. Arousals are reported using the arousal index, which is the number of arousals divided by the hours of sleep. Studies of normal children have found mean arousal indices of 8.8–9.5 events·h^{-1}.

Heart rate/rhythm

The ECG should be reviewed for evidence of bradyrhythms or tachyrhythms, as well as abnormal ECG rhythms. Respiratory events may be associated with a decrease in heart rate, with subsequent increase in heart rate after the event has resolved or in association with arousals.

Leg movements

Criteria for periodic leg movements include leg movements noted in either or both legs that have a minimum amplitude of 8 μV increase from baseline lasting 0.5–10 s. Leg movements must be separated by ≥5 s, but not >90 s, and must occur in clusters of at least four to be considered periodic leg movements. These leg movements should not be related to other events, such as respiratory events or arousals. The periodic leg movement index is calculated by dividing the total number of periodic leg movements

Table 3. Description of respiratory events

Obstructive apnoea	Drop in thermal sensor amplitude by ≥90% baseline ≥2 missed breaths Continued or increased inspiratory effort during reduced airflow
Central apnoea	Drop in thermal sensor amplitude by ≥90% baseline Either duration ≥20 s or ≥2 missed breaths and associated with arousal, awakening or ≥3% desaturation ≥2 breaths associated with a decrease in heart rate <50 min for ≥5 s or <60 min for 15 s (infants aged <1 year only) Absent inspiratory effort
Mixed apnoea	Drop in thermal sensor amplitude by ≥90% baseline ≥2 missed breaths Absent inspiratory effort in one portion of the event and presence of inspiratory effort in the other portion, regardless of which portion comes first
Hypopnoea	Drop in nasal air pressure transducer amplitude by ≥30% ≥2 missed breaths Associated with arousal, awakening or ≥3% desaturation
Respiratory effort related arousal	≥2 missed breaths that do not meet criteria for apnoea or hypopnoea Sequence leads to arousal associated with one or more of the following: Flattening of inspiratory portion of nasal air pressure transducer waveform Increased work of breathing Snoring Increase in P_{ETCO_2} above pre-event baseline
Periodic breathing	≥3 episodes of central apnoea lasting >3 s separated by ≤20 s of normal breathing
Hypoventilation	P_{aCO_2}, P_{tcCO_2} or P_{ETCO_2} >50 mmHg in >25% of TST
Apnoea index	Number of obstructive and central apnoeic and mixed apnoeic events per hour of sleep: (obstructive + central + mixed)/TST (hour)
Obstructive apnoea index	Number of obstructive apnoeic events per hour of sleep
Hypopnoea index	Number of hypopnoeas per hour of sleep
AHI	Sum of the apnoea index and hypopnoea index
Obstructive AHI	Sum of obstructive apnoeic events and hypopnoeic events per hour of sleep

Figure 2. Central apnoea.

by the number of hours of sleep. A periodic leg movement index of ≥5 events·h^{-1} is considered abnormal.

Gas exchange

The pulse oximetry tracing should be reviewed for desaturation, with careful attention to whether the desaturation is associated with a respiratory event, arousal or leg movement. Median baseline S_{pO_2} in preterm infants, term-born babies and infancy is ~98%, ~98% and ~96%, respectively.

In children beyond infancy a normal oximetry recording should have:

- A median S_{pO_2} level ≥95%
- No more than four desaturations of ≥4% per hour
- No abnormal clusters of desaturation

In addition, carbon dioxide tracing should be reviewed. Baseline carbon dioxide levels before sleep onset should be noted. Children may have a pattern of obstructive hypoventilation with OSAS, resulting in increases of carbon dioxide without apnoeas. Abnormal levels of carbon dioxide vary, with some studies reporting >25% of TST

Figure 3. Periodic breathing.

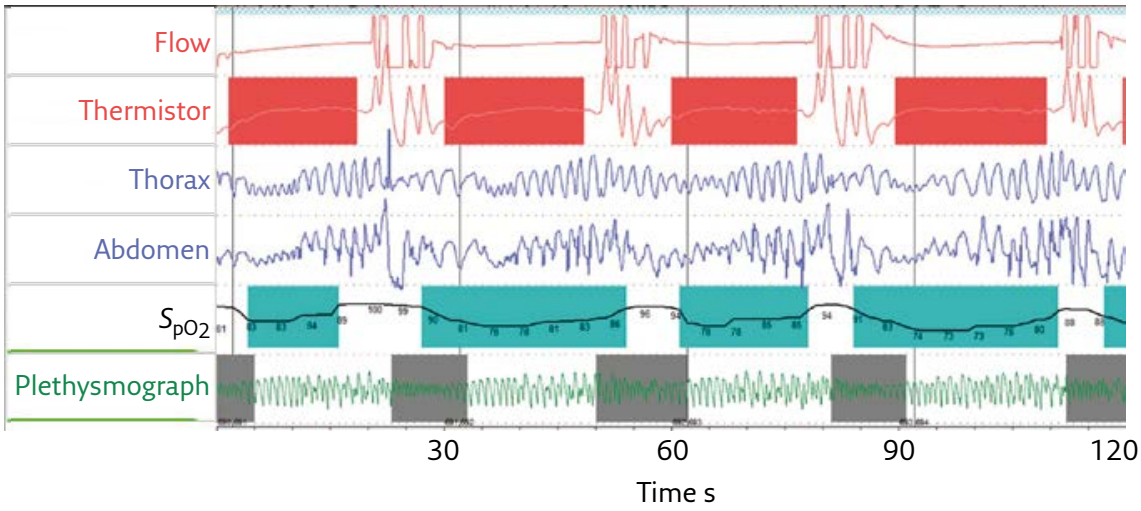

Figure 4. Four obstructive apnoeas in a 120-s epoch in a child with severe OSA.

spent with carbon dioxide >50 mmHg as abnormal, and some reporting that in normal children 2.8±11.3% of TST was spent with carbon dioxide ≥50 mmHg.

Respiratory events

Respiratory scoring in children is different from that in adults. Paediatric scoring must be used for children aged <18 years, but in children aged ≥13 years, adult criteria can also be used. Small studies indicate that adolescents have breathing patterns similar to those of younger children and the use of paediatric scoring criteria would be appropriate for adolescents. For identification of apnoea or hypopnoea, airflow and respiratory effort need to be compared simultaneously. For apnoea, an oronasal thermal airflow sensor is used to monitor airflow, and for hyponea a nasal pressure transducer is used. Definitions of respiratory events are summarised in table 3. Examples of central apnoea, periodic breathing, obstructive apnoea and hypopnoea are shown in figures 2–5.

Normal PSG values and treatment indications

There are very few studies assessing the polysomnographic predictors of morbidity in children. Table 4 shows normative data for the different PSG variables. These are statistical norms rather than clinical criteria upon which to base treatment decisions. Normal values are different in newborn babies, and age should be taken into account when results of PSG is interpreted. AHI is the most commonly used PSG parameter for the description of OSAS severity. However, gas exchange during sleep should also be considered when treatment is planned for an individual patient. It is generally accepted that OSAS is mild if the obstructive AHI is ≤5 events·h^{-1}, moderate if it is

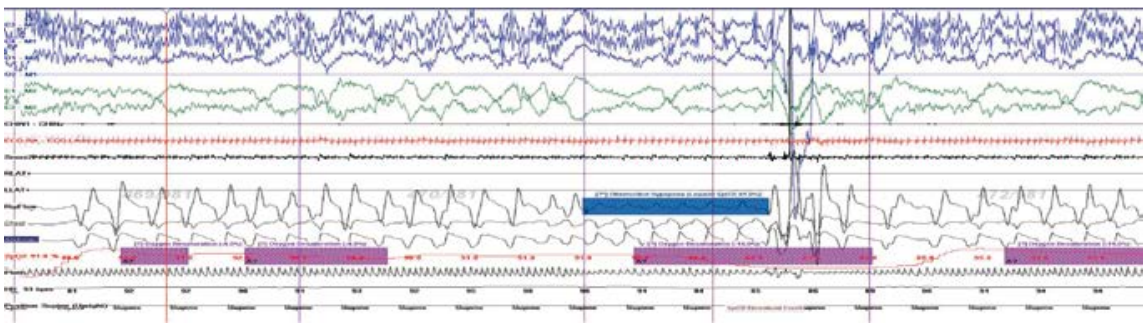

Figure 5. 2-min epoch with an obstructive hypopnoea.

Table 4. Normal PSG values in children

	Montgomery-Downs (2006)		Verhulst (2007)	Uliel (2004)	Traeger (2005)	Daftary (2019)
Subjects n	542		60	70	66	30
Age	3–5¶ years	≥6+ years	6–16 years	1–15 years	2.5–9.4 years	7–30 days
Sleep latency min	24.1±25.6	23±25.3	45.6±29.4			
Sleep efficiency %	90±7.0	89.3±7.5	80.5±8.5	90.8±6.5	89±8.0	71.9±8.8
Arousals events·h^{-1}	9.3±4.8	6.1±1.8			8.8±3.8	14.7±3.9
RERA events·h^{-1}	0.92±2.0	1.2±1.0				
Hypopnoea index# events·h^{-1}	0.03±0.07	0.10±0.18			0.3±0.5	6.3±3.4
Apnoea index events·h^{-1}	0.86±0.75	0.5±0.52				
Obstructive apnoea index events·h^{-1}	0.03±0.10	0.05±0.11	0.06±0.16	0.02±0.1	0.1±0.03	2.3±2.5
AHI events·h^{-1}	0.9±0.78	0.68±0.75	1.98±1.39		0.4±0.6	14.9±9.1
Obstructive AHI events·h^{-1}	0.08±0.16	0.14±0.22	0.08±0.17			
% TST S_{pO_2} >95%	99.6±0.95					
S_{pO_2} nadir %	92.7±4.5	92.6±3.6	91.8±2.7	94.6±2.2	92±3.0	84.4±4.8
S_{pO_2} lower limit %	84	85	86	90	86	
ODI events·h^{-1}	0.29±0.35	0.47±0.96	0.8±0.9			17.6±11
P_{ETCO_2} % TST >50 mmHg	4.0±15.3	2.0±7.1		0.29±0.24		0.6±2.5

Data are presented as n, range or mean±SD. RERA: respiratory effort related arousal; ODI: oxygen desaturation index. #: with desaturation (3–4%) and/or arousal; ¶: n=173; +: n=369.

>5 events·h^{-1} but <10 events·h^{-1}, and severe if it is >10 events·h^{-1}. If the snoring child has moderate or severe OSAS, treatment is recommended. Treatment indications for children with mild OSAS are less clear. The ERS task force for OSAS in children recommended treatment of OSA in children if:

- AHI >5 events·h^{-1} irrespective of the presence of morbidity
- AHI 1–5 events·h^{-1} in the presence of:
  - Morbidity from the cardiovascular system (systolic or diastolic blood pressure consistently >95th percentile for sex, age and height, or documented pulmonary hypertension or cor pulmonale)
  - Morbidity from the central nervous system (excessive daytime sleepiness, hyperactivity, inattention and academic difficulties, increased frequency of behavioural disorders)
  - Enuresis
  - Somatic growth delay or growth failure
  - Decreased quality of life
  - Risk factors for persistence of sleep disordered breathing (obesity and increasing BMI, male sex, African-American ethnicity, persistent tonsillar hypertrophy and a narrow mandible)
- OSAS in the presence of major craniofacial abnormalities, neuromuscular disorders, achondroplasia, Chiari malformation, Down syndrome, mucopolysaccharidoses and Prader–Willi syndrome

Summary

Paediatric PSG is the gold standard for evaluation of children with OSAS. Responses to various treatment modalities are objectively evaluated by PSG. It is also used to evaluate cardiorespiratory function during sleep in infants and children with alveolar hypoventilation, chronic lung disease or neuromuscular disease when indicated. Paediatric PSG should be performed in a child-friendly environment and should be evaluated according to the paediatric rules.

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OSAS and upper airway resistance syndrome

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The term obstructive sleep disordered breathing (SDB) is used to describe a spectrum of abnormal respiratory patterns during sleep, characterised by snoring and increased respiratory effort resulting from increased upper airway resistance and pharyngeal collapsibility. Depending on the severity of upper airway obstruction during sleep, SDB may be classified as: 1) primary snoring (no detected apnoeas, hypopnoeas, arousals from sleep or gas exchange abnormalities); 2) upper airway resistance syndrome (snoring, increased respiratory effort and frequent arousals, but no recognisable obstructive events or gas exchange abnormalities); 3) obstructive hypoventilation (snoring and hypoventilation); and 4) OSAS (recurrent obstructive or mixed apnoeas and hypopnoeas accompanied by hypoxaemia, hypercapnia and arousals from sleep).

In most studies, the prevalence of OSAS ranges between 1% and 4%. Although no specific genes have been identified for OSAS to date, it is likely that it is a polygenic disease. Specific genes affecting the structure and function of the upper airway are probably involved in the pathophysiology of OSAS.

Pathogenesis of OSAS

Increased pharyngeal collapsibility during sleep is one of the mechanisms implicated in the pathogenesis of OSAS, since the activity of the upper airway dilator muscles may not be adequate to compensate for an anatomically narrow upper airway and the highly negative pressure that develops during inspiration. Children with OSAS often have enlarged adenoids and tonsils. However, adenotonsillar hypertrophy may not always lead to OSAS. A complex interaction between anatomical and functional factors contributing to upper airway lumen stability has been postulated.

Key points

- OSAS in children is due to increased upper airway resistance and pharyngeal collapsibility.
- OSAS manifests as habitual snoring, witnessed apnoea, sleep fragmentation and diurnal symptoms.
- Adenotonsillar hypertrophy is the most frequent abnormality predisposing to OSAS and adenotonsillectomy is the main treatment; however, in many cases further interventions will be necessary, such as orthodontic therapy.

Despite their impact on public health, orthodontic and craniofacial abnormalities predisposing to OSAS are widely ignored. A narrow upper airway with maxillary constriction and/or some degree of mandibular retrusion is a common paediatric phenotype of OSAS. In such cases, children may have a narrow, long face, retrognathic mandible and increased posterior facial height with or without coexisting tonsillar hypertrophy. Whether these skeletal characteristics are genetically determined or influenced by the early onset of habitual snoring has not been clarified. Another common abnormality in patients with OSAS is a high arched (ogival) palate, that results in posterior tongue displacement, forcing the lateral palatine processes to expand over the abnormally placed tongue.

Diagnosis of OSAS

Signs, symptoms and associated conditions

Recognition of the child who is at risk of OSAS is based on the presence of symptoms related to nocturnal upper airway obstruction, physical examination findings indicative of increased upper airway resistance and conditions associated with SDB (table 1). Identification of OSAS-associated morbidity (*e.g.* enuresis, failure to thrive) increases the index of suspicion for the disorder (see table 1 and section about morbidities associated with OSAS).

Polysomnography and validated questionnaires

The American Academy of Pediatrics recommends that if a child or adolescent snores regularly and has any features indicative of OSAS (table 1), clinicians should obtain a PSG or refer the patient to a sleep specialist or ENT surgeon for further evaluation. Although history and physical examination are useful to screen for OSAS and determine which patients need further investigation, their sensitivity and specificity are limited. The Sleep Clinical Record is a validated tool that is based on physical examination,

Table 1. Major symptoms, signs, associated conditions and morbidities accompanying paediatric OSAS

Symptoms	Signs	Associated conditions	Associated morbidities
Snoring	Adenoidal facies	Achondroplasia	Attention deficit and hyperactivity symptoms
Gasps/laboured breathing during sleep	Tonsillar hypertrophy	Allergic rhinitis	Daytime sleepiness
Mouth breathing	Obesity	Asthma	Learning problems
Observed episodes of apnoea	High-arched palate	Chiari malformation	Hypertension
Sleeping in a seated position or with the neck hyperextended	Micrognathia	Craniofacial syndromes (*e.g.* Apert syndrome, Crouzon syndrome)	Inadequate somatic growth
Cyanosis	Retrognathia	Down syndrome	Nocturnal enuresis
		Mucopolysaccharidoses	Pulmonary hypertension
		Neuromuscular disorders (*e.g.* cerebral palsy or Duchenne muscular dystrophy)	Cor pulmonale
		Prader–Willi syndrome	
		Prematurity	

Data from Marcus *et al.* (2012) and Bhattacharjee *et al.* (2010).

subjective symptoms and clinical history consistent with OSAS. If the Sleep Clinical Record score is negative, PSG is not necessary. The Pediatric Sleep Questionnaire sleep-related breathing disorder (PSQ-SRBD) scale contains 22 items asking for the presence of symptoms of upper airway obstruction (snoring, apnoeas, mouth breathing) or morbidity accompanying OSAS and more specifically enuresis, somatic growth failure, overweight, excessive daytime sleepiness, inattention, hyperactivity or impulsivity. A PSQ-SRBD score ≥0.33 indicates high risk of moderate-to-severe OSAS (AHI ≥5 events·h^{-1}).

The gold-standard test for the diagnosis of OSAS is overnight, attended, in-laboratory video PSG (sleep study). Video PSG is a noninvasive test involving the overnight recording of a number of physiological variables, typically including electroencephalogram (EEG), submental and tibial electromyogram, electro-oculogram (right/left), oronasal airflow, abdominal and chest wall movements, oxygen saturation of haemoglobin by pulse oximetry, partial pressure of carbon dioxide (end-tidal or transcutaneous) and video recording. Paediatric PSG scoring criteria have been published by the American Academy of Sleep Medicine and are summarised in the chapter "Polysomnography". If PSG is not available, then clinicians may use alternative diagnostic tests, such as daytime nap PSG, home PSG, nocturnal video recording or nocturnal oximetry recording, although they have weaker positive and negative predictive values than PSG for the diagnosis of OSAS.

AHI is defined as the average number of mixed, obstructive and central apnoeas and hypopnoeas per hour of total sleep time. Obstructive AHI is the average number of mixed and obstructive apnoeas and hypopnoeas per hour of total sleep time. In a European Respiratory Society (ERS) statement on the diagnosis and management of obstructive SDB in children aged 2–18 years, two definitions of OSAS have been proposed. According to the first definition, OSAS is diagnosed when SDB symptoms are present in combination with an obstructive AHI ≥2 events·h^{-1} or an obstructive apnoea index (obstructive apnoeas per hour of total sleep time) ≥1 events·h^{-1}. According to the second definition, OSAS is diagnosed when SDB symptoms are evident in combination with an AHI ≥1 events·h^{-1}. In a second ERS statement on obstructive SDB in children aged 1–23 months, OSAS in the first 2 years of life was defined as an obstructive AHI ≥1 events·h^{-1} in the context of relevant risk factors.

Flexible nasopharyngoscopy, drug-induced sleep endoscopy and upper airway CT or MRI are helpful tools in the evaluation of upper airway patency, especially in complex cases with OSAS. Cephalometry is essential for the quantification of craniofacial abnormalities.

Morbidities associated with OSAS

Paediatric OSAS is associated with multiple end-organ morbidities such as daytime sleepiness, neurocognitive impairment, behavioural problems, failure to thrive, elevated blood pressure and enuresis. Effects on cardiac structure and function and enhanced systemic inflammation have also been reported.

The exact prevalence of excessive daytime sleepiness (EDS) in children with OSAS is unclear. When objective measures were used (*i.e.* multiple sleep latency test), the prevalence of EDS ranged from 13% to 20%. Furthermore, the presence of obesity appeared to increase the likelihood of EDS.

It is estimated that ~30% of all children with frequent and loud snoring manifest symptoms of hyperactivity and inattention as well as learning problems. A high prevalence of paroxysmal EEG activity in a population of children with OSAS has been

reported (14.3%). Interictal epileptiform discharges (IEDs) occurred predominantly over the centrotemporal regions, suggesting some similarities with IEDs of benign epilepsy with central temporal spikes. Since IEDs during sleep may disrupt cognitive function and impair learning and memory in children, these findings may explain at least in part the neurocognitive dysfunction in children with OSAS.

Failure to thrive used to be frequent in young children with OSAS and was attributed to the increased work of breathing and metabolic expenditure during sleep, reduced caloric intake due to enlarged tonsils and disrupted growth hormone–insulin growth factor pathway as a result of recurrent hypoxaemia and disturbed sleep patterns. In more recent years, obesity has emerged as a frequent finding in children with OSAS, which occurs in up to 60% of obese children. The concomitant presence of OSAS and obesity further amplifies the risk of abnormalities in the serum lipid profile. Increased circulating leptin levels have been reported in children with OSAS, independent of the severity of obesity. Leptin is an adipokine, which are cytokines released from adipose tissue with an important role in the regulation of appetite, metabolic homeostasis, sleep and control of breathing. Moreover, accumulated evidence suggests that paediatric OSAS constitutes a systemic low-grade inflammatory condition. The induction of systemic inflammatory responses is probably the consequence of systemic oxidative stress secondary to the recurrent hypoxic and arousal episodes that characterise OSAS.

Of particular interest are the cardiovascular complications that may develop in children with OSAS, since they may not have only an immediate impact on cardiovascular health during childhood, but may also affect cardiovascular outcomes in adult life. Studies in children with OSAS have reported changes in cardiac structure and function, increased fasting insulin and lipid levels, and endothelial dysfunction. Other investigations have demonstrated increases in baseline heart rate and nocturnal and diurnal systolic and diastolic blood pressure in children with OSAS (~17%). Enhanced sympathetic activity has been demonstrated by peripheral arterial tonometry and measurement of catecholamine concentrations in plasma and urine. An increase in basal sympathetic activity, even during wakefulness, has been shown in patients with OSAS.

Children with moderate-to-severe OSAS can present with pulmonary hypertension and cor pulmonale, which may improve following adenotonsillectomy. Of note, it has been found that the higher the AHI, the higher the risk of increased right cardiac ventricle end-diastolic dimension. Other investigators have reported a correlation between severity of OSAS and left cardiac ventricle mass index and diastolic function. After controlling for age, sex and BMI z-score, children with moderate-to-severe OSA had a 4.2-fold increased risk of abnormal left ventricular geometry compared with the reference group. A common pathophysiological pathway for these cardiovascular alterations is thought to be the enhanced generation of reactive oxygen species in the context of recurrent hypoxaemia, which directly or indirectly promote myocardial changes and vascular remodelling.

Treatment

In the ERS statement on the diagnosis and management of obstructive SDB in children aged 2–18 years, indications for treatment of OSAS were summarised as follows: 1) AHI >5 events·h^{-1} irrespective of the presence of morbidity; 2) AHI 1–5 events·h^{-1} in combination with comorbidities from the central nervous or cardiovascular systems, enuresis, somatic growth delay, decreased quality of life or risk factors for SDB persistence (male sex, African-American race, obesity, increasing BMI percentile, tonsillar hypertrophy, narrow mandible); 3) OSAS treatment is a priority in the presence

of major craniofacial abnormalities, neuromuscular disorders, achondroplasia, Chiari malformation, Down syndrome, mucopolysaccharidoses and Prader–Willi syndrome, because these patients may be at risk of developing pulmonary hypertension, and it is unlikely that SDB will resolve without treatment.

In children aged 1–23 months, treatment is recommended when 1) upper airway obstruction is obvious even during wakefulness; 2) there are symptoms of SDB or physical examination findings indicative of increased upper airway resistance in combination with obstructive AHI ≥1 events·h^{-1}; 3) the child has a complex disorder other than isolated adenotonsillar hypertrophy (major craniofacial abnormality, neuromuscular disorder, achondroplasia, Chiari malformation, Down syndrome, mucopolysaccharidosis, Prader–Willi syndrome) and obstructive AHI ≥1 events·h^{-1}.

In children aged 2–18 years, a stepwise treatment approach for SDB is usually implemented until the complete resolution of OSAS. Figure 1 presents an algorithm for the diagnosis and treatment of OSAS in children aged 2–18 years using a multistep approach based on the ERS statement.

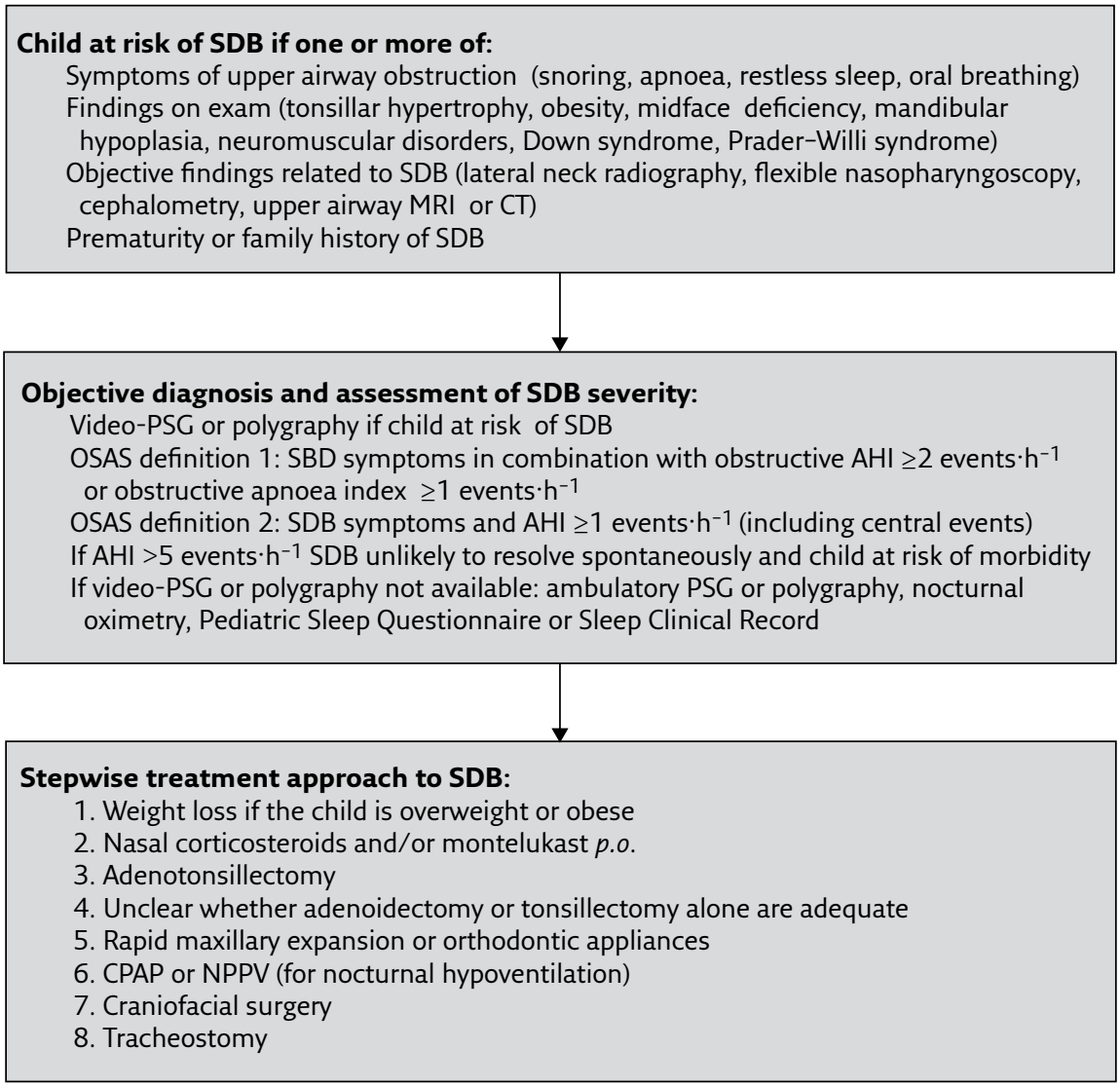

Figure 1. Algorithmic approach to the diagnosis and treatment of paediatric OSAS (ages 2–18 years). NPPV: noninvasive positive-pressure ventilation. Reproduced and modified from Kaditis et al. *(2016) with permission.*

Adenotonsillectomy is recommended when a child with OSAS has adenotonsillar hypertrophy. Adenotonsillectomy offers some relief in upper airway obstruction, even in obese children with OSAS and enlarged adenoids and tonsils. Among nonsyndromic and uncomplicated children with moderate-to-severe OSAS, residual disease may occur post-operatively in 20–40% of cases. Residual OSAS is particularly prevalent in obese children, children aged >7 years, those with severe disease pre-operatively (AHI >20 events·h^{-1}) and patients with history of asthma. Residual OSAS has been reported not only after adenotonsillectomy, but also after rapid maxillary expansion.

Risk factors for complications post-adenotonsillectomy include:

- Age <3 years
- Cardiac disease
- Craniofacial anomalies or neuromuscular disorder
- Current respiratory infection
- Failure to thrive
- Obesity
- Severe OSAS on PSG

Topical intranasal corticosteroids and montelukast decrease the size of the adenoidal tissue and have been administered to children with mild-to-moderate OSAS for 6–12 weeks and to patients with mild OSAS post-adenotonsillectomy (AHI <5 events·h^{-1}). Nasal corticosteroids have been used in children aged ≥2 years.

Orthodontic treatment by means of oral devices is one of the treatment interventions for children presenting with OSAS. Although the use of oral appliances has received relatively little attention in the literature, interest in this approach has been growing rapidly. Oral appliances may improve upper airway patency during sleep by enlarging the upper airway lumen and/or by decreasing upper airway collapsibility and improving upper airway muscle tone. The orthodontic treatment options available for growing children are rapid maxillary expansion, mandibular retropositioning and modified monobloc. Rapid maxillary expansion is a dentofacial orthopaedic treatment procedure used in patients aged ≥4 years with constricted maxillary arches; it is considered an effective treatment for OSAS.

CPAP is applied mostly for residual OSAS after adenotonsillectomy (AHI >5 events·h^{-1}) and OSAS related to obesity, craniofacial abnormalities or neuromuscular disorders. If nocturnal hypoventilation is recognised, noninvasive positive-pressure ventilation (NPPV) is preferred. A few studies have demonstrated specific benefits with CPAP or NPPV treatment, such as improvement in gas exchange, behaviour, attention deficits, sleepiness and quality of life. Potential complications include nasal congestion, rhinorrhoea, epistaxis, facial skin damage related to the mask (interface) and midface retrusion.

An accurate oropharyngeal evaluation, targeted to identify mouth breathing, nasal disuse, muscle hypotonia and incorrect swallowing patterns, should be part of the assessment of children with OSAS to identify oropharyngeal characteristics that may contribute to upper airway obstruction. Oropharyngeal exercises can help to resolve oropharyngeal muscle dysfunction and airway collapse that persists following standard treatment measures for paediatric OSAS. Villa *et al.* (2013) have demonstrated that oropharyngeal exercises improve nasal patency and augment correct labial seal in children with residual SDB after adenotonsillectomy.

In children aged 1–23 months, adenoidectomy and/or tonsillectomy and CPAP or NPPV are the main treatment approaches, with additional targeted measures for

specific causes of upper airway obstruction, *e.g.* supraglottoplasty for laryngomalacia or nasopharyngeal airway insertion, and tongue-to-lip adhesion and mandibular distraction osteogenesis for Pierre Robin sequence.

Summary

OSAS in children is the result of increased upper airway resistance and pharyngeal collapsibility and it is manifested as habitual snoring, witnessed apnoea, sleep fragmentation and diurnal symptoms. Although adenotonsillar hypertrophy is the most frequent abnormality predisposing to OSAS, and adenotonsillectomy is the main treatment measure, additional interventions such as CPAP or orthodontic therapy may be required. As a series of therapies might act synergistically to relieve upper airway obstruction, collaboration between sleep medicine physicians, ENT surgeons, respiratory physiologists, specialist nurses and orthodontists is warranted to achieve optimal results.

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Central sleep apnoeas and hypoventilation syndromes

Ha Trang and Iulia Ioan

Breathing is a rhythmic, automatic and permanent respiratory activity that originates in the neural networks of the hindbrain. In order to meet physiological needs, breathing is modulated by influences from the cortex or other structures (*i.e.* hypothalamus) *via* multiple physiological factors (*e.g.* sleep, movement, cognition, emotion). Major groups of respiratory neurons are located within the ventrolateral medulla; the pre-Bötzinger complex where automatic respiratory activity is generated interacts with many important groups such as the locus coeruleus, the nucleus of the solitary tract and the retrotrapezoid nucleus. Central sleep apnoea (CSA) and central hypoventilation syndromes, which are caused by dysfunction of these complex neural circuits controlling breathing, are discussed in this chapter.

Central sleep apnoea

CSA is defined as the cessation of airflow with simultaneous absence of breathing efforts lasting for >20 s or more than two breaths and associated with ≥3% oxygen desaturation and/or arousal in children, and/or heart rate <60 bpm for 15 s or <50 bpm for 5 s in infants, as recommended by the American Academy of Sleep Medicine (AASM). Periodic breathing is defined as more than three recurrent CSAs lasting >3 s interrupted by <20 s of normal breathing.

CSA can be observed in healthy newborns, infants and children. Premature newborns are more likely to present with CSA due to their unstable respiratory control and immature peripheral chemoreceptors, especially during active or rapid eye movement (REM) sleep. In term newborns, CSA occurs frequently at birth and decreases with

Key points

- Central sleep apnoea may be present in healthy newborns, infants and children.
- Hypoventilation is more severe during non-rapid eye movement (non-REM) sleep than during REM sleep in congenital central hypoventilation syndrome (CCHS).
- CCHS is associated with mutations of the *PHOX2B* gene.
- Hypothalamic dysfunction with central hypoventilation syndrome is a complex disease with myriad clinical manifestations.

Table 1. The main aetiologies of CSA (with/without hypoventilation) in children

Primary CSA with hypoventilation	Secondary CSA (with/without hypoventilation)
Congenital central hypoventilation syndrome	Brainstem tumours
Late-onset congenital central hypoventilation syndrome	Chiari malformation with associated myelomeningocele
Hypothalamic dysfunction with central hypoventilation syndrome	Mucopolysaccharidosis
	Achondroplasia
	Prader–Willi syndrome
	Joubert syndrome
	Cardiomyopathy
	Hypothyroidism

advancing age. In healthy children aged >1 year, CSA occurs during REM sleep; some authors consider an index of >1 CSA·h^{-1} of sleep as pathological, but previous reports in preschool and school-aged healthy children found a CSA index of 0.08±0.14 (mean±SD) with a range of 0–6.0 CSA·h^{-1} of sleep (Traeger *et al.*, 2005).

The pathophysiology of CSA in children is yet to be fully investigated. CSA may be caused by hyperventilation or hypoventilation. Few data are available on hyperventilation-induced CSA. It is thought that CSA is elicited when carbon dioxide levels decrease below a certain point called the "apnoea threshold". This point is very close to the baseline carbon dioxide level in infants and preterm babies, so common events such as sighing, brief hypoxic events or movements may cause repetitive CSA. Other factors may also contribute, including resetting of peripheral carotid chemoreceptors at birth and biphasic ventilatory responses to hypoxia in the first days of life leading to an unstable breathing pattern. Another factor is a high loop gain system, a term defining an exaggerated ventilatory response to changes in carbon dioxide or oxygen levels, with resulting repetitive CSA alternating with hyperventilation.

CSA may be caused by hypoventilation, as discussed in the following section. In Chiari malformation identified by brain MRI, CSA is due mainly to brainstem compression and disappears after surgical decompression. Children with a variety of diseases such as cardiomyopathy or Prader–Willi syndrome (table 1) are more likely to present with CSA. Rare cases of isolated CSA have been reported.

Central hypoventilation syndromes

Alveolar hypoventilation during sleep is defined as a transcutaneous or end-tidal carbon dioxide tension (P_{CO_2}) >50 mmHg for >25% of sleep time during spontaneous breathing (as defined by the AASM). Alveolar hypoventilation during wakefulness is defined as P_{aCO_2} (or surrogate P_{CO_2}) >45 mmHg during spontaneous breathing. Hypoventilation occurs when insufficient ventilation produces increased levels of P_{CO_2} and hypoxaemia, and subsequently apnoeas or bradypnoeas. Hypoventilation may result from central or peripheral causes. Only central hypoventilation is covered in this chapter.

Central hypoventilation may be secondary to other events such as adverse drugs or central nervous system diseases such as cerebrovascular accidents, trauma, tumours, bone compression (*i.e.* Chiari malformation) and metabolic disorders. Central hypoventilation is referred to as "primary" if abnormal control of breathing has its origins in the hindbrain respiratory centres. Central hypoventilation may be one of the multiple clinical features present in a number of specific diseases such as Prader–Willi

syndrome and familial dysautonomia. Of more interest, central hypoventilation may be a major feature of a number of complex disorders, the main two of which are congenital central hypoventilation syndrome (CCHS) and hypothalamic dysfunction with central hypoventilation syndrome (HD-CHS).

Congenital central hypoventilation syndrome

CCHS (MIM 209880, https://omim.org/entry/209880) is a rare disease characterised by an abnormal ventilatory response to hypoxia and hypercapnia, leading to hypoventilation at least during sleep. Additional dysfunction of the autonomic nervous system is associated with CCHS, such as Hirschsprung disease, neural crest tumours and autonomic dysfunction of various systems (*e.g.* cardiovascular, digestive and ocular). The prevalence of CCHS is estimated to be around one in 555 000 of the population, and the incidence to be one in 200 000 livebirths. Nearly 20% of patients with CCHS have associated Hirschsprung disease and 5% of patients with CCHS have associated neural crest tumours. More than 90–92% of patients with CCHS harbour *PHOX2B* mutations, the most frequent being polyalanine expansions. Management is currently supportive, with lifelong ventilatory support and multi-subspecialty follow-up.

Respiratory phenotype

CCHS typically presents at birth. Neonates with CCHS demonstrate repeated apnoeas, cyanosis during sleep and bradycardia, and despite severe hypoxaemia, fail to increase their breathing. PSG shows severe alveolar hypoventilation during sleep with shallow breathing and a slow respiratory rate. Hypoventilation is most severe during sleep, and especially during non-REM sleep, a sleep state during which central control of breathing depends nearly exclusively on the central carbon dioxide level (figure 1 and table 2). The hallmark feature of CCHS is absent or markedly reduced central

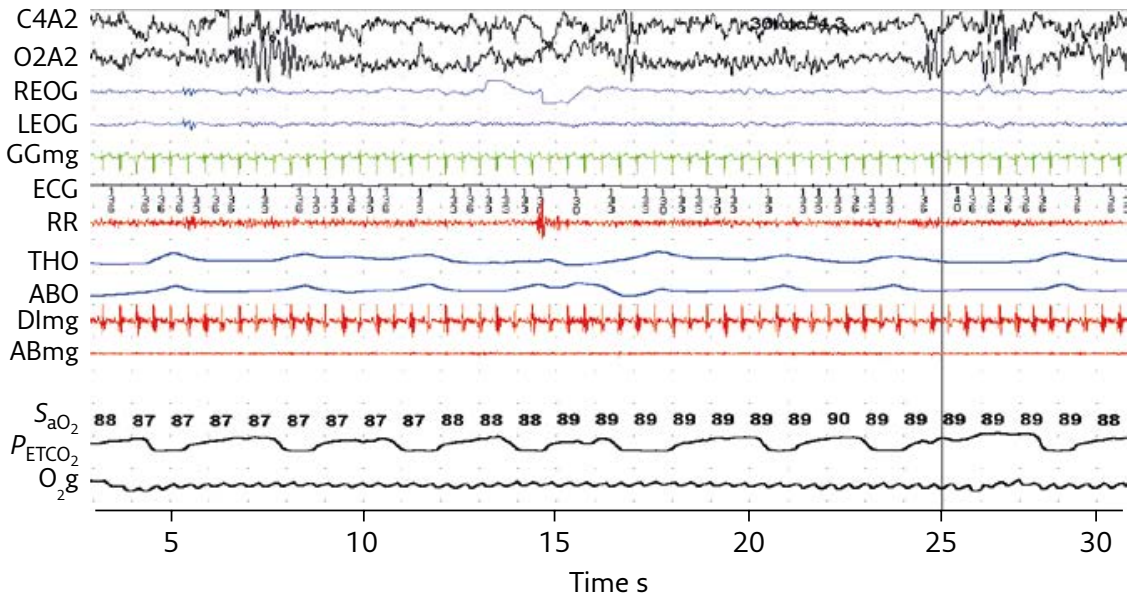

Figure 1. Typical respiratory pattern observed in a newborn with CCHS, showing a low respiratory rate and reduced amplitude of breathing, desaturation and hypercapnia resulting in hypoventilation during spontaneous breathing of room air. Hypoventilation is more marked during sleep than during wakefulness and more marked during non-REM sleep than during REM sleep. C4A2 and O2A2: electroencephalogram channels; REOG and LEOG: right and left electro-oculogram; GGmg: genioglossus electromyogram; RR: R-R interval; THO and ABD: respiratory movements of the thorax and abdomen; DImg and ABmg: electromyograms of diaphragm and abdominal muscles; P_{ETCO_2}*: end-tidal carbon dioxide tension;* O_2g*: plethysmographic measurement of* S_{pO_2}*.*

Table 2. Decreased hypercapnic and hypoxic ventilatory responses in all states of alertness in a newborn with CCHS

	Wake	REM sleep	Non-REM sleep
Room air			
V_T mL·kg^{-1}	8.0	8.5	4.6 (↓)
RR breaths·min^{-1}	45	27 (↓)	20 (↓)
V'_E mL·min^{-1}·kg^{-1}	359	227 (↓)	90 (↓↓)
Hypercapnic ventilatory response			
$\Delta V'_E/\Delta P_{ETCO_2}$ mL·min^{-1}·kg^{-1}·mmHg^{-1}	6.7 (↓)	ND	1.6 (↓)
Hypoxic ventilatory response			
$\Delta V'_E/\Delta S_{aO_2}$ mL·min^{-1}·kg^{-1}·%$^{-1}$	–1.8 (↓)	–8.7 (↓)	ND

V_T: tidal volume; RR: respiratory rate; P_{ETCO_2}: end-tidal carbon dioxide tension; ↓: decrease; ND: not done.

hypercapnic ventilatory responses. The ventilatory deficit persists over the lifetime. With increasing age, most patients can breathe spontaneously while awake.

In the last few years, broader phenotypes have emerged and gained awareness among practitioners. Symptoms (typically cyanotic apnoea spells and unexplained convulsions resistant to treatment, with a normal electroencephalogram, and the ability to hold breath for prolonged periods) may present during late infancy or childhood, and even during adulthood. These cases are called late-onset CCHS. In most cases, triggering factors are found, such as cold weather, lung infections, anaesthesia, and swimming or diving leading to near-drowning. Some cases of CCHS can also be identified by a familial genetic study.

There is large inter-individual variability in the respiratory deficits in patients with CCHS. The mechanisms underlying respiratory variability are yet to be fully determined. Early studies showed a correlation between the length of the alanine expansions and the severity of the respiratory deficit, with the longest alanine expansions being associated with the most severe respiratory phenotype and the smallest (+5 alanines) associated with late onset as well as neonatal onset of central hypoventilation. However, more recent studies have shown that as yet undetermined factors may contribute to the degree of respiratory deficit, and the hypercapnic ventilatory response slope is not correlated with the length of the alanine expansion.

Hypoventilation is severe during sleep, and patients with CCHS require assisted ventilation during sleep as life support; 5–10% also require ventilatory support during the daytime. Breathing is also challenged by everyday activities during wakefulness (*e.g.* quiet activity, eating, exercise, cognitive activity, infections), and strategies used by patients with CCHS to adapt breathing under various conditions remain unclear.

Genetics

CCHS is caused by heterozygous mutations of the *PHOX2B* gene, encoding a transcription factor crucial for central nervous system development. Most of the mutations are *de novo* at the first generation, and transmission is autosomal dominant with incomplete penetration. Studies show nearly 10% mosaics in parental DNA.

Most of the mutations are polyalanine repeat expansion mutations (PARMs) in exon 3 of the gene. In-frame duplications leading to polyalanine expansions of +4 to +13 alanines are the most frequent *PHOX2B* mutations, and the length of expansion is thought to correlate with the severity of the respiratory phenotype, except in cases of

unexplained reduced penetrance and variable expressivity. Rarer missense, nonsense, frameshift and stop-codon mutations can also occur in CCHS patients and are known as non-PARMs. Gene deletion (detected using the multiplex ligation-dependent probe amplification technique) is rarely found. Polyalanine expansions have been associated with cytoplasmic retention of the mutant PHOX2B protein, aggregate formation *in vitro* and defective PHOX2B autoregulatory control.

Longer alanine expansions in PARMs (+9 to +13 alanines) and non-PARMs are significantly associated with a higher prevalence of tumours of neural crest origin. Hirschsprung disease is not found in individuals with the +5 alanines genotype.

Future studies

The picture of CCHS is still evolving. CCHS is a paediatric and an adult disease, affecting not only newborns but also infants, children and adults. Familial cases result in issues in management of the disease. Research is still ongoing, with newly discovered mutations of the *PHOX2B* gene as well as the involvement of new genes (*e.g. MYOH1*). Further research should aim to untangle additional pathogenic mechanisms and to identify sensitive drug targets and effective molecules.

Hypothalamic dysfunction with central hypoventilation syndrome

HD-CHS is a very rare disease and has had a variety of names since its first description in 1965 as primary alveolar hypoventilation syndrome associated with hypothalamic disease, including late-onset central hypoventilation syndrome with hypothalamic dysfunction, rapid-onset obesity hypoventilation, hypothalamic and autonomic dysfunction (ROHHAD) and ROHHAD-NET (for neuroendocrine tumours). However, some authors thought that ROHHAD might be misnamed, as obesity may not be present and this might induce delayed diagnosis and care. In this chapter, we use the name HD-CHS as most features are caused by hypothalamic dysfunction and the presence of central hypoventilation further worsens prognosis. The number of patients is unknown (fewer than 100 reported worldwide).

HD-CHS is a clinical entity characterised by myriad hypothalamic and autonomic dysfunction-related symptoms, including: hormonal deficits; autonomic dysfunction regarding control of body temperature, sweating, heart rate and blood pressure changes; behaviour changes (*i.e.* aggression or excessive hunger); ocular disorders (*i.e.* strabismus or different pupil sizes); and respiratory arrest needing resuscitation.

A large inter-individual variability of symptoms is observed. Phenotype evolves with advancing age. In a recent study including 100 cases (65 female and 35 male), the median age of diagnosis was 4 years (Lee *et al.*, 2018). The prevalence of rapid onset of obesity was 83%, hypoventilation 73% (OSA 44%, ventilatory support 44%) and neuroendocrine tumours 52%, and for endocrine disorders the prevalence of deficiency in growth hormone was 25%, diabetes insipidus 15% and central precocious puberty 15%.

Central hypoventilation caused by absent or attenuated responses to hypercapnia and to hypoxaemia needs to be investigated regularly during follow-up. Hypoventilation is not found at birth or in the first months of age. It may not manifest clinically until an intercurrent illness produces abrupt deterioration. At younger ages, there is no or minimal hypoventilation, and some responsiveness to exogenous challenges is present. There may then be severe hypoventilation during sleep with a limited response to the exogenous hypercapnia and hypoxia. Later, hypoventilation occurs during wakefulness after trigger events (lung infections) or becomes permanent.

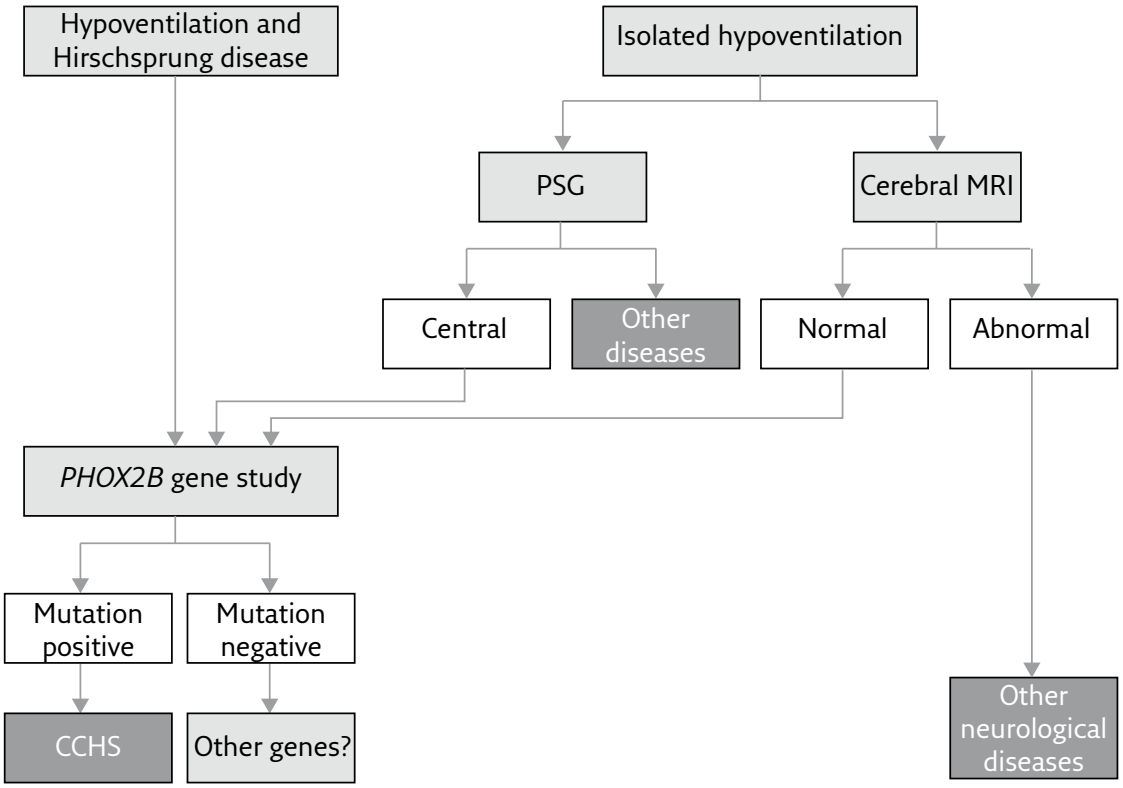

Figure 2. Diagnosis of neonatal hypoventilation (<1 month of age), after exclusion of cardiovascular, bronchopulmonary, neuromuscular and metabolic diseases and drug interference.

Despite the disease being thought to have a genetic origin, no genetic defect has been identified so far in many unbiased massive sequencing analyses performed in these patients and their families. HD-CHS is still a mysterious disease, the cause of which remains unknown; hypotheses include alterations of early neurological development and epigenetic or paraneoplastic mechanisms. Management is life-support-assisted ventilation and lifetime multi-subspecialty care and follow-up.

Other central hypoventilation syndromes

Other idiopathic central hypoventilation syndromes without *PHOX2B* mutations have been described, and recently two consanguineous families have been reported with autosomal-recessive central hypoventilation syndrome in association with mutations of the *MYO1H* and *LBX1* genes.

Diagnosis of central hypoventilation

Figure 2 shows suggested pathways of diagnosis of neonatal central hypoventilation (in the first month of age), while figure 3 shows pathways of diagnosis of late-onset hypoventilation with or without obesity.

Summary

CSA and central hypoventilation syndromes are due to dysfunction of the central control of breathing. The clinical manifestations are poor and nonspecific, thus delaying recognition. Diagnosis relies on full nocturnal PSG with recording of S_{pO_2} and P_{CO_2}. CSA and central hypoventilation syndromes are rarely observed in children; however, this group of diseases has gained more interest and awareness among practitioners in recent years. Further research is required to better understand the mechanisms underlying pathogenesis in order to identify potential targets for treatment.

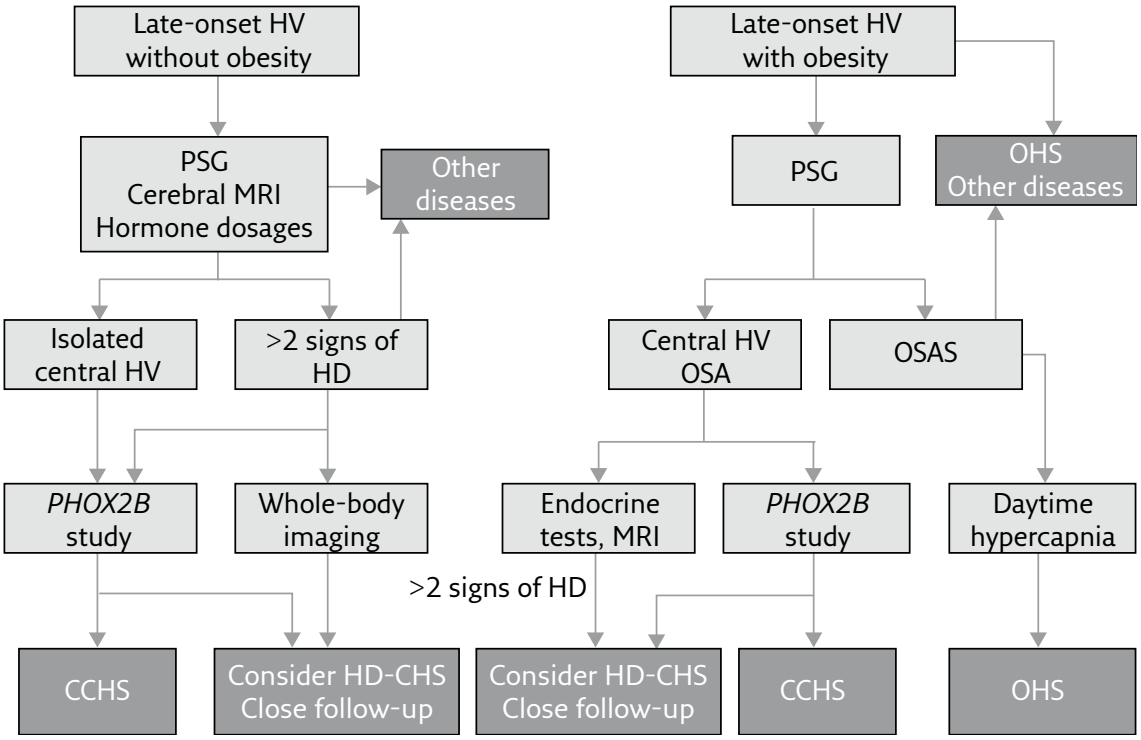

Figure 3. Diagnosis of late-onset hypoventilation (HV) without and with obesity. OHS: obesity hypoventilation syndrome.

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Breathing pattern disorders

Samatha Sonnappa and Charlotte Wells

Breathing is an automatic, involuntary action controlled by the pontine and medullary neuronal networks. An important characteristic of the human respiratory system is its ability to adjust breathing patterns to changes in both the internal milieu and the external environment. Consequently, some volitional control can be exercised over breathing, and prolonged inappropriate breathing may develop into a habitual breathing pattern disorder. This chapter provides a broad overview of such disorders.

When a breathing pattern disorder occurs as a physiological response to a respiratory disease such as asthma and CF, it is termed a secondary breathing pattern disorder, while in the absence of respiratory disease, it is considered a primary breathing pattern disorder and indicates psychogenic causes. Multiple terms have been used to describe breathing pattern disorder symptoms, including dysfunctional breathing, hyperventilation syndrome, behavioural breathlessness, anxiety-related breathlessness, psychogenic functional breathing disorder and somatic form respiratory disorder. We prefer to use the overarching term "breathing pattern disorder", as this encompasses all abnormal breathing patterns. Breathing pattern disorders are best described as chronic or recurrent changes in breathing pattern that cannot be attributed to a specific medical diagnosis, causing respiratory symptoms such as breathlessness and non-respiratory symptoms such as anxiety, light-headedness and fatigue.

Key points

- Breathing pattern disorders can be divided into primary, which occur in the absence of disease and indicate psychogenic causes, and secondary, which are a physiological response to respiratory diseases such as asthma and CF.
- The mechanisms of breathing pattern disorders involve dynamic interactions among pathological, physiological, psychological and biomechanical components.
- The clinical presentation includes both common dysfunctional breathing patterns and specific conditions such as exercise-induced laryngeal obstruction and hyperventilation syndrome.
- It is important to distinguish breathing pattern disorders from other respiratory diseases so that each can be managed appropriately.

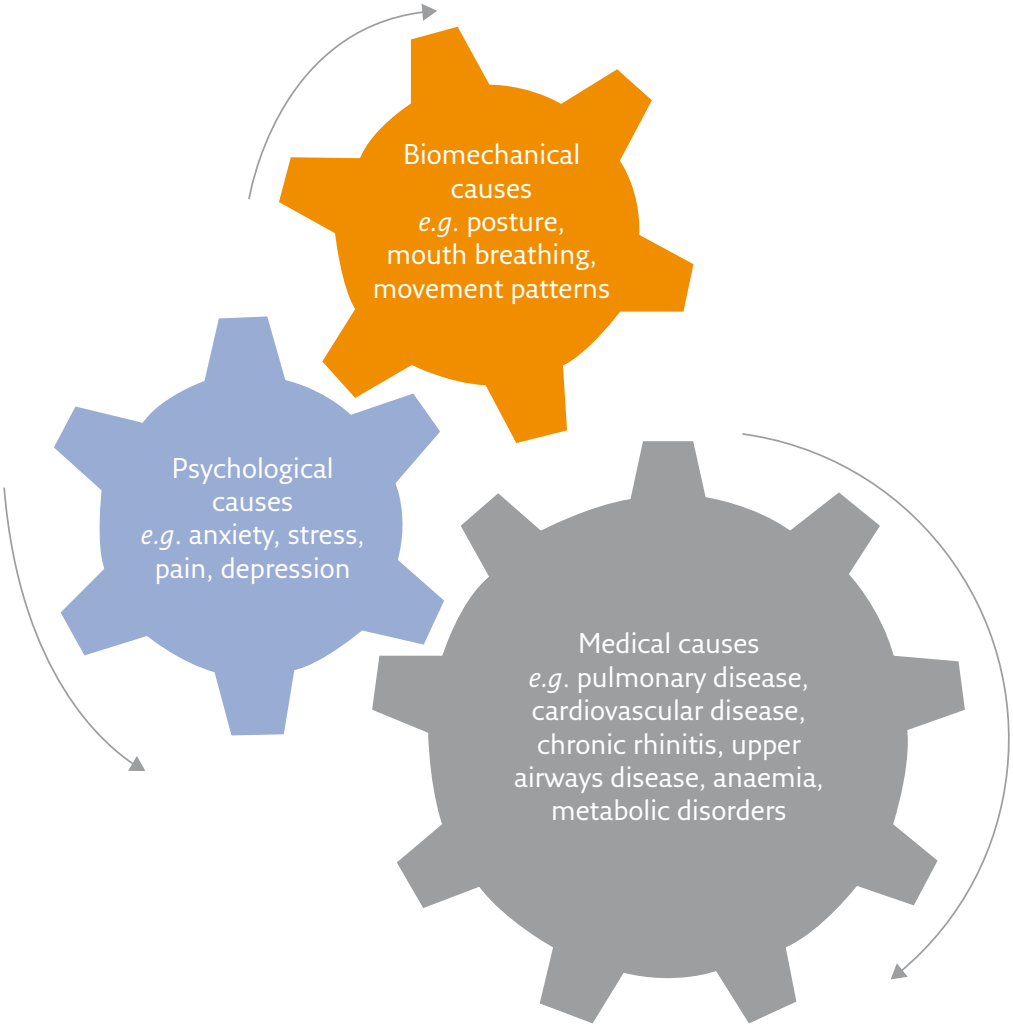

Figure 1. The dynamic association of medical, psychological and biomechanical causes in breathing pattern disorders.

Disruption of an optimal breathing pattern can contribute to multiple distressing and debilitating symptoms that impact significantly on the quality of life. The mechanisms underlying breathing pattern disorders involve pathological, physiological, psychological and biomechanical components. The different components cannot easily be separated as there is significant overlap, with a dynamic interaction between them (figure 1). Symptoms of breathing pattern disorders may masquerade as asthma or other respiratory diseases and can also occur in association with any respiratory disease. It is this association that makes it challenging to isolate breathing pattern disorders and not over- or undertreat an underlying respiratory disease.

Clinical presentation

The broad umbrella of breathing pattern disorders includes the dysfunctional breathing patterns described in table 1, as well as the following common dysfunctional patterns:

- Periodic deep sighing: regular sighing defined as a tidal volume three times the volume of a normal tidal breath, leading to an irregular breathing pattern associated with dyspnoea
- Thoracic-dominant breathing: predominant use of the apical or upper part of the thorax

- Forced abdominal expiration: inappropriate or excessive abdominal activity during expiration
- Thoraco-abdominal asynchrony: paradoxical movement of the abdomen and chest

Also included are specific conditions such as exercise-induced laryngeal obstruction (EILO) and hyperventilation syndrome (HVS), which can occur in isolation or coexist with other dysfunctional breathing patterns.

Exercise-induced laryngeal obstruction

EILO is a condition where inappropriate supraglottic or glottic narrowing occurs during exercise. It is characterised by exercise-induced stridor, a harsh inspiratory sound caused by turbulent airflow through a narrow laryngeal opening. The condition is believed to be prevalent in adolescents, particularly athletes. A history of inspiratory symptoms during exercise that resolve within a few minutes of stopping exercise is key to a correct diagnosis of EILO. Causal mechanisms are poorly understood, and underlying factors include the aerodynamic effects of high inspiratory flow rates, neurally mediated laryngeal hyperreactivity and environmental factors, such as inhaling cold air and swimming in a heavily chlorinated pool. EILO can coexist with exercise-induced asthma and is frequently misdiagnosed as asthma in the absence of genuine asthma.

Inducible laryngeal obstruction, the involuntary narrowing of the upper airway during inspiration, is more complex and multifactorial. In affected subjects, anxiety and psychological factors predominate, particularly when symptoms occur spontaneously at rest.

A continuous laryngoscopy during exercise test is currently the gold standard for diagnosis of EILO, as this condition cannot be diagnosed at rest when symptoms are

Table 1. Differential objective breathing pattern characteristics

Optimal breathing pattern	Dysfunctional breathing pattern
Preferential nose breather	Preferential mouth breather: Signs of "air hunger" including excessive yawning, sighing and deeper breaths Habitual dry, irritable cough or throat clearing
Predominant diaphragmatic breather: Diaphragm descends into abdominal cavity during inspiration leading to lower rib movement out and up, and upper abdomen is pushed out Diaphragm relaxes and returns to domed position on exhalation	Predominant apical breather
Silent breathing at rest	Audible breathing indicating higher flow
Inspiration/expiration ratio of 1/1.5–2	Altered inspiration/expiration ratio, often with a reduced exhalation phase
Normal resting respiratory rate	Raised resting respiratory rate
No alteration to tidal volumes	Altered resting tidal volumes, which could be either small and fast or larger
Exhalation is passive	Active upper abdominal muscles on expiration
Steady rhythmical pattern to breath	Altered rhythm of breath including breath-holds, judders and breath stacking
Symmetry of rib movement	Paradoxical breathing; asymmetry of rib movement

absent. A flexible laryngoscope is inserted through the nostril into the larynx at rest. The scope is positioned just above the aryepiglottic folds, while externally the laryngoscope is attached to headgear that holds it in place during exercise. The subject is connected to a cardiopulmonary exercise unit and exercises incrementally to symptom limitation on a treadmill, exercise bike or rowing machine. This allows continuous video assessment of laryngeal movement while the subject is exercising.

The management of EILO is personalised by considering the structural and functional components in each subject. Physiotherapy, speech and language therapy, inhaled ipratropium before exercise and biofeedback techniques have been used as nonsurgical treatment options. Laser supraglottoplasty has been effective in treating subjects with severe supraglottic EILO and is usually performed in adulthood.

Hyperventilation syndrome

The term hyperventilation was used synonymously with dysfunctional breathing in the past and is the most widely recognised form of breathing pattern disorder. Hyperventilation is a sustained abnormal increase in breathing frequency or tidal volumes, during which P_{aCO_2} in the blood decreases, resulting in respiratory alkalosis and subsequent cerebral vasoconstriction. The resultant constellation of symptoms including dyspnoea, light-headedness, paraesthesia, chest pain, palpitations and sweating is attributed to HVS. While most patients complain of attacks of breathlessness occurring at rest for no apparent reason, many experience breathlessness on exertion that bears little or no relation to the severity of the exercise. HVS is produced when a patient has some stimulus that produces overbreathing and overventilation with the resultant loss of carbon dioxide from the lungs, and varies in severity.

Anxiety and panic disorder, a severe episodic form of anxiety, are the most common causes of HVS. Acute asthma attacks are also associated with an increased prevalence of hyperventilation as demonstrated by low P_{aCO_2}, which may further worsen the asthma attack by airway dehydration and bronchoconstriction.

While demonstration of hypocapnia and respiratory alkalosis during attacks of hyperventilation were considered mandatory in the past, studies report that some symptoms can also occur in normocapnia. A hyperventilation provocation test was once considered the gold standard to diagnose HVS. This test requires patients to breathe as deeply and quickly as possible for 2–3 min. If a patient reports symptoms and sensations that are similar to those experienced during hyperventilation, the presence of HVS is confirmed. However, this is controversial, as HVS symptoms can also occur in normocapnic states. Cardiopulmonary exercise testing (CPET) may facilitate the diagnosis of HVS and help exclude other causes of dyspnoea.

Management of breathing pattern disorders

Assessment and treatment of breathing pattern disorders forms a vital element of clinical management of children with symptoms of breathlessness, particularly with exercise. While a specialised physiotherapist is integral in the management of patients with a breathing pattern disorder, a multidisciplinary approach is considered ideal (figure 2).

Assessment

Subjective assessment

Specialist subjective history taking is required to review breathlessness, cough, sputum, wheeze and chest pain in order to identify the duration, severity,

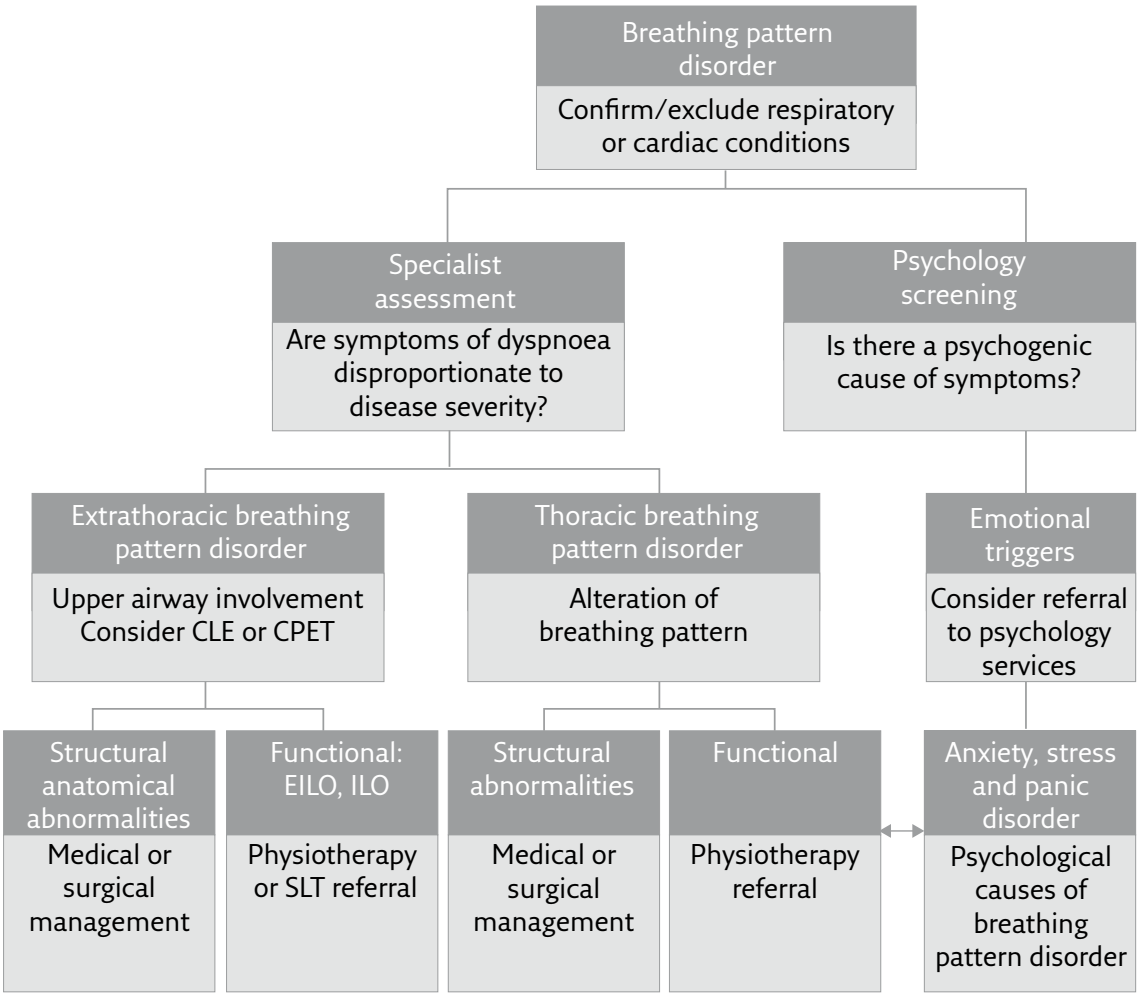

Figure 2. Schematic approach to the diagnosis and management of breathing pattern disorders. CLE: continuous laryngoscopy during exercise; ILO: inducible laryngeal obstruction; SLT: speech and language therapy. Adapted from Barker et al. *(2015).*

pattern, and precipitating and relieving factors. Specialist questions on exercise-induced symptoms are required to differentiate between exercise-induced bronchoconstriction and EILO. There are currently no validated respiratory symptom questionnaires for children to diagnose breathing pattern disorders; however, scores of >23 using the Nijmegen Questionnaire have been shown to indicate a breathing pattern disorder.

Objective assessment

Assessment of breathing patterns (table 1) should occur when the patient enters the clinic, when they are unaware of observations and therefore less likely to consciously alter their breathing pattern.

Posture

Prolonged alteration to breathing patterns leads to habitual postural changes. These commonly include a slumped posture with a "chin poke", stiffness in the thoracic and cervical spine, and rounded shoulders.

Exercise capacity

CPET should be considered when symptoms occur during activity or exercise. This can exclude other causes of breathlessness during exercise and help diagnose exercise-induced bronchoconstriction or EILO. Although the identification of HVS through CPET has not yet been standardised, lower end-tidal carbon dioxide tension, higher V'_E,

slower recovery time and disproportionate perception of breathlessness to exertion are indicative of HVS.

Psychological assessment

There is a strong correlation between stress and anxiety and breathing pattern disorders. Inclusion of a psychological assessment of anxiety and depression and health-related quality-of-life measures helps guide psychology referrals.

Treatment

Physiotherapy

The primary focus of physiotherapy intervention is breathing pattern retraining that focuses on re-establishing normal diaphragmatic breathing. Methods such as the Papworth, Buteyko and Bradford techniques teach nose breathing, diaphragmatic breathing and reduction of respiratory rates, re-establishing a gentle flow and rhythm to the breathing pattern. Musculoskeletal interventions help correct postural changes, and saline sinus rinsing helps clear a blocked nose, which may hinder the return to a normal breathing pattern. Management strategies should be taught to help suppress a chronic cough or throat clearing.

Children with EILO are taught good laryngeal "hygiene", normal laryngeal function and breathing exercises to help relieve symptoms during high-intensity exercise. Several EILO biphasic inspiratory breathing techniques have been described to be useful during high-intensity exercise. These techniques change airflow by splitting inhalation into a high-resistance and a low-resistance phase.

Psychology

It is important for children with a primary breathing pattern disorder where symptoms are triggered by psychogenic causes such as stress and anxiety to have a psychological review. Psychologists can highlight the interactions between psychogenic and physical symptoms, exploring the emotional responses and offering alternative coping mechanisms to help prevent chronic symptoms.

Speech and language therapy

Guided speech-behavioural therapy using several techniques such as relaxation of the oropharyngeal muscles, quiet rhythmic breathing, pulsed exhalation and laryngeal control therapy may be beneficial in patients with inducible laryngeal obstruction and EILO.

Summary

Clinicians should screen for breathing pattern disorders while taking a history and during examination of patients presenting with breathlessness, as there is a wide spectrum of breathing pattern disorder presentation. This will provide a valuable insight into non-organic causal factors of breathlessness, enabling comprehensive management of the patient.

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Rehabilitation programmes and nutritional management

Andreas Jung

Targets of rehabilitation programmes in childhood and adolescence

Pulmonary rehabilitation is defined as an evidence-based multidisciplinary and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Integrated into the individualised treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimise functional status, increase participation, and reduce healthcare costs through stabilising or reversing systemic manifestations of the disease. Recuperation of impaired function, activity and participation as defined by the International Classification of Functioning, Disability and Health (ICF) of the World Health Organization (WHO) are key features of any medical rehabilitation. Rehabilitation programmes in children and adolescents also target preventative measures, which aim to slow down disease worsening, improve self-management and restore quality of life. It is anticipated that the child, or the adolescent, will be

Key points

- Rehabilitation programmes in children and adolescents with chronic respiratory disorders aim to prevent worsening of the disease, improve self-management and restore quality of life to enable full participation in daily life, and consist of standardised multidisciplinary interventions.
- The programmes address a broad spectrum of chronic respiratory conditions and can contribute efficiently to a general improvement in morbidity and mortality in the context of a complex disease management.
- Advanced lung disease results in increased energy expenditure, an augmented level of inflammation and diminished appetite, contributing to a loss of body weight and requiring specific nutritional management, including counselling, installation of a daily nutrition plan, high-protein calorie supplementation, and substitution of vitamins and micronutrients.
- In asthma and other diseases, the role of behaviour changes in counteracting obesity, including introduction of exercise and nutritional counselling, needs to be addressed in educational programmes.

Table 1. Goals of pulmonary rehabilitation programmes in children and adolescents

Maintenance and restoration of social, educational and professional activities
Improvement and long-term maintenance of the health condition
Preventative measures to reduce disease worsening or progression
Amendment of disease perception, acceptance and management
Improvement of adherence to treatment
Restoration of quality of life
Changes of lifestyle
Reduction of healthcare costs

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able to fully participate in daily life, such as school, social activities and sports, in the same ways as their healthy peers. Rehabilitation programmes have been developed in many countries in inpatient and outpatient settings. Inpatient programmes are often more standardised than outpatient programmes, as the latter are often tailored to meet local needs. In addition, inpatient programmes provide the possibility of individual daily monitoring of patients over several weeks in specific institutions in order to optimise therapeutic interventions and complete diagnostic procedures that are beyond the possibilities of an outpatient setting. Independent of the rehabilitation setting, the objectives of current rehabilitation programmes include a number of specific considerations, as shown in table 1. Rehabilitation centres and sponsors of healthcare systems have defined criteria for the eligibility of an individual intending to participate in a rehabilitation programme (table 2). If the criteria of the rehabilitation institution, the patient and their family are met, the most important preconditions for successful pulmonary rehabilitation are achieved. As a result, paediatric rehabilitation programmes have been shown to result in a reduction in school or work absence, healthcare utilisation and healthcare costs in a number of studies.

Components of paediatric rehabilitation programmes for respiratory diseases

Pulmonary rehabilitation programmes consist of standardised, multidisciplinary interventions performed by a range of highly qualified health professionals. Depending on the disease spectrum addressed by rehabilitation centres, essential elements potentially include a wide range of actions such as extended diagnostic procedures, specific medical care, educational interventions and a multidisciplinary team approach (table 3). Exercise training is a common focus of such programmes,

Table 2. General criteria for children and adolescents to participate in rehabilitation programmes

Ability for rehabilitation is fulfilled: willingness to actively participate in the programme, capacity to fulfil rehabilitation aims and ability to integrate into groups
Improvement of prognosis can be achieved: improvement of health and restoration of professional and/or social activity
Measures of outpatient care are exhausted but not sufficient to adequately ameliorate health or suspend health impairment
Secondary damage to health is imminent or has already occurred
Psychosomatic or psychosocial problems are difficult to address in an outpatient setting (demarcation from the social environment)
Interventions to promote coping and adherence to treatment are necessary

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Table 3. Essential components of a comprehensive paediatric pulmonary rehabilitation programme

Respiratory diagnostics including body plethysmography
Comprehensive allergy testing including provocation tests
Routine laboratory tests including blood gas analysis
Chest radiography
Disease-specific nursing
Separation of patients according to microbiological profile
Monitoring of vital parameters and possibility of oxygen application
Respiratory physiotherapy
Physical exercise training and sports therapy
Occupational therapy
Nutritional intervention and advice by a dietician
Psychological counselling and family support
Standardised specific education in disease understanding and management
Advice in matters of financial, educational and occupational aspects

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with a general goal to return to regular sports, if possible. While current exercise guidelines are characterised by the FITT principle (frequency, intensity, time and type) of the American College of Sports Medicine (ACSM), some authors, in addition to the clinical experience, suggest also including other motivating factors such as enjoyment as well as cognitive, environmental and socioeconomic considerations to make exercise treatment successful in the longer term. Standardised care may also include consultation of specific medical professionals in cases of multiorgan or psychiatric symptoms and diseases. In inpatient programmes, children and adolescents often participate in educational preschool or school activities for the duration of the hospitalisation period. Some rehabilitation centres offer a family-centred intervention, and treat parents and other family members together with their children (figure 1). These programmes have come into focus recently with increasing awareness that sustainability of rehabilitation is related to the successful restoration of impairments in functioning, activity and participation of the whole family. Consequently, initial studies have demonstrated a beneficial effect on the quality of life of the accompanying parents.

A multidisciplinary team closely follows each patient or family during the whole interventional period. This approach facilitates individual treatment in the context of an often group-based rehabilitation programme. As patients can be monitored intensively over a longer period of time, individual symptoms and risk factors, as well as psychological aspects, can be evaluated continuously and, as a result, specific diagnostic procedures can be applied. In the same way, treatment modifications can be carried out and the subsequent course of the disease can be observed over time.

Patient education: a core element of rehabilitation programmes

Educational programmes are important components of contemporary rehabilitation programmes, featuring theoretical instructions accompanied by practical exercises. Knowledge is disseminated to promote disease understanding, recognition of individual risk factors and coping strategies, consequently improving self-management in daily life. Practical training is provided to improve medication application skills and techniques. Written action plans foster adherence to the individual treatment

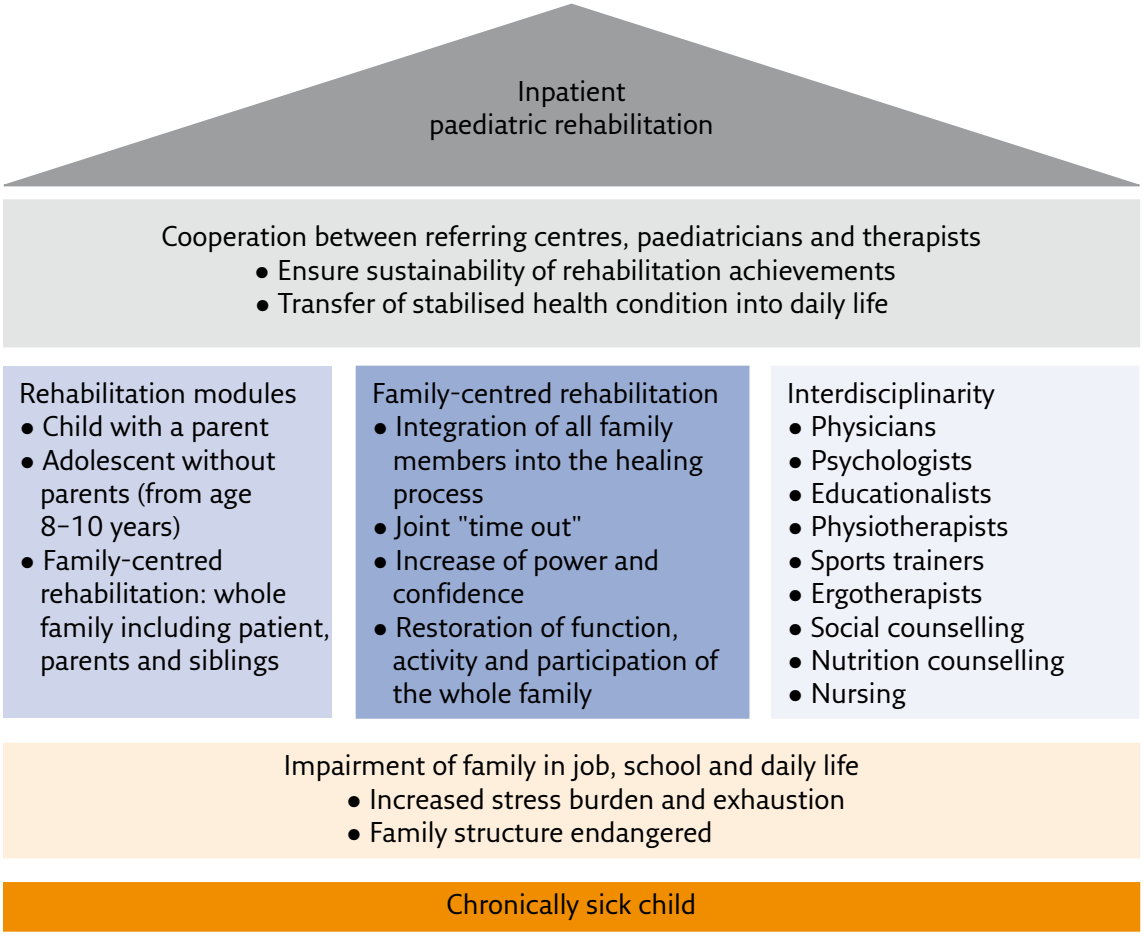

Figure 1. Structure of a family-centred inpatient rehabilitation programme.

strategy. As a result, compliance, self-management and a positive outcome of the disease are often significantly increased.

Educational programmes for children and adolescents have been developed for various diseases in many countries. In the respiratory field, the most widespread and best standardised protocols exist for asthma. Asthma education programmes have often been developed independently of pulmonary rehabilitation programmes and are frequently performed in an outpatient setting. Inpatient rehabilitation programmes have integrated sections or whole protocols of national or regional asthma education programmes, resulting in standardised *en bloc* interventions.

Disease-specific rehabilitation programmes

A vast spectrum of chronic respiratory conditions are addressed by paediatric rehabilitation programmes, including asthma, CF, bronchiectasis, BPD, PCD, neuromuscular disorders, ILDs, cardiovascular diseases, dysfunctional breathing, and before and after lung transplantation. In recent years, there has been a closer focus on psychosomatic and dysfunctional comorbidities secondary to chronic respiratory diseases, as targeting these symptoms has proved important in supporting a favourable disease outcome. There is a growing body of evidence that rehabilitation programmes for chronic respiratory diseases in the paediatric population are efficient in terms of health improvement. Most published studies have investigated protocols and outcomes in patients with asthma and CF, as these disorders constitute the majority of indications for pulmonary rehabilitation in the first two decades of life. In the future, structured interventions before and after lung transplantation will become

increasingly important in light of a growing number of patients on the transplantation waiting list, as well as a rapidly increasing number of transplanted individuals.

Asthma

In the USA, asthma camps often focus on health education and interaction with peers. Despite the fact that asthma camps cannot replace specific rehabilitation programmes, there is evidence that these interventions can:

- Improve the parent's and child's knowledge of asthma
- Increase a child's locus of control
- Improve self-efficacy and attitude to the disease
- Improve asthma-related behaviour and pulmonary function measures
- Improve the child's metered-dose inhaler technique

Furthermore, asthma camps decrease anxiety, symptoms, exacerbations, school absences, emergency department visits and hospitalisations. Although asthma camps also exist in Europe, standardised inpatient asthma rehabilitation programmes in specialised hospitals are predominant. Nevertheless, literature on protocols and the outcome of the intervention is relatively limited. Studies have found significant improvements in pulmonary function and bronchial inflammation, as well as a decrease in days absent from school and in visits to a physician, supporting the importance of multidisciplinary rehabilitation programmes for disease management and compliance modification. Long-term effects following an inpatient intervention in terms of better lung function parameters, less asthma-related school absence and improved asthma management compared with an outpatient reference group have been documented. Likewise, improvements in quality of life not only of the patients but also of their caregivers have been shown in a series of investigations.

Several studies have implicated lifestyle changes, specifically decreased physical activity, as a contributor to the increase in asthma prevalence and severity. Moreover, the capacity for asthmatic subjects to exercise safely and to significantly improve their cardiovascular fitness and quality of life has been demonstrated. From this perspective, it seems logical to subject asthmatic patients to exercise training to increase fitness and strength. Indeed, many rehabilitation centres focus on exercise interventions with remarkable success in terms of quality of life and exercise capacity, leading to the assumption that exercise training should be part of all asthma rehabilitation programmes.

In addition to encouraging patients to exercise regularly and supporting their sportive ambitions, it is crucial to provide individuals and their families with specific education on the prevention of and their behaviour in emergency situations. This includes knowledge about individual risk factors, awareness of the available rescue medication and an action plan, which the patient needs to follow in the case of severe respiratory symptoms. The goal is to foster trust of the patient and their family in their self-management skills and in the implemented treatment strategies in order to overcome the fear of respiratory symptoms in situations of increased physical activity.

Cystic fibrosis

During the past decades, the fear of cross-infection, especially for *Pseudomonas aeruginosa*, has determined the evolution of rehabilitation programmes for CF patients. To date, rigorous hygiene standards addressing disinfection and segregation (spatial and temporal) are a widely accepted prerequisite to qualify centres for inpatient CF rehabilitation programmes. Nevertheless, in view of potential cross-infections, close

interaction between the CF centres and the rehabilitation clinics is advisable to foster mutual trust, minimise risk for the patient and optimise intervention outcome. To achieve this goal, structured interventions need to take into account all aspects of CF multiorgan disease and therefore exceed the general requirements of pulmonary rehabilitation programmes. Physiotherapists, sports therapists, psychologists, dieticians, diabetologists, gastroenterologists, pulmonologists and other healthcare specialists need to work closely together in a multidisciplinary setting. If this aspect is properly addressed, rehabilitation programmes are likely to significantly ameliorate the short- and long-term quality of life of affected individuals and improve symptom score, pulmonary function, grade of inflammation and BMI. Exercise and endurance training result in significant improvements in exercise tolerance, aerobic fitness, peak work capacity, strength, coordination and ventilation parameters. Moreover, clinical experience demonstrates a remarkable improvement in treatment adherence after rehabilitation as a result of educational activities, possibly leading to longer periods of mild symptoms and prolonging the time between intravenous antibiotic cycles, thus demonstrating the importance of such programmes in CF care.

Lung transplantation

Published data on protocols and the outcome of rehabilitation programmes for patients with chronic lung diseases before and after lung transplantation are largely lacking. However, with the increasing number of paediatric and adult transplanted patients, specific rehabilitation programmes will have to be established. The majority of the transplanted paediatric population consists of patients with CF, followed by those with pulmonary fibrosis. Rehabilitation programmes for severely affected individuals clearly exceed the general requirements for pulmonary rehabilitation. Next to medical experience and know-how, specific psychological and educational interventions have to be provided by the rehabilitation centre. Access to acute interventions and intensive care units should be available, as well as an emergency laboratory and advanced respiratory diagnostics, such as bronchoscopy.

Major objectives for programmes pre-transplantation are the stabilisation of general and pulmonary health in conjunction with psychological priming with respect to the intervention. Available data demonstrate improvements in physical capacity and endurance as well as quality of life in subjects of all age groups with various lung diseases as a result of rehabilitation before transplantation. Rehabilitation programmes following lung transplantation have to consider various complex aspects, from education in adherence to treatment to early recognition of organ rejection, while, at the same time, promoting physical fitness to prepare the individual for re-entry into the social community, including school or the workplace. As well as inpatient interventions, protocols for outpatient rehabilitation programmes have been established, with reported success in terms of patient satisfaction. Nevertheless, both inpatient and outpatient interventions need to be scientifically evaluated and better standardised in future to meet the complexity of the requirements of paediatric transplant rehabilitation programmes and to improve their outcome.

Nutritional management

In many chronic respiratory disorders, nutritional interventions are mandatory to improve respiratory function and ameliorate disease symptoms and outcome, although the available literature in this field focuses on the pancreatic insufficiency type of CF. However, advanced lung disease in many other conditions can lead to an enhanced

calorie requirement and subsequently to a decreased BMI. This process is often a result of increased energy expenditure due to respiratory work, as well as of a general augmented level of inflammation and/or regular use of systemic corticosteroids. Diminished appetite and a consequently decreased energy intake might contribute to a loss of body weight. If weight gain cannot be achieved by regular nutrition, coordinated actions need to be implemented to improve the patient's condition. These potentially include intensive counselling by a dietician, installation of a daily nutrition plan, prescription of high-protein calorie supplements, or substitution of vitamins and micronutrients. In the case of progressive weight loss or failure to regain weight over a longer period of time, insertion of a percutaneous gastrointestinal tube and subsequent additional feeding might become necessary. The specific nutritional management of CF patients with pancreatic insufficiency leading to malnutrition, which includes regular counselling by a nutritionist, oral substitution of pancreatic enzymes and fat-soluble vitamins, and high-protein calorie supplementation, is discussed elsewhere in this *Handbook* (see chapter "Extrapulmonary manifestations of CF").

When respiratory disease leads to general inactivity, uncontrolled weight gain and obesity can result. Prevention of becoming overweight is therefore an important element of the management of chronic respiratory disorders such as asthma, and can often be achieved by regular exercise and nutritional awareness. At the same time, nutritional education should be implemented to support the efforts of physical activity when excess weight is imminent or already an issue and weight reduction is desired. This might include shopping and cooking guidance, education in nutritional components and meal plans, and even offering temporary household support, where available. The role of behaviour changes in counteracting obesity in patients with asthma is crucial to sustain any successful weight loss and needs to be addressed in educational programmes.

In situations where increased physical activity is very difficult or not possible, such as in patients with neuromuscular disorders, optimisation of nutritional management by the families is of general importance, especially because many parents tend to allow their sick or disabled children any desired foods, which may be high in carbohydrates, as comfort. Empathic nutritional guidance (*e.g.* by a dietician) can often strengthen awareness of a more reasonable food composition, and must include regular and thorough diet education and advice.

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Respiratory physiotherapy

Marlies Wagner

In the last decades, respiratory physiotherapy (RPT) has developed rapidly. Initially, the focus of RPT lay in the removal of tracheobronchial secretions. Today, a broad spectrum of techniques and methods enable RPT to be applied as an evidence-based additional treatment option in acute and chronic lung disease. The role of the respiratory physiotherapist as part of a multidisciplinary team in paediatric units differs widely among centres and countries, depending on local traditions, professional expertise, and legal and administrative frameworks. In order to maintain high-quality therapy in this rapidly developing area, specialised training is required. This educational task should be adopted by international scientific medical societies such as the European Respiratory Society to establish standards and guidelines for RPT.

General principles

RPT represents an additional treatment option for patients with acute and chronic lung diseases. It can be used for acute support in intensive care units and as regular inpatient care, as well as in patients with chronic diseases in outpatient settings and during rehabilitation. To tailor therapeutic strategies to the individual patient's needs, detailed knowledge of the structure and function of the immature and growing and developing respiratory tract is crucial. Depending on the age of the patient, the respiratory physiotherapist has to deal with different particularities of the airways, lung and rib cage, all of which influence the therapeutic strategies.

Key points

- Paediatric respiratory physiotherapy is a rapidly developing area and encompasses a broad spectrum of techniques and methods for patients with acute and chronic lung diseases.
- Inhalation therapy, airway clearance, rehabilitation, exercise testing, management of ineffective cough, tracheostomy management and NIV are the most commonly used treatment options in paediatric respiratory physiotherapy.
- Therapeutic strategies have to be individualised according to the patient's needs and to the structure and function of the immature and growing and developing respiratory tract.
- Applying strategies to improve adherence is crucial.

RPT can support and optimise treatment in many patients with respiratory problems. To establish a treatment plan for an individual patient, conditions such as knowledge about the predominant pathology, the ability to interpret results of PFTs and other relevant investigations, and awareness of the side-effects of any manipulation of the respiratory tract have to be met. In addition, applying strategies to improve adherence among patients with chronic lung disease and their caregivers is crucial. Adherence problems have to be tackled on an individual basis, tailored to the patient's actual needs.

Inhalation therapy

Inhalation therapy is a crucial component of RPT. Bronchodilators, mucolytic agents, hydrators, antibiotics and anti-inflammatory agents can all be deposited in targeted areas of the lungs. Thus, there are many different techniques, devices and interfaces to choose from in order to apply an aerosol. Inhalation therapy has to be adapted to the patient's needs and abilities to be a successful part of respiratory therapy (see chapter "Inhalation therapy").

Airway clearance techniques

Aims and pathophysiology

The main objectives of airway clearance techniques (ACTs) are to clear secretions, to ensure adequate ventilatory distribution and to lower the work of breathing. Retention of secretions typically causes proteolytic stress on the airway walls and local proliferation of infectious agents, and therefore secretions should be removed from the tracheobronchial tree. The mucociliary transport system may be impaired due to:

- Dehydration of the periciliary mucus layer
- The absence of lubricant activity, which normally prevents adhesion of mucus to airway surfaces
- An inherent defect within the cilia
- Immunodeficiencies including cellular defects

ACTs are applied in patients with atelectasis, local hyperinflation and bronchiectasis, both for therapeutic and diagnostic indications. The quality of life of patients with chronic suppurative lung diseases (*e.g.* CF, PCD, respiratory disease associated with immunodeficiencies) relies strongly on ACTs. The choice of a specific ACT depends on the child's age, abilities and preferences. As a child matures, the type of ACT prescribed is likely to change with increasing ability to apply self-administered techniques. ACTs are also used in patients with neuromuscular disease, in term and preterm newborns who are highly vulnerable to airway obstruction caused by mucus impaction, and in patients undergoing thoracic surgery.

Mechanisms

ACTs are based on natural airway clearance and focus on enhancing mucus transport by improving the rheological properties of the mucus layer, stimulating ciliary action or utilising compensatory physical mechanisms (*i.e.* imitating coughing). Airflow increases the transport of secretions in more central airways; thus, there is a need to get air distal to the secretions to open the airways and create higher airflow velocities. The airflow in peripheral airways is negligible. In this compartment, gas–liquid pumping drives the transport of secretions. A change in the airway calibre while breathing is one of the key mechanisms in this zone, but the mechanisms have not been completely understood until now.

Some ACTs concentrate on the rheological properties of secretions, some modulate the airflow to transport mucus, and some combine these principles.

Sports and physical activity increase peripheral gas–liquid pumping and thus have to be considered complementary means for airway clearance, especially in the long-term management of patients.

Techniques

There is little evidence to support the use of one ACT over another. In preparation for ACTs, appropriate and individualised inhalation therapy is crucial. Therefore, the respiratory physiotherapist has to check and optimise inhalation therapy routinely. The various ACTs can be distinguished by activity level into active and passive techniques.

Active ACTs include the following:

- Active cycle of breathing techniques. These techniques combine breathing control, thoracic expansion exercises and the forced expiration technique to mobilise and clear excess bronchial secretions. They can be performed independently and in a position of choice.
- Autogenic drainage. This technique is a complex concept of flow and breathing-level modulation, working with the physical mechanisms of shearing forces induced by airflow.
- Positive expiratory pressure (PEP). This technique is used to recruit obstructed and collapsed airways while breathing through a flow-regulating resistor. The technique temporarily increases FRC and helps to homogenise ventilation. Additional air distal to mucus plugging enables the mobilisation of secretions, which can then be transported and evacuated.
- Oscillating PEP. This technique combines the principle of PEP therapy with an oscillating component. By loosening secretions from the airway wall, the mobilisation and clearance of secretions is improved.
- Hi-PEP. This technique implies forced expiratory manoeuvres against a flow-regulated resistor to mobilise and transport secretions. High intrabronchial pressures result in progressive homogenisation of the behaviour of different lung units during expiration. Thus, higher airflow velocities at the end of expiration are generated. This technique supports full chest mobility and inspiratory and expiratory muscle training. It is an energy-consuming exercise and is not recommended for self-treatment in exhausted patients.
- Intrapulmonary percussive ventilation. Ventilator-generated small bursts of high-flow air at high rates are superimposed on spontaneous breathing. The high-frequency gas pulses expand the lungs, vibrate and enlarge the airways, and thus deliver gas into distal lung units beyond accumulated mucus.

Passive ACTs include:

- Gravity-assisted drainage and manual techniques. Different positions of the chest have an effect on ventilatory distribution. When positioning is combined with clapping and/or vibration, flow transients are generated in the airways. This increases gas–liquid interactions and enhances the removal of secretions.
- High-frequency chest wall oscillation. A vest around the thorax produces oscillations, and at the same time it inflates and deflates causing thoracic compressions. Thus, it influences the intrabronchial liquid layer while transporting secretions with forced expiratory manoeuvres.

- Assisted autogenic drainage. This technique is based on the principles of autogenic drainage and is commonly used in infants and noncooperative patients. Modulated airflows are generated manually and/or using elastic straps.
- Baby-PEP. By breathing several times against a flow-regulating resistor, the lung volume is passively raised. This is followed by passive forced expiration manoeuvres to move secretions or to initiate coughing. With the right equipment (tight stenosis and a small dead space), this technique even works in neonates.

Management of ineffective cough

Aims

The aims of management techniques are: 1) to assist coughing in order to transport and evacuate secretions from the lungs resulting in a decrease in the respiratory load, 2) to obtain and support respiratory muscle function, and 3) to prevent or decrease recurrent pneumonia and/or atelectasis.

Pathophysiology

Neuromuscular diseases and neurological disorders causing respiratory muscle weakness and fatigability are the most frequent causes of ineffective cough (see chapter "Neuromuscular disorders"). Patients show an increased respiratory load due to the increasing immobility of the rib cage and consecutive micro-atelectasis.

Thoracic scoliosis aggravates the respiratory load by adding a mechanical disadvantage to the diaphragm and intercostal muscles.

Techniques

Before the application of assisted coughing techniques, inhalation therapy and ACTs have to be performed. Coughing techniques should be applied on a daily basis; manual techniques are differentiated from mechanical ones. The manual cough assist technique focuses on increasing expiratory flows by compression of the chest or abdomen or both. Hyperinflation should be considered if volitional deep breathing is not possible, both to increase the lung volume for a more efficient cough and to expand the chest to increase ventilatory distribution.

Assisted coughing with a mechanical insufflator–exsufflator device is particularly important when an effective cough is not achieved with manual techniques. This device generates positive pressure for insufflation and negative pressure for exsufflation, resulting in an increase in the expiratory airflow that allows the removal of secretions.

In patients with neuromuscular diseases, it is important to commence ACTs proactively, so that, in the case of an acute pulmonary exacerbation, the patients have already made themselves familiar with these techniques.

Noninvasive ventilation

Role of the respiratory physiotherapist

NIV is increasingly gaining importance in the paediatric age range. With sophisticated ventilators and smart and smooth interfaces, it is possible to apply NIV at home, even in very young children. There has been increasing involvement of respiratory physiotherapists in NIV as the goals of RPT and NIV frequently overlap. Despite this, the role of respiratory physiotherapists in the management of patients with ventilatory disorders varies among institutions.

Aims

The goals of NIV are to reduce breathlessness and the work of breathing, to improve the efficiency of ventilation, to mobilise secretions and aid their expectoration, and to maintain or improve exercise tolerance and functional capacity. It is crucial to closely monitor the patient, and to train and retrain patients and parents with regard to the special circumstances at home.

The most common indications for NIV are BPD, central hypoventilation syndrome, severe progressive neuromuscular disease and acute hypercapnic respiratory failure. NIV is also used as a bridge to lung transplantation in patients with chronic lung failure.

Tracheostomy management

Aims

The tasks in the long-term management of patients with tracheostomy are numerous. It is crucial to secure humidification of the lower airways to ensure transport and evacuation of secretions from the lungs despite impaired coughing and swallowing. The respiratory physiotherapist may help in weaning the patient from the ventilator. Of particular importance is education of parents/caregivers and patients to enable them to recognise and appropriately manage emergency situations. Regular evaluation of the (underlying) condition of the respiratory tract is necessary to optimise treatment.

Techniques

The inhalation or instillation of saline and/or mucolytic agents to humidify the airway mucosa and mobilise secretions is essential to aid expectoration.

ACTs are applied to transport secretions from the lower airways to facilitate tracheal suctioning and thus thorough cleaning of the tracheobronchial tree. Manual hyperinflation results in better ventilatory distribution and lung volume recruitment. Respiratory muscle training is crucial to lower the work of breathing.

Rehabilitation and exercise testing

Aims

Chronic respiratory diseases are associated with abnormalities in posture, decreased thoracic mobility and decreased performance in daily life. Body image as a core component also affects social life.

Pulmonary rehabilitation should be considered in all patients with chronic respiratory disorders, respiratory tract malformations, or severe respiratory complications and side-effects from other disorders and/or treatments.

Techniques and exercise testing

Patient-tailored therapies, including endurance and strength training, respiratory muscle training and age-specific thorax mobility exercises, as well as education and self-management strategies, are of relevance.

Exercise testing should be standard in paediatric chronic lung diseases and performed at least once a year. Exercise testing determines the level of functional impairment and activity limitations, as well as the factors that limit exercise capacity. The choice is between incremental tests and tests with continuous workload. Incremental cardiopulmonary exercise testing on a cycle ergometer or a treadmill is the gold

standard. Field tests such as walk tests, step tests and shuttle tests provide more functional information. Exercise testing provides information to guide exercise prescription while also providing valuable information with regard to disease progression. It is also a tool for screening exercise-related adverse reactions.

Management of musculoskeletal complications

Depending on the underlying disease, there are various implications for the musculoskeletal system. Chest wall pathologies, postural problems and muscle imbalance all increase the workload of the respiratory system. This results in muscle pain and joint problems, especially in the spinal and costovertebral regions, followed by pain and mechanical disadvantage to the diaphragm and intercostal muscles. It is crucial to start mobility and strengthening exercises to achieve good muscle function and posture at diagnosis to avoid or slow down the development of anatomical disadvantages. Reducing the workload of respiratory muscles and optimising the recovery of overloaded muscles using ACTs and NIV are recommended. Adequate pain relief is beneficial.

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Sports medicine

Giancarlo Tancredi, Giovanna De Castro and Ambra Nicolai

Sports medicine concerns the scientific and medical aspects of sports performance, physical activity and fitness. The World Health Organization (WHO) defines physical activity as any bodily movement produced by skeletal muscles that requires energy expenditure, and physical fitness as the ability to perform muscular work satisfactorily.

Sports activity can be differentiated as "competitive" and "noncompetitive" or leisure-time sports. According to the American Heart Association (AHA), a competitive athlete is defined as someone who participates in a team or individual sport requiring systematic training and regular competition against others and that places a high premium on athletic excellence and achievement.

An important part of preventive measures to detect possible compromising health conditions in competitive athletes is pre-competition medical assessment and screening. The physical examination should include, but not be limited to, cardiovascular, pulmonary and musculoskeletal assessment. Many countries (*e.g.* Italy) have mandates that every participant engaged in competitive sports must undergo a clinical evaluation to obtain eligibility. Furthermore, a medical history, physical examination and any required additional assessments are recommended for all subjects who practice physical activity, even leisure-time sports.

Key points

- A physically active lifestyle including sports and supervised participation programmes provides physiological improvements in muscle function, cardiopulmonary efficiency and immune system function, helps prevent obesity and noncommunicable diseases, and improves self-esteem.
- Pre-participation medical assessment and screening is important to detect possible compromising health conditions, especially in competitive athletes and in children with chronic or congenital lung diseases.
- Cardiopulmonary exercise testing provides a global assessment of the integrative exercise responses involving the pulmonary, cardiovascular and skeletal muscle systems.
- Maximal oxygen uptake reflects the maximal ability of the body to take in, transport and utilise oxygen, and is the best single measure of aerobic fitness.

Benefits of sports programmes

Participation in sports programmes provides the opportunity for children to increase their physical activity and develop both physical and social skills.

In particular, the American Academy of Pediatrics (AAP) and WHO guidelines recommend that organised sports programmes for pre-adolescents should complement, not replace, the regular physical activity that is a part of free play, child-organised games, recreational sports and physical education classes at school.

Growth and development in children and adolescents is related to physical activity. Inactivity is considered a global pandemic and has been identified as one of the four leading causes of global mortality, and as a contributor to and a risk factor for overweight and obesity and many other chronic diseases such as hypertension, diabetes, depression, cancer and cardiovascular diseases. Conversely, a physically active lifestyle helps to maintain body weight and leads to favourable health habits, such as not smoking and a healthy diet.

Emphasis has shifted to the benefits of regular physical activity on physiological skeletal muscle improvements, cardiopulmonary efficiency, immune system function, obesity prevention, self-esteem and psychological conditions. In particular, physical activity may induce beneficial immune system changes such as a reduction in pro-inflammatory cytokines of allergic inflammation and may have a positive effect on depressive symptoms. Recent studies have underlined the positive effects of physical activity on the risk factors for noncommunicable diseases that typically manifest in adulthood.

In children and adolescents with chronic diseases, an overprotective parental attitude is often observed, resulting in reduced physical activity of these children leading to reduced exercise tolerance and an increased risk of obesity.

Risks of physical activity

The most significant, but extremely rare, risk associated with exercise in youth is a sudden death event. Among children and adolescents, cardiovascular causes of death include hypertrophic cardiomyopathy, myocarditis, anomalous coronary artery anatomy, exercise-induced arrhythmias and Marfan syndrome.

Becker *et al.* (2004) reported that sudden fatal asthma can occur in competitive and recreational athletes during sporting activities. These subjects were usually white males in the age range of 10–20 years with mild asthma. Possible causes of this type of fatal asthma attack include sudden severe asphyxia as well as a reduced chemosensitivity to hypoxia and blunted perception of dyspnoea by the subject. Thus, it is essential to ensure that athletes with asthma receive proper care and therapy.

Sports injuries are also associated with physical activity. The most common are musculoskeletal injuries, which can occur from excessive activity or the sudden beginning of an activity for which the body is not conditioned, and include muscle tears, acute damage to joints and ligaments, and fractures. However, many of the injuries associated with physical activity can be prevented by gradually increasing the level of activity, avoiding excessive amounts of activity and performing stretching at the beginning and end of the activity.

Doping in sports is a big social problem. Adolescents may use drugs in the hope of improving their athletic performance, and studies report that 3–12% of male adolescents admit to having used an anabolic–androgenic steroid.

"Female athlete triad" is a syndrome that occurs in female athletes and is characterised by the presence of eating disorders, amenorrhoea, and osteopenia or osteoporosis. Early identification of symptoms and their progression is important to prevent short- and long-term consequences.

Children or adolescents engaged in contact sports following infectious mononucleosis are at potential risk of splenic rupture secondary to abdominal trauma. It is safe to allow these athletes to return to contact sports after a period of 3–6 months.

Sports-related concussion is another important consideration at all levels of sports for children and adolescents. The differential diagnosis should include more severe intracranial injuries. Because every case of concussion has its own spectrum of symptoms and severity, management should be individualised.

Physical activity in children with chronic pulmonary diseases

Most children with congenital lung diseases (*e.g.* pulmonary hypoplasia) or other conditions such as BPD have a sedentary lifestyle. It is important to motivate these children to increase their fitness level through participation in regular physical activity. Before starting a sport, it is important to carry out a pre-participation evaluation, including an accurate clinical and functional assessment, to minimise any potential risk.

Asthma

Exercise-induced bronchoconstriction (EIB) is a common problem in physically active children with asthma. EIB is defined as transient, reversible bronchoconstriction that happens during or after strenuous exercise in the presence or absence of asthmatic symptoms. In patients with asthma, EIB is a marker of poor control of the underlying asthma.

The pathophysiology of EIB is not completely clear. Hyperventilation occurring during exercise causes water loss and drying of the airways, leading to transient osmotic changes on the airway surface. This hyperosmolar state leads to mast cell degranulation with release of inflammatory mediators including histamine, leukotrienes and cytokines, which may induce EIB.

The prevalence of EIB has been reported to be 10–20% in school-aged children. EIB is more common in athletes performing in cold weather and in sports that need high $\dot{V}_E$ rates. For example, in US Olympic winter sports athletes, the prevalence of EIB was found to be 26% in females and 18% in males using an exercise challenge test (Wilber *et al.*, 2000).

Exercise challenge in the assessment of children with asthma requires effort using a treadmill or cycle ergometer to reach a heart rate of 85–95% of maximum within 2–3 min and for an exercise duration of 6 min. The required decrease in FEV_1 after the exercise test needed to diagnose EIB is ≥10%. This is discussed in more detail in the chapter "Asthma".

A systematic review by Crosbie *et al.* (2012) evaluating the effect of physical training in children with asthma confirmed that these children had an increase in aerobic capacity as measured by maximal oxygen uptake ($\dot{V}_{O_2max}$) with physical training, with a response similar to healthy controls. However, their pulmonary function was not improved by physical training.

Scuba diving is considered a risky physical activity in patients with asthma because of the well-documented presence of bronchospasm, particularly in cold and/or deep water, or in the event of exposure to allergens. Scuba diving is not considered a risk

in patients whose asthma is perfectly controlled with drug therapy, who have normal PFTs and who are in good physical condition, but is contraindicated in patients with moderate-to-severe persistent asthma, FEV_1 <80% predicted, active asthma in the last 48 h, exercise- or cold-induced asthma, and poor physical fitness.

It is important to emphasise that asthmatic children can be active and participate in any sport when their asthma is well controlled.

Exercise-induced anaphylaxis

Exercise-induced anaphylaxis is a rare but potentially life-threatening clinical syndrome characterised by anaphylaxis concomitant with exercise. It may occur independently of allergen ingestion or may require the ingestion of sensitising food (*e.g.* shellfish, wheat gliadin) before exercise to trigger symptoms. The clinical features and management do not differ from other types of anaphylaxis, and therapy includes epinephrine, antihistamines and systemic corticosteroids.

Cystic fibrosis

CF is the most common hereditary disease in white populations and is caused by mutations in the *CFTR* gene. Evidence suggests that the pulmonary function of children with mild-to-moderate CF can benefit from an aerobic or resistance training programme, and it has been shown that team sports are important for the social integration of any child with a chronic disease.

Children with CF who have significant air trapping should beware of undertaking activities such as scuba diving or high-altitude sports. In both of these activities, oxygen can become limited and severe life-threatening desaturation episodes can occur. Pulmonary barotrauma is the most relevant complication in scuba diving, resulting in overdistention of alveoli and rupture of alveolar walls as a consequence of expanding gases during ascent.

Other problems that may occur include pneumothorax caused by weightlifting, rupture of the spleen and oesophageal varices in patients with portal hypertension during contact sports, and dehydration and electrolyte losses during prolonged exercise.

For further details, please refer to the chapter “CF lung disease”.

Physical activity in children with other chronic diseases

Solitary functioning kidney

Solitary functioning kidney (SFK) is a congenital or acquired condition that can be associated with chronic kidney disease (CKD) and/or end-stage renal disease. Congenital SFK is due to unilateral renal agenesis, renal aplasia or multicystic dysplastic kidney. Acquired conditions leading to nephrectomy in children are Wilms tumour, renal trauma and hydronephrosis. The risks and benefits of regular physical activity in children with CKD are not clear. Some studies have suggested that trained SFK subjects showed a better cardiorespiratory fitness than sedentary SFK subjects. In particular, trained SFK subjects had significantly higher mean values of aerobic capacity ($\dot{V}_{O_2max}$) and exercise tolerance than sedentary subjects. Sports participation can reduce blood pressure and cardiovascular risk in patients with CKD. There is no type of sport suggested as particularly suitable for children with SFK, but some authors recommended that these children should avoid contact and collision sports.

Evidence suggests that SFK subjects starting a physical activity should have a preliminary medical examination including recent imaging to confirm the normal

position and anatomy of the single kidney and to show that there is no evidence of renal insufficiency, hypertension or proteinuria.

Kidney transplantation

Cardiorespiratory fitness is significantly reduced in children with end-stage renal disease. The role of renal transplantation in improving cardiorespiratory fitness has not been thoroughly investigated. CKD has a progressive negative impact on cardiorespiratory fitness and is worsened by peritoneal dialysis or haemodialysis. Several studies have shown that physically active transplanted children reach a fitness level comparable to sedentary healthy controls and better than sedentary transplanted children. Renal transplanted children benefit from physical activity; 3–5 h of weekly exercise is the threshold for a significant improvement in cardiorespiratory fitness. Resumption of adequate physical activity after successful renal transplantation should be strongly encouraged.

Clinical exercise testing

Cardiopulmonary exercise testing provides a global assessment of the integrative exercise responses involving the pulmonary, cardiovascular and skeletal muscle systems. The cardiovascular parameters measured during exercise testing are ECG, heart rate, blood pressure, cardiac output, stroke volume and systemic vascular resistance, measured using noninvasive techniques. Cardiopulmonary exercise testing is essential because resting pulmonary and cardiac function cannot reliably predict exercise performance or functional capacity, and overall health status will correlate more closely with exercise tolerance than with measurements taken at rest. Exercise testing is useful to differentiate between cardiovascular and pulmonary causes of exercise intolerance and to identify disorders of pulmonary gas exchange, certain muscle diseases and psychological disorders.

$\dot{V}_{O_2max}$ reflects the maximal ability of the body to take in, transport and utilise oxygen and is widely recognised as the gold standard indicator of aerobic fitness. It can be determined using standardised testing on a treadmill or cycle ergometer.

$\dot{V}_{O_2max}$ is defined by the Fick equation:

$$\dot{V}_{O_2max} = Q \times (C_{aO_2} - C_{vO_2})$$

when these values are obtained during exertion at a maximal effort, and where Q is the cardiac output and C_{aO_2} and C_{vO_2} are the arterial and venous oxygen content, respectively. $\dot{V}_{O_2}$ can be measured noninvasively by the product of ventilation and the difference in oxygen concentration of inhaled and exhaled air that has been utilised by the working muscles. $\dot{V}_{O_2max}$ can be influenced by age, sex, exercise habits, body size, hereditary factors and cardiovascular status.

S_{pO_2} can be measured noninvasively at rest and during exercise. Assessment of S_{pO_2} is an important indication in patients with chronic lung disease, as neither the presence nor the severity of desaturation during exercise can be predicted readily from resting S_{pO_2}.

Another useful physiological measure is metabolic equivalent (MET), which expresses the amount of oxygen consumed at rest (normally ~3.5 $mL \cdot kg^{-1} \cdot min^{-1}$) and is used to assess the amount of oxygen used by the body during physical activity. Activity that burns 3–6 METs is considered moderate-intensity physical activity.

It is established that well-directed aerobic training programmes result in a significant improvement in $\dot{V}'_{O_2max}$, which typically increases by ~15–20%, although there may be a large intersubject variation.

Studies have measured $\dot{V}'_{O_2max}$ during cardiopulmonary exercise testing in children with different pathologies (*e.g.* girls with Turner syndrome and children after a renal transplant). In these patients, $\dot{V}'_{O_2max}$ provides valuable information on health status and the effects of exercise training programmes. For further details, please refer to the chapter "Cardiopulmonary exercise testing".

Prescription of physical activity

Exercise prescription has received growing interest in general clinical practice and in the care of people with chronic health conditions. The objective of such a prescription would be to recommend a particular quantity of physical activity to an individual in order to obtain a specific therapeutic goal such as health benefits or improved cardiorespiratory fitness.

The principles that rule exercise prescription are based on the FITT principle (frequency, intensity, time and type). The recommended mode of aerobic exercise in chronic respiratory disease is walking or any aerobic exercise that uses large muscles; the optimal frequency is 3–5 days per week and the intensity of exercise is at 50–85% of $\dot{V}'_{O_2max}$ or at limits as tolerated by the patient. The duration of exercise should be 20–60 min of continuous aerobic activity.

In patients with significant cardiac or pulmonary disease, interval training (a physical training that consists of high-intensity work alternating with periods of rest or low activity) can be a valid alternative.

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Lung transplantation and management after transplantation

Paul D. Robinson and Paul Aurora

Lung transplantation is now a well-established treatment for children with end-stage lung disease, with typically 100–120 paediatric lung transplantations performed worldwide each year across 40–50 centres. The majority of centres (>80%) perform fewer than five transplantations a year, with only one centre performing more than 10 procedures each year in recent years. Infant lung transplantation has been established at centres in North America, but this remains a small proportion of total paediatric transplantations (<5% of paediatric lung transplants in recent years).

The procedures that are performed have changed. Bilateral single sequential lung transplantation now is preferred to heart–lung transplantation, with the latter reserved mainly for cases with significant left heart dysfunction (*e.g.* left heart dysfunction associated with idiopathic pulmonary arterial hypertension, and congenital heart disease).

Single lung transplantation is rarely performed in the paediatric age range, mainly reflecting its contraindication in suppurative lung diseases such as CF.

Key points

- Lung transplantation is now a well-established treatment for children with end-stage lung disease.
- Short- and long-term outcomes have improved but still lag behind other solid-organ transplant groups. Chronic graft rejection remains a significant barrier to further improvements in survival.
- Donor organ shortage remains a critical issue. Given the limited resources, optimal timing of transplantation is both essential and challenging, especially in conditions where survival can be difficult to predict.
- A lifelong regimen of triple immunosuppression is used, consisting of a calcineurin inhibitor, a cell-cycle inhibitor (or antimetabolite) and a corticosteroid. Post-transplantation management focuses on ongoing rehabilitation, careful surveillance, and treatment of acute and chronic complications.

Table 1. Common indications for lung transplantation, by age group

Infancy (<1 year)
Pulmonary hypertension (38%, of which 14% is idiopathic)
Surfactant protein B deficiency (21%)
ILD (19%)[#]
BPD (6%)
Preschool age (1–5 years)
Pulmonary hypertension (50%, of which 28% is idiopathic)
ILD (15%)[#]
Obliterative bronchiolitis (non-re-transplant) (9%)
Re-transplant (8%, of which 3% is for obliterative bronchiolitis)
Early school age (6–11 years)
CF (51%)
Pulmonary hypertension (14%, of which 10% is idiopathic)
Obliterative bronchiolitis (non-re-transplant) (11%)
Re-transplant (6%, of which 3% is for obliterative bronchiolitis)
Adolescence (12–17 years)
CF (66%)
Pulmonary hypertension (11%, of which 9% is idiopathic)
ILD (7%)[#]
Re-transplant (7%, of which 3% is for obliterative bronchiolitis)

Data are shown as the percentage of cases. [#]: excludes surfactant protein B and C deficiency and ABCA3 (ATP-binding cassette subfamily A member 3) transporter mutations; this separation is an historic approach in the International Thoracic Organ Transplant Registry and is maintained for the purpose of this table. Data from Goldfarb *et al.* (2018).

Indications for lung transplantation

The commonest indication for lung transplantation in the paediatric age range is CF, although the indications are age dependent (table 1). CF is the commonest indication at school age, whereas in younger children, alternative pathologies such as pulmonary hypertension (idiopathic and nonidiopathic causes), ILD and obliterative bronchiolitis (non-re-transplant) are more common indications.

Selection for lung transplantation

Current international guidelines for the referral and selection of lung transplant recipients are based on limited paediatric data, and the decision to list a child for transplant is often based on a multidisciplinary team consensus within the individual lung transplant centre. Potential survival and quality-of-life benefits are offset against an individual's risk of perioperative mortality and the short- and long-term complications of transplantation. Early referral is preferable, as late referral potentially affects the ability of the family to make a carefully considered decision about whether they want a transplant, and poor clinical status may adversely affect suitability for listing. The broad criteria for listing are:

- Progressive lung disease on maximal medical therapy
- Predicted life expectancy, without transplantation, of ≤2 years
- Poor quality of life, which is likely to be improved by transplantation; assessment of quality of life is taken ideally from the child's perspective, and includes their ability to complete daily routine activities and to participate in school and social activities, and the time spent in hospital

- No absolute contraindications (table 2); relative contraindications are assessed on a case-by-case basis
- An acceptable psychological profile
- Fully informed commitment by the child and family; this includes appropriate child and family support in place to aid rehabilitation following transplantation surgery and a commitment to the procedure involved, the required lifestyle adjustments and strict adherence to the medication regimen

The life expectancy criterion also affects the probable waiting period for a suitable organ to become available and may vary depending on the centre. Existing survival prediction models for CF are only estimations, and their limitations include changing CF survival rates over time, a lack of paediatric-specific validation and a lack of validation in children being assessed for transplantation. The referral criterion of FEV_1 <30% predicted is widely quoted, but referral should also be considered at higher FEV_1 levels if patients 1) have advanced disease with a rapidly falling FEV_1 despite optimal therapy (particularly female patients), 2) are infected with non-tuberculous mycobacterial (NTM) disease or *Burkholderia cepacia* complex, and/or 3) have diabetes. Other criteria include clinical decline characterised by increasing frequency of exacerbations associated with any of the following:

- Acute respiratory failure associated with NIV
- Increasing antibiotic resistance and poor clinical recovery from exacerbations
- Worsening nutritional status despite supplementation
- Massive haemoptysis or pneumothorax

Donor allocation

Standard donor criteria exist but have been criticised for being too restrictive. Only 20–35% of lungs offered for use in organ transplantation are usable. "Marginal donors" are considered but are only used with informed consent from the recipient and family. Recent paediatric data suggest equivalent post-transplant outcomes.

Organs procured from brain-dead donors, the use of nonheart-beating donors and *ex vivo* lung perfusion attempt to address this imbalance, with encouraging results. Living-relative lobar lung transplantation has decreased in recent years, in part due to the potential 300% mortality risk across the recipient and the two donors.

The lung allocation score is used to allocate organs to North American lung transplant recipients based on calculated survival benefit but is not applied to children <12 years of age due to a lack of paediatric data. Paediatric allocation is based on donor–recipient blood group compatibility, size matching and the current clinical conditions of individual waiting-list patients at that centre. The mechanism for prioritising recipients and allocating organs varies among countries and transplant centres.

Management following referral

Changes in clinical status during the pre-transplant period may affect suitability, necessitating regular review. Optimisation of current management during the pre-transplantation period is an essential component of managing future transplantation risk. This includes:

- Maintaining good nutrition and bone density
- Optimising anti-infective and anti-inflammatory therapies
- Screening for and treatment of associated respiratory failure with NIV

The use of more invasive measures as a "bridge" to transplantation, such as ventilation and extracorporeal membrane oxygenation, is controversial and not universally

Table 2. Absolute and relative contraindications to lung transplantation in children[#]

Absolute	Relative
Active malignancy within the last 2–5 years, depending on type of malignancy	Infection with panresistant or highly virulent bacteria, fungi or certain mycobacteria
Active TB	Infection with *Burkholderia cenocepacia*, *Burkholderia gladioli* and multidrug-resistant *Mycobacterium abscessus*[§]
Major psychiatric illness	Other organ failure
Hepatic, brain, renal and left ventricular failure[¶]	HIV infection
Irreversible and significant respiratory muscle dysfunction	Invasive ventilation and/or extracorporeal life support
Severe scoliosis or thoracic rib cage deformity	Long-term, high-dose steroid therapy
Nonadherence to treatment, or a history of repeated or prolonged episodes of nonadherence	Hepatitis B or C
	Severe tracheomegaly and/or tracheomalacia
Absence of an adequate or reliable social support system	Severe transpleural systemic to bronchial artery collateral arteries
Severely limited functional status with poor rehabilitation potential	Severe pleural disease (*e.g.* pleuroparenchymal fibroelastosis)
Chronic infection with highly virulent and/or resistant microbes that are poorly controlled pre-transplant[+]	

[#]: contraindications vary among transplant centres and the referring physician should always check with their own centre; [¶]: multiorgan transplantation (*e.g.* lung–liver, heart–lung or lung–kidney) may be considered in this situation; [+]: most centres will not now transplant patients chronically infected with *Mycobacterium abscessus* or *Burkholderia cenocepacia*; [§]: a minority of centres will consider transplanting children with these infections but only if the infection is sufficiently treated pre-operatively and there is a reasonable expectation for adequate control post-operatively. Data from Weill *et al.* (2015).

adopted. Despite demonstrated feasibility in paediatric patients, post-transplantation outcomes remain inferior. The projected time frame of bridging until a suitable donor organ becomes available is an unknown factor.

The early post-transplant period is characterised by the establishment of effective immunosuppression (started immediately prior to surgery), minimisation of infection risk, rehabilitation and protection of both the newly implanted donor organ plus other important organ systems.

A lifelong regimen of triple immunosuppression is used, consisting of:

- A calcineurin inhibitor (CNI), most commonly tacrolimus, which acts by binding to calcineurin in the cytoplasm and interfering with the transcription of important cytokines, thereby inhibiting T-cell stimulation; tacrolimus is preferred over cyclosporine in paediatric centres due to its more favourable side-effect profile, aiding compliance (less hirsutism and gingival overgrowth but a greater incidence of diabetes)
- A cell-cycle inhibitor (or antimetabolite), most commonly mycophenolate mofetil; cell-cycle inhibitors inhibit the proliferation of T- and B-cells by interrupting DNA, RNA and purine synthesis
- Corticosteroids, initially high-dose methylprednisolone, with subsequent weaning to oral prednisolone

Many centres further augment this regimen with "induction therapy" at the time of transplantation (used in >70% of paediatric transplants), which comprises: polyclonal antibodies, antilymphocyte or antithymocyte globulin, or the monoclonal antibody basiliximab or daclizumab, which acts as a T-cell interleukin-2 receptor antagonist. Increasing levels of immunosuppression must be balanced against the increased risk of severe infection or later malignancy (*e.g.* Epstein–Barr virus (EBV)-driven post-transplant lymphoproliferative disease).

Anti-infective prophylaxis starts with attempts to minimise the bacterial load prior to transplantation and continues with stringent surgical aseptic techniques and in some cases thoracic cavity washout with antibiotic solutions prior to organ implantation. Other aspects after lung transplantation include:

- Intravenous antibiotics based on the sensitivities of organisms present pre-transplantation, especially in CF, given at least until the patient is mobilising and able to clear secretions; nebulised antibiotics are often continued for a prolonged period if the recipient lungs are chronically infected with *Pseudomonas aeruginosa* pre-transplantation, as it is assumed that the sinuses will remain chronically infected
- Antifungal prophylaxis in children with CF and others in whom fungal colonisation pre-transplantation is suspected: oral nystatin during the first 6–12 months, and either oral itraconazole or voriconazole, or nebulised amphotericin for a minimum of 6 months but sometimes longer
- Antiviral prophylaxis in patients at increased risk: prophylactic valganciclovir in those at risk for cytomegalovirus (CMV) re-activation (high risk: donor CMV positive, recipient CMV negative; medium risk: donor and recipient CMV positive), and valaciclovir in those at increased risk of herpes simplex virus re-activation
- Prophylaxis against *Pneumocystis jirovecii* with co-trimoxazole

The patient is weaned from ventilation as rapidly as can be tolerated, with extubation often within the first 24 h. Inotropic support may be brief, particularly if transplantation occurs on cardiopulmonary bypass. A relative hypovolaemia strategy protects the lung from ischaemia–reperfusion injury and pulmonary oedema.

Primary graft failure occurs in ~10% of transplant recipients and resembles the clinical appearance of acute respiratory distress syndrome. Risk factors include marginal donors and longer graft ischaemia times (>6 h). Management is supportive.

In CF patients, regular aperients (*e.g.* lactulose, *N*-acetylcysteine, macrogol) and early introduction of enteral feeds are used to prevent distal ileal obstruction syndrome, which may occur in 10% post-transplantation. Physical mobilisation following chest drain removal aids respiratory secretion clearance in conjunction with regular chest physiotherapy. A typical post-operative inpatient stay in uncomplicated cases is 4 weeks. Patients requiring treatment for resistant pre-transplant infection will require longer.

Ongoing management

Management focuses on ongoing rehabilitation, surveillance for and treatment of acute complications, including infection and graft rejection, and education regarding transplant-orientated medication and follow-up regimens.

Careful surveillance and monitoring of both immunosuppression (using tacrolimus trough levels) and graft function (using daily home spirometry) aim to maintain adequate immunosuppression and protect the graft from both immune and

nonimmune insults to prevent rejection (both cellular and antibody mediated). EBV-guided immunosuppression may be used when EBV PCR titres are rising. This often coincides with CMV (re-)activation.

Bronchoscopy and transbronchial biopsy are performed in almost all transplant recipients, across centres, at defined surveillance points during the first year after transplantation and additionally as clinically indicated, based on respiratory symptom monitoring and daily home spirometry readings, with drops of >10% triggering urgent clinical review.

CNIs operate within a narrow therapeutic window, which gradually shifts to lower targeted trough levels during the first year, before plateauing at a suitable level dictated by the relative balance between minimising the risk of rejection and minimising the risk of infection and other CNI side-effects.

Regular monitoring is important for infection and other unwanted side-effects of immunosuppressive therapy (in particular, renal dysfunction). Infection, particularly graft infection, must be treated promptly.

Specific drug-related side-effects and medication interactions must also be monitored and considered (tables 3 and 4). Adopting a strict routine of drug timing, administration and compliance is a key element in achieving better outcomes.

Graft rejection

The clinical picture of early acute rejection is nonspecific and may be difficult to distinguish from infection. As a result, periods of coughing, malaise, low-grade

Table 3. Common side-effects of maintenance immunosuppression

Drug	Side-effect
Tacrolimus	Nephrotoxicity Tremor Paraesthesia/hypersensitivity Hypertension Hypercholesterolaemia Neurotoxicity Diabetes mellitus Alopecia
Mycophenolate mofetil	Bone-marrow suppression Nausea, dyspepsia, diarrhoea, constipation Hyperglycaemia Hypercholesterolaemia
Prednisolone	Cushing syndrome Dyspepsia Peptic ulceration Osteoporosis Proximal myopathy Increased appetite Neuropsychiatric effects Glaucoma, papilloedema, cataracts Skin atrophy, striae, bruising, acne

Note that foods such as grapefruit should be avoided with tacrolimus (as this interaction increases tacrolimus levels) and ibuprofen-related nonsteroidal anti-inflammatory drugs should be avoided because of their renal side-effects.

Table 4. Medications interacting with CNIs

CYP3A inhibitors (increase CNI levels)	CYP3A inducers (decrease CNI levels)
Antibiotics	**Antibiotics**
Erythromycin	Rifampicin
Clarithromycin	Clindamycin
Chloramphenicol	Ethambutol
Ciprofloxacin (rare)	**Antifungals**
Antifungals	Caspofungin
Itraconazole	**Anti-epileptics**
Fluconazole	Phenytoin
Voriconazole	Phenobarbitone
Imidazoles (*e.g.* ketoconazole)	Carbamazepine
Triazoles (*e.g.* posaconazole)	**Others**
Cardiovascular drugs	Cigarette smoking
Amiodarone	St John's wort
Calcium-channel blockers (*e.g.* verapamil, diltiazem and felodipine)	
Nifedipine (rare)	
Gastrointestinal drugs	
Cimetidine	
Omeprazole (rare)	
Others	
Grapefruit juice	
Antiretrovirals (*e.g.* atazanavir, nelfinavir and ritonavir)	
Danazol	

Note that this is not intended to be an exhaustive list. CYP3A: cytochrome P450, family 3, subfamily A.

pyrexia or a minor drop in lung function should be thoroughly evaluated. Chest radiographs may be normal and do not distinguish the two pathologies. Urgent flexible bronchoscopy, BAL and transbronchial biopsy are often indicated.

The presence and severity of rejection in biopsy specimens is classified based on the presence of perivascular and interstitial mononuclear cell infiltrates in alveolar tissue (from grade A0 for no acute rejection to grade A4 for severe rejection), with an additional classification for associated airway inflammation (from B0 for no airway inflammation to B4 for severe airway inflammation).

The clinical relevance of A1 rejection is unclear, although frequent A1 episodes have been linked to a greater risk for chronic graft rejection in adults. A1 classification at present is not always treated unless it is clinically significant. More severe episodes (A2, A3 or A4) are managed with a 3-day course of high-dose methlyprednisolone (typically 10 $mg \cdot kg^{-1} \cdot day^{-1}$), although some centres will occasionally treat A2 rejection with oral corticosteroids. Steroid-resistant rejection is exceptionally rare, although true cases may require second-line therapy such as polyclonal antilymphocyte or antithymocyte globulin.

The clinical relevance of airway inflammation and the optimal method of treatment remain unclear.

Positive bacterial or fungal cultures should be treated. Many centres use specific therapies such as ribavirin for proven cases of lower respiratory tract infection with respiratory syncytial virus and paramyxoviruses (*e.g.* parainfluenza virus and human metapneumovirus). The role of viral infections in acute and chronic rejection remains more controversial, but it is estimated that 15–25% of lung transplantation patients develop chronic allograft dysfunction in the year following community-acquired respiratory viral infection. This is particularly relevant in children given their increased incidence of viral infection, particularly in the infant and preschool age range. Compliance with active immunisation is critical, and prophylactic palivizumab may be considered in infants.

The role of antibody-mediated rejection is increasingly recognised, although the true frequency after paediatric lung transplantation remains unclear. Recent diagnostic criteria and a working consensus definition have been developed. Routine monitoring of circulating donor-specific antibodies is recommended. The diagnostic criteria for antibody-mediated rejection include:

- Positive donor-specific antibodies
- Graft dysfunction
- Histopathological features (*e.g.* capillaritis)
- C4d positivity

Treatment options include plasmapheresis, *i.v.* immunoglobulin and potentially targeted suppression of B-cells (rituximab) or plasma cells (bortezomib).

Initial descriptions of progressive irreversible obstructive allograft dysfunction (*i.e.* chronic graft rejection) were accompanied by a histological description of obliterative bronchiolitis or "bronchiolitis obliterans". Histological diagnosis is challenging due to its patchy distribution, and a clinical diagnostic surrogate was subsequently developed based on the pattern of lung function seen following transplantation, termed bronchiolitis obliterans syndrome (BOS) (table 5). Chronic lung allograft dysfunction (CLAD) has since been introduced as an overarching descriptor of chronic graft dysfunction, as recognition that other phenotypes exist in addition to BOS, such as restrictive allograft dysfunction. Many centres are starting to use the CLAD nomenclature. However, most of the literature on the origins of chronic rejection still uses the term obliterative bronchiolitis/BOS, so for that reason this terminology will be used in the rest of this chapter.

BOS is defined as an irreversible fall in lung function when other causes, such as infection, have been excluded. Important potential contributing factors include GOR disease and microaspiration, and airway infection (*e.g.* with respiratory syncytial virus or *Pseudomonas* spp.), which should be treated aggressively to try to reverse this

Table 5. Grading of BOS

Grade	Definition
BOS 0	FEV_1 >90% of baseline and FEF_{25-75} >75% of baseline
BOS 0-p	FEV_1 81–90% of baseline and/or FEF_{25-75} ≤75% of baseline
BOS 1	FEV_1 66–80% of baseline
BOS 2	FEV_1 51–65% of baseline
BOS 3	FEV_1 ≤50% of baseline

Baseline lung function is defined as the average of the two highest values achieved post-transplantation, recorded ≥3 weeks apart. FEF_{25-75}: forced expiratory flow at 25–75% of FVC. Reproduced and modified from Estenne *et al.* (2002) with permission.

dysfunction. GOR disease is common in transplant recipients, and emerging data in adults appear to support early surveillance and fundoplication, although equivalent paediatric data are lacking. Low-dose macrolide therapy appears to be beneficial in those with neutrophilic inflammation.

In general, advanced BOS is poorly responsive to therapy, and interventions aim to stabilise and prevent ongoing lung function decline. Other BOS therapeutic options include leukotriene receptor antagonists, augmentation of immunosuppression, total body lymphoid irradiation and photopheresis. Re-transplantation is offered in some centres, but the risks are often increased due to previous thoracotomy, making explantation more challenging, and the increased prevalence of other complications such as renal dysfunction.

Graft monitoring with spirometry is challenging in the preschool age range owing to the cooperation and coordination required. Modification of reported indices may be required (*e.g.* $FEV_{0.75}$ rather than FEV_1). The use of age-appropriate reference equations is essential for monitoring and longitudinal spirometry, and CT data suggest the lungs continue to grow with age.

Complications

After lung transplantation, a variety of noninfectious complications may be encountered (table 6). Early surgical complications, beyond the immediate post-transplantation period include:

- Bronchial anastomosis stenosis, which is managed with balloon dilatation with or without lasering (repeated as necessary)
- Damage to the phrenic nerve affecting diaphragmatic function
- Damage to the vagus nerve causing delayed gastric emptying

Common later complications include the following:

- Hypertension (~70% at 5 years), typically managed with calcium-channel blockers such as amlodipine
- BOS (~50% by 5 years)
- Diabetes mellitus (~33% at 5 years); corticosteroids and CNIs are major risk factors
- CNI-induced nephropathy (~33% at 5 years); due to the prevalence of renal dysfunction in survivors, exposure to other agents associated with potential renal toxicity should be minimised or avoided (*e.g.* nonsteroidal anti-inflammatory drugs, amphotericin, aminoglycosides)
- Increased malignancy risk due to ongoing immunosuppression, with post-transplant lymphoproliferative disease (typically EBV-driven B-cell expansion) and skin cancers being the most relevant to the paediatric population; advice about sunlight exposure is important
- Risk for nonrespiratory complications of the underlying disease in CF children (*e.g.* distal ileal obstruction syndrome, malabsorption and bone disease)

Long-term outcomes

International median survival after lung transplantation is now ~7 years and is identical in children and adults. Better survival of recipients aged 1–11 years is seen compared with those aged 12–17 years. The onset of puberty and adolescence brings with it various challenges, including risk-taking behaviour and noncompliance, with adverse effects on post-transplantation outcomes. While there is little evidence of how best to manage this, most centres encourage adolescents to take increasing

Table 6. Common noninfectious complications after lung transplantation

Time	Complication
Early	Anastomotic dehiscence or stenosis Pulmonary vein or artery stenosis Nerve damage (phrenic or vagal nerve injury, loss of cough reflex, swallowing difficulty)
Intermediate and late	Malignancy (*e.g.* lymphoproliferative disease) Nephrotoxicity Hypertension Hyperlipidaemia Osteopenia and osteoporosis Avascular necrosis of the femoral head Growth failure Diabetes mellitus Hyperuricaemia/gout Cytopenias (anaemia, leukopenia, thrombocytopenia) Thromboembolism GOR disease

responsibility for their own care, to maintain adherence to therapy, and to develop long-term goals and ambitions.

Summary

Lung transplantation is now an established, accepted treatment option for children with end-stage lung disease at many centres around the world. Long-term outcomes are steadily improving for paediatric patients but have yet to reach those achieved by other solid-organ transplants. There are many similarities in management between adult and paediatric subjects, but several differences unique to the paediatric age range exist. Future work to improve the availability and allocation of suitable organs will hopefully see this therapeutic option offered to a greater proportion of children who are eligible.

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Inhalation therapy

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Inhalation therapy for the management of paediatric respiratory disorders has gained importance in recent decades. Inhalation therapy is considerably more complex than oral therapy, as the drugs must be delivered to an organ that is specialised in excluding foreign material.

As a rule of thumb, one needs to consider the "five Ds" for prescribing optimal inhalation therapy:

- Disease
- Drug
- Deposition
- Device
- Disability of the patient

Thus, one needs to be informed about the pathophysiology and severity of the lung disease, the pharmacological aspects of the various drugs, and how the disease, drug, device and patients characteristics will influence the deposition of the aerosol into the lungs. This information and the technical qualities of the aerosol delivery devices are needed to be able to match the device to the patient. Last but not least, the abilities and disabilities of the child and parents should be known to ensure they can use the device correctly; in other words, "Does the patient use the device correctly and is it

Key points

- To match the correct inhalation device to a patient, a clinician should always consider the "five Ds": disease, drug, deposition, device and disability.
- A pressurised metered-dose inhaler/valved holding chamber with an attached face mask is the first choice for asthma maintenance treatment in young children.
- Dry-powder inhalers are convenient for older children who can perform a firm and deep inhalation.
- The correct inhalation technique and adherence are mandatory for successful inhalation therapy.

used regularly?" This chapter will focus mainly on the last three points by discussing some basic principles of aerosol technology and the different aerosol delivery devices with arguments for the correct choice and the importance of inhalation instructions.

Disease

Inhalation therapy is the mainstay of asthma management in children and is increasingly important for the treatment of other respiratory disorders such as CF and BPD. Other indications for inhalation therapy are: impaired mucociliary clearance such as in PCD, neuromuscular diseases, tracheobronchomalacia, non-CF bronchiectasis, croup and atelectasis. Inhalation therapy has been best studied in asthma and CF, and therefore most therapies are evidence based for these diseases. However, for all other indications, although aerosol therapy is frequently used, there is a lack of evidence for its clinical efficacy.

Inhalation therapy is mostly used in pulmonary diseases with airway obstruction and inflammation in the small airways. Therefore, targeting the inhaled drugs to the place of action is especially challenging because of the obstructed airways. Small airways may be reached by choosing the right inhalation device and instructing the right inhalation technique.

Drug

Inhaled drugs are available for steroids, bronchodilators, mucolytics and antibiotics for children. Other inhaled drugs such as prostaglandins, antiproteases, analgesics, anticarcinoid therapy, proteins and surfactant are not yet registered for use in children. Many more inhalation therapies are in development. Disease-specific treatment options are available in many cases. Many of the inhaled drugs are used off-label, as most are not registered for use in young children or are used for different indications from those they were intended for. The clinician should be aware of possible side-effects and should inform patients and parents about the off-label use of drugs.

Deposition: basic aerosol technology

Drugs need to be in the form of an aerosol to be inhaled. An aerosol is best described as a cloud of fine particles that are small enough to remain suspended in air for a considerable length of time. Aerosol deposition and the distribution pattern in the respiratory tract depend on particle characteristics, the anatomy of the respiratory tract and the breathing pattern. The most important particle characteristics are size, density and shape. Particle deposition occurs by three mechanisms: impaction, sedimentation and diffusion (figure 1). Large particles and/or particles with high velocity tend to deposit by impaction in the upper and central airways at airway bifurcations. Smaller particles have a higher probability of reaching the small airways where they are deposited by sedimentation under the influence of gravitational forces. The smallest particles can travel all the way to the alveoli, where they are deposited by diffusion through Brownian movements of the molecules.

Table 1 shows frequently used terms in aerosol technology. These terms are usually derived from *in vitro* studies and include particle characteristics such as particle size and particle size distribution of an aerosol. These different terms are used interchangeably by commercial companies and in the literature. Knowledge about the differences in these terms is important to be able to interpret data. Aerosol particles between 1 and 5 µm in diameter are thought to have a high probability of being deposited in bronchi and therefore are often referred to as respirable particles. Particles <1 µm

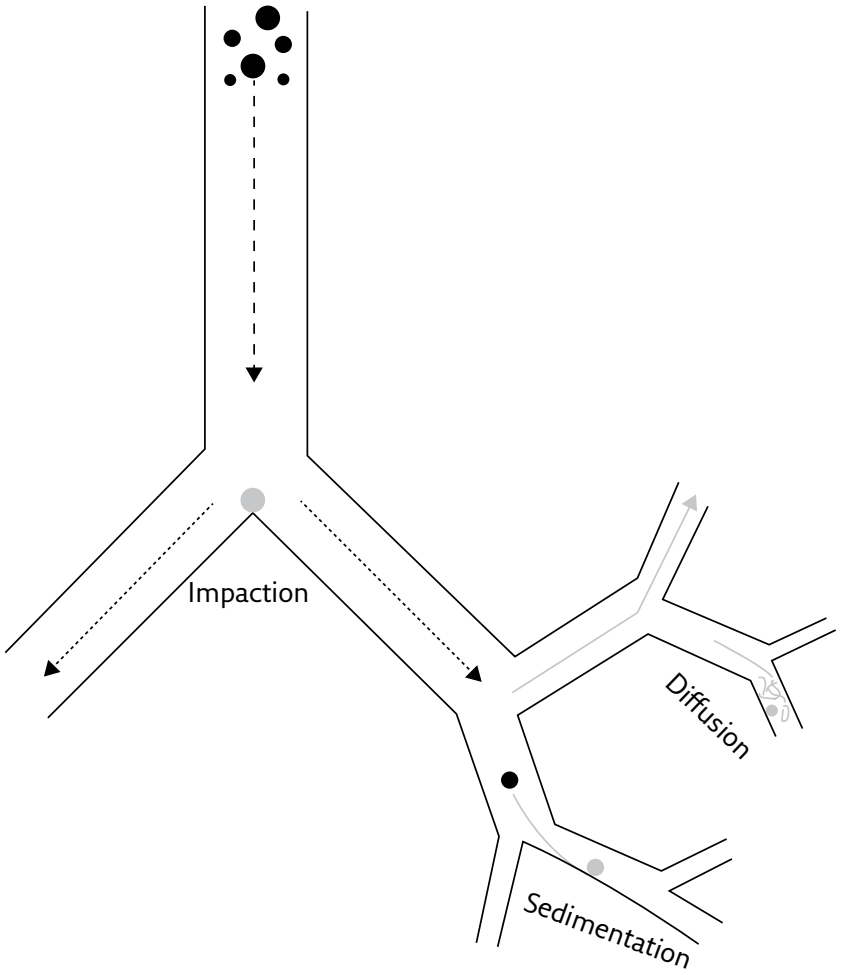

Figure 1. Aerosol deposition mechanisms. Aerosol particles are deposited by three main mechanisms in the bronchial tree: impaction, (gravitational) sedimentation and (Brownian) diffusion. Impaction occurs when (larger) particles are not able to adjust to a sudden change in airflow direction and instead follow their original angle. Sedimentation occurs when (smaller) particles are deflected from their original angle by gravitational forces. Diffusion occurs when (small) aerosols collide with air molecules, which results in random Brownian motion of the particles.

in diameter are likely to be exhaled. It is important to realise that this 1–5 µm range is mostly derived from studies with healthy adult subjects. In cases of severe airway obstruction such as CF, the deposition pattern is nonhomogeneous and will move from the peripheral to the more central airways. Little is known about the relationship between particle size and deposition in young children. However, it is likely that the respirable fraction is in the smaller particle range. It has been shown in models, animal studies and deposition studies that smaller particles are more effective for bypassing the upper airways and reaching the peripheral airways, even in young children and in CF patients with airflow obstruction.

Besides particle size, deposition and the distribution of aerosols in the airway depend on the breathing pattern. With high inspiratory flows, even small particles will deposit centrally, but with a slow deep inhalation, larger particles can also reach peripherally into the lungs.

When taking all principles of aerosol deposition into account, the most optimal lung deposition is reached by inhaling small particles using a slow deep inhalation and a breath-hold, if possible.

Table 1. Terms used in aerosol technology

Term	Definition
Labelled or nominal dose	The mass of drug that is available within the aerosol generator per actuation (metered dose)
Total emitted dose (TED) or delivered dose	The mass of drug emitted per actuation that is actually available for inhalation at the mouth; part of the nominal dose will stay behind in the device and is not part of the emitted dose
Label claim	This can be either the nominal dose or the emitted dose, depending on the country and drug
Fine-particle dose (FPD)	The mass of particles <5 µm in size within the TED
Fine-particle fraction (FPF) or respirable fraction	The FPD divided by the TED; the FPF is considered to be the part of an aerosol that can potentially reach the lungs
Lung deposition	The percentage of either the nominal or the emitted dose that is deposited in the lungs; note that these two parameters are not the same
Mass median aerodynamic diameter (MMAD)	The diameter at which 50% of the particles of an aerosol by mass are larger and 50% are smaller
Geometric standard deviation (GSD)	This measures the dispersion of particle diameter and is defined as the ratio of the median diameter to the diameter at ±1 SD (σ) from the median diameter; in a cumulative distribution plot of the aerodynamic diameter and mass of particles, the GSD is calculated as the ratio of the median diameter to the diameter at 15.9% of the probability scale, or the ratio of the diameter at 84.1% on the probability scale to the median diameter; aerosols with a GSD >1.22 are considered polydisperse; most therapeutic aerosols are polydisperse and have GSDs in the range of 2–3

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Device: matching the right inhalation device to the patient

Current inhalation devices can be classified into four categories:

- Nebulisers
- Pressurised metered-dose inhalers (pMDIs), which can be used with a press-and-breathe technique, as a breath-actuated device (BA-pMDI) or in combination with a valved holding chamber (VHC)
- Dry-powder inhalers (DPIs)
- Soft-mist inhalers

The choice of inhalation device depends on the ability of a child to perform a specific inhalation manoeuvre and availability of the intended drug for this device (figure 2). In addition, not all devices are available in all countries. For several devices, specific inhalation manoeuvres are required, such as the press-and-breathe technique for pMDIs and a firm inspiration with a flow of ~30–60 $L \cdot min^{-1}$ for DPIs. Sufficient inspiratory flow is especially important for DPIs because the particle size increases and the dose decreases with lower inspiratory flows. Young children and dyspnoeic patients are often not able to achieve an inspiratory flow of 60 $L \cdot min^{-1}$. For BA-pMDIs,

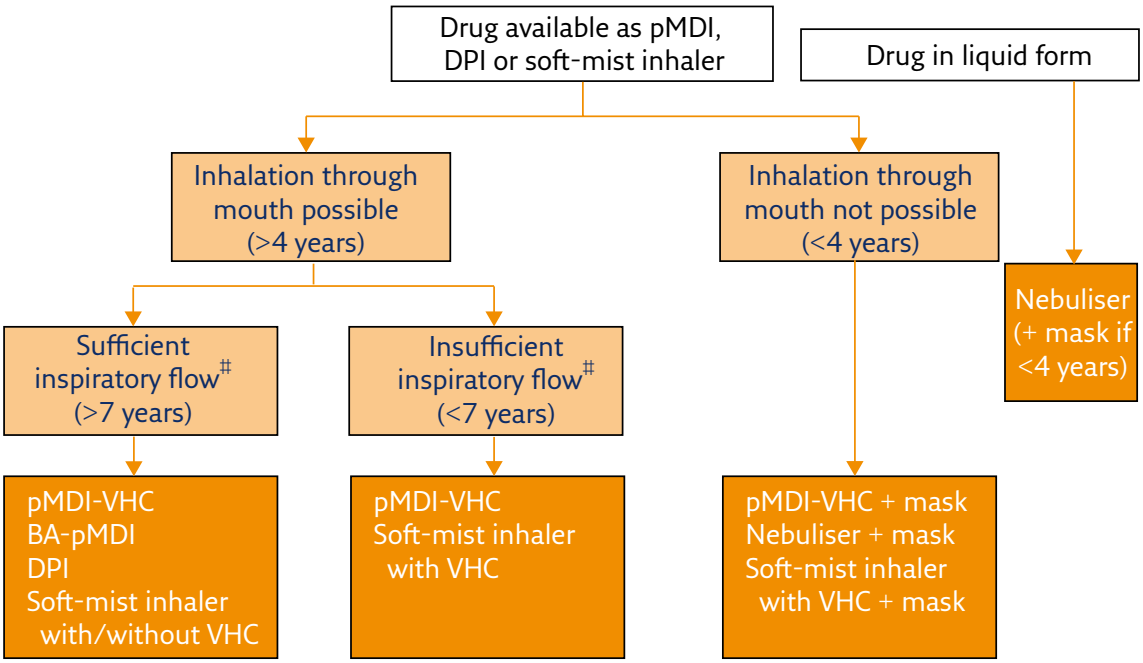

Figure 2. How to choose the right inhalation device for a child. #: sufficient inspiratory flow depends on the intended inhaler; it is usually >30 L·min^{-1}, but for some inhalers (DPIs) it is ≥60 L·min^{-1}.

an inspiratory flow of 20–30 L·min^{-1} (depending on type) is required. For children <7–8 years of age, it is generally recommended that they use a pMDI in combination with a VHC and should use an additional face mask if the child cannot breath consciously through the mouth (usually <3–4 years). For children of all ages, it is not recommended that they put the pMDI directly into the mouth, because the press-and-breathe technique requires careful hand–mouth coordination, which is often not performed correctly. This leads to high oropharyngeal and low lung deposition. In young children with asthma, the use of a pMDI-VHC with a face mask is the mainstay of asthma home treatment. Nebulisers can be used when a child refuses to use a VHC, when medication is not available in other forms, when large doses need to be given or when aerosol inhalation needs to be combined with oxygen therapy.

Nebulisers

Nebulisers can convert a liquid into a mist for inhalation and can therefore deliver a wide range of drug formulations. There are various types of nebuliser, which differ in the way the aerosol is generated. These are jet, ultrasonic and vibrating mesh nebulisers, with or without smart nebuliser technology. The traditional view of nebulisers is that they are expensive and bulky, as well as inconvenient to handle and maintain. However, innovations in the field of nebuliser and inhalation technology have introduced modern (smart) nebulisers that are more effective than traditional jet nebulisers, making them more attractive to use in clinical practice.

Nebulisers can be used to deliver drugs that are available as liquids. Examples of inhaled drugs that are only available as liquids are recombinant human deoxyribonuclease (rhDNase), aztreonam, levofloxacin and hypertonic saline. Tobramycin and colistin are both available as a liquid and as a dry powder. Aztreonam and levofloxacin are registered to be delivered by well-defined nebuliser–compressor combinations, and the drug and nebuliser are provided as a complete package. Other CF drugs, such as rhDNase and inhaled tobramycin and colistin, are registered for use with jet nebulisers and some other nebulisers, but the choice needs to be made by the

prescribing clinician. Bronchodilators and inhaled steroids can be delivered faster, more efficiently and more safely using a pMDI-VHC, BA-pMDI or DPI. Even in acute asthma attacks, delivery of bronchodilators by a pMDI-VHC is equally as effective as using a nebuliser. Therefore, a pMDI-VHC, BA-pMDI or DPI is the preferred device for asthma management. If a child is very distressed during administration of aerosols by pMDI-VHC, a nebuliser can be a more acceptable alternative for the fighting toddler.

In the European guidelines for nebulisers, it is recommended that drugs are registered for use with a specified nebuliser. Therefore, inhaled drugs must be tested with a pre-specified nebuliser before official registration in order to provide recommendations for use and information on efficacy. However, there are few to no regulations when a new nebuliser (without the drug) is introduced into the market, except for a CE marking. Using an alternative drug or system can have an unpredictable effect in terms of both efficacy and toxicity, especially for potentially toxic drugs such as inhaled antibiotics. Efficacy and toxicity should therefore be monitored closely if a nebuliser or drug combination is chosen that is different to the recommended one.

New nebuliser technology is attractive for patients as it offers greater convenience and portability and may significantly increase aerosol deposition compared with old nebulisers. However, adaptation of this new and improved nebuliser technology without due consideration of the consequences of increased dosing presents potential risks.

Jet nebulisers

Jet nebulisers are the oldest and most well-known and widely used nebulisers. The advantages of nebulising over using a pMDI-VHC or DPI are that oxygen can be given during inhalation and that high doses can be administered over a prolonged time. Furthermore, only tidal breathing is required, so nebulisers can be used in patients of all ages and disease severities. There are numerous disadvantages. For the home setting, the equipment is expensive, cumbersome and noisy, and needs a power supply. The administration time can be as long as 20–30 min several times a day. This is not beneficial for patient compliance. Furthermore, the nebuliser requires regular cleaning, with a high risk of contamination if the cleaning instructions are not followed correctly. Jet nebulisers use an electric compressor or compressed gas source (oxygen or air) to create the aerosol. There are numerous technical factors that can affect aerosol output and the particle size distribution of a jet nebuliser. These may result in highly variable doses and poor reproducibility of particle size. These technical factors include the operational flow, fill volume, viscosity, concentration and temperature of the solution or suspension, nebuliser design and breathing pattern. It is important that the correct operational flow or compressor is used while nebulising. Usually, a flow of 6–8 $L \cdot min^{-1}$ is the optimal operational flow. A lower flow leads to larger particles and prolonged nebulisation time. The fill volume determines the concentration, particle size and nebulised dose. For each nebuliser and drug, there is a recommended fill volume. If a smaller volume is used, there might be less drug delivered, largely because there is a residual volume of 1–1.5 mL that remains in the nebulising equipment. There are different types of jet nebulisers. The most widely used unvented nebulisers, with continuous output of aerosol, are inefficient because there is loss of aerosol during exhalation. They are also inefficient when a patient is not breathing through the nebuliser. Lung deposition from jet nebulisers ranges from 1.3% in infants to 11% in older children. More efficient systems have been developed, such as open-vent and breath-enhanced nebulisers with inhalation and exhalation valves. The latest technology uses breath-actuated systems, which only deliver during inspiration. This is either by using a mechanical mechanism opening when an inspiratory flow threshold

is reached, or by using electronics, which follow the patient's breathing pattern and give a precise dose during inhalation. The use of breath-actuated systems results in improved lung deposition and dose reproducibility and reduced loss by exhalation. Breath-actuated devices are suitable for children aged ≥4 years.

Ultrasonic nebulisers

Ultrasonic nebulisers use a piezoelectric crystal to convert fluid into a fine mist. The output of ultrasonic nebulisers is higher compared with jet nebulisers, which is useful for administration of large volumes. However, ultrasonic nebulisers are not suitable for nebulising suspension (*e.g.* steroids) and viscous (*e.g.* antibiotics) fluids. Furthermore, the fluid in the ultrasonic nebuliser may become too warm because of the crystal producing heat by vibrating at high speed. This could inactivate certain drugs such as rhDNase. Ultrasonic nebulisers are not widely used because they are expensive and produce relatively large particles compared with jet nebulisers.

Vibrating mesh and smart nebulisers

Mesh nebulisers use either a vibrating or a fixed membrane with a piezoelectric element with microscopic holes to generate an aerosol. Vibrating mesh devices have a number of advantages over other nebuliser systems. They are highly efficient, quiet and generally portable. Lung deposition is substantially increased, varying from 30% to 80%, depending on the device. Unfortunately, this comes at a price as they are significantly more expensive than other nebulisers and require a significant amount of maintenance and cleaning after each use. Cleaning is necessary to prevent colonisation by pathogens and to prevent the build-up of deposit and blockage of the apertures, especially when suspensions are aerosolised. They are most widely used for the treatment of patients with CF.

Smart nebulisers are nebulisers with dosimetric aerosol delivery. There is a smart mesh nebuliser and a jet nebuliser with a smart compressor. With dosimetric aerosol delivery, the breathing pattern is controlled (slow and deep), and aerosol is delivered only during the first 50–80% of inspiration: a deeper and longer inhalation shortens the nebulising time. Almost no drug is lost during exhalation. Smart nebulisers can achieve a lung deposition of 60–80%, compared with 5–11% for the traditional jet nebulisers. In addition, more peripheral lung deposition can be achieved, which may result in improved treatment of small airway obstruction/disease. Another advantage is that adherence is data logged electronically and can be downloaded afterwards. This provides a useful tool to monitor adherence to aerosol therapy and discuss this with the patient in order to improve the efficacy of the treatment. Despite the advantages, vibrating mesh and smart nebulisers have still not been studied extensively in children, and therefore little clinical information is available. Dose recommendations are lacking or are based on *in vitro* or adult data. There might be indications that, especially in young children, higher lung deposition of aerosols can lead to toxic side-effects. There are many good arguments to use one of the new-generation nebulisers, but efficacy and toxicity should be carefully monitored, especially when using potentially toxic drugs (*e.g.* inhaled antibiotics).

pMDIs, pMDI-VHCs and BA-pMDIs

Almost all drugs available for inhalation therapy in asthma are available in pMDIs. In pMDIs, the drug is present in a solution or suspension with propellants and surfactants. In the case of a suspension, the pMDI should be shaken before use to mix the drug homogeneously in the propellant. An accurately metered dose is released at high velocity when the pMDI is fired. The mass of drug and its aerosol characteristics from the device are independent of the inspiratory effort by the patient.

To resolve the difficulties with the press-and-breathe technique, as explained earlier, a BA-pMDI or pMDI-VHC can be used. BA-pMDIs automatically actuate when a patient is inhaling. When using a BA-pMDI, the patient should be able to perform a maximal exhalation followed by a slow inhalation with a breath-hold. Lung deposition is improved using a BA-pMDI compared with a pMDI, but oropharyngeal deposition is still high. VHCs are used to facilitate inhalation from a pMDI with normal tidal breathing and decrease the oropharyngeal deposition. In principle, the use of a VHC is recommended for all patients when using pMDIs, especially using inhaled corticosteroids, but particularly for those who have difficulties with the press-and-breathe technique with the pMDI. There are several VHCs available commercially. *In vitro* testing shows significant differences among the different VHCs. However, whether these differences are clinically relevant is not clear. For bronchodilator responsiveness, there seems to be no difference among several VHCs, but for inhaled corticosteroids, this is not known. In clinical practice, the choice of a specific VHC may be restricted by its availability in different countries, by the preferential policy of an insurance company or by the type of pMDI that can fit in the VHC. Clinicians have to be aware of possible differences in aerosol deposition among different VHCs, especially when switching from one to the other. One of the differences can be the material from which the VHC is made. A plastic VHC can be electrostatically charged, which reduces the inhaled dose considerably. However, when a plastic VHC is coated with detergent, electrostatic charge is effectively minimised and lung deposition will increase substantially. Coating with detergent is easily done by washing the VHC in warm water with household detergent. It is important not to rinse the VHC but to let it air dry. Several antistatic VHCs are now available commercially to overcome this problem.

Lung deposition increases two-fold when using a mouthpiece, compared with using a face mask; therefore, a VHC with a mouthpiece should be used whenever possible. It increases even more when a nonstatic VHC and extra-fine particles are used, up to a maximum of 55%. A face mask attached to the VHC should be used in children <3–4 years old, when they are not able to breathe consciously through the mouth. It is important to instruct the parents to achieve a good face mask seal, as even a small gap of 0.2 cm will dramatically reduce the inhaled dose. Each VHC comes with its own face mask. A suboptimal mask seal may almost completely undo the advantage gained by using a nonstatic VHC or a pMDI with small particles. A good fit with a small volume is important when choosing a face mask. A face mask can add a considerable dead space to the inhalation device if it is too big. This may especially be a problem in young children who have a low tidal volume, causing a lower lung deposition. It can be difficult to obtain a proper seal between the face and mask in uncooperative children. Crying also dramatically reduces lung deposition, as high inspiratory flows cause impaction of particles in the upper airways. Cooperation of a child when using the inhaler device remains the most important factor for efficient dose delivery. A recently developed face mask that incorporates a pacifier stimulates both cooperation and face mask seal by suckling of the infant on the pacifier. Parents of young children should be carefully instructed about the importance of a good face mask seal and the importance of a good administration technique and cooperation during the administration procedure to achieve optimal lung deposition.

Dry-powder inhalers

The majority of anti-asthma drugs are available as DPIs. DPIs are small, portable, handheld devices. There are numerous different DPIs available, each with its own directions for use. Older children and adults prefer DPIs because they are “easy” to use in daily life, which may stimulate adherence. In a DPI, the drug is present in either

a single or multiple dosing chamber. DPIs are formulated with their drug particles attached to a carrier, or as agglomerates in the form of pellets. To facilitate deposition in the lungs, drug particles are deagglomerated during inhalation. Airflow through a DPI combined with its internal resistance creates turbulent energy inside the DPI. This internal energy is required to deagglomerate the particles and aerosolise the dose. The turbulent energy created during inhalation is the product of the patient's inspiratory flow multiplied by the DPI's resistance. Thus, for a set energy, a DPI with a high resistance will require a lower inspiratory flow than a DPI with a lower resistance. The mass of released drug and the mass median aerodynamic diameter (MMAD) and geometric standard deviation of the aerosol cloud are dependent on the inspiratory flow of the patient. In cases of insufficient inspiratory flow through the DPI (<60 $L \cdot min^{-1}$ for most DPIs), the mass of drug that is released will be reduced and the MMAD will be increased. This emphasises that DPIs can only be used when a patient is able to generate sufficient flow to achieve optimal drug dispersion. Sufficiently high and reproducible inspiratory flows through a DPI can generally be obtained in asthmatic children ≥7 years. Careful inhalation instructions are important for correct use and effective aerosol delivery of DPIs. Insufficient inspiratory effort, mistakes in dose preparation, no maximal exhalation before inhalation, no breath-hold and storage in humid places can lead to decreased or no lung deposition. There are different inhalation manoeuvres for each DPI. For several DPIs, it is recommended to inhale as fast and deep as possible for optimal deagglomeration of the particles. For others, the recommendation is to inhale as deeply as possible with steady, moderate force. The difference between inhalation manoeuvres is dependent on the magnitude of the internal resistance. Exactly regulating the correct inspiratory flow is difficult, and it is often done too fast. Consequently, this causes high impaction of particles in the oropharynx, which could increase local side-effects. The high inspiratory flow also causes aerosols to deposit mainly in the central rather than the peripheral airways.

DPIs are also available for inhaled tobramycin and colistimethate. Tobramycin inhalation powder uses a new spray-drying technique, creating hollow porous particles. These porous particles behave like small particles because a lower density decreases the aerodynamic diameter. The different types of DPI for inhaled antibiotics vary in internal resistance and particle size.

The newest technology uses feedback mechanisms and dose counters to check compliance, and stimulates good inhalation. The clinician needs to be informed which drugs are available in the different devices. Most of the new DPIs are not well studied in children.

Soft-mist inhalers

A soft-mist inhaler atomises the drug solution using mechanical energy imparted by a spring. When the spring is released, the solution is forced through an extremely fine nozzle system. This produces a fine mist that is slow moving, giving the patient time to inhale after the press-and-breathe technique, leading to lower deposition in the mouth and throat and relatively high lung deposition (~39%). The soft-mist inhaler can be used in combination with a VHC (with a lung deposition in young children of ~4%). There is currently only one commercially available soft-mist inhaler.

Disability: does the patient use the device correctly?

Correct use of the aerosol delivery device is crucial for the optimal effect of inhalation therapy. Any mistake during the inhalation procedure can substantially influence the delivered dose. It is known that inhalation instruction needs to be repeated several times before the inhalation is performed correctly.

Cooperation during administration is crucial in young children. Crying and leakage of the face mask have been shown to dramatically reduce the amount of drug delivered to the lungs. Administration during sleep may be an alternative, but children often wake during this procedure, causing an even more unsettling situation.

Adherence to inhalation therapy is as important as choosing a correct device and practising an accurate inhalation technique. It is known that adherence to inhalation therapy is generally low, which can lead to more severe disease and hospital admissions. In good partnership with patients, parents and doctor, the treatment, device selection and use need to be discussed and explained.

For detailed inhalation instructions for each device, we would refer to the various useful websites in the further reading list.

Summary

Consider the "five Ds" when prescribing inhalation therapy:

- Disease. For many paediatric pulmonary conditions, inhalation therapy plays an important role in the management of the disease. Inhalation therapies for asthma and CF are the most well known and also best studied. For most other indications, aerosol therapy is recommended, but this is not evidence based.
- Drug. The selection of the drug determines the possibilities for the choice of inhalation device. For both disease and drug, it is important to know where in the lungs the drug needs to be deposited. Mostly, drugs need to be deposited in the small airways for optimal effect.
- Deposition. Deposition of aerosol in the lungs is dependent on the density and size of the particles, the breathing pattern, the airway calibre and obstruction of the airways. In general, optimal aerosol delivery is achieved by small particles with a slow and deep inhalation and, if possible, a breath-hold.
- Device. There are four different groups of inhalation devices: nebulisers, pMDIs, DPIs and soft-mist inhalers. The choice of device depends on the choice of drug, the availability in a country and the ability of the patient to use the device. For children using asthma maintenance treatment, a pMDI-VHC with or without a face mask, or a DPI when older, is the first choice. There are marked differences in lung deposition among devices, but it is mainly dependent on cooperation of the child and use of the correct inhalation technique.
- Disability. Does the patient use the device correctly? After selection of the device, it is crucial to give the patient and parents detailed inhalation instructions. Each device comes with its own specific inhalation instructions. Incorrect administration of aerosols will lead to no or hardly any drug delivered into the lungs, leading to treatment failure. Adherence also needs to be checked. Optimal inhalation therapy is only possible with repeated inhalation instructions and well-informed patients and parents, which will stimulate adherence.

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Home oxygen therapy, noninvasive and invasive ventilation, and home ventilatory support

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Pathophysiology of respiratory failure

The respiratory system consists of a gas-exchanging organ (the lungs) and a ventilatory pump (respiratory muscles and the thorax). Either or both of these can fail and cause respiratory failure (figure 1). However, the physiopathology and the treatment differ according to the type of respiratory failure.

Hypoxaemic (type I) respiratory failure

Diseases that damage lung tissue, and consequently the gas exchange at the alveolar–capillary level, cause hypoxaemia with normal or low carbon dioxide levels. Greater diffusion of carbon dioxide through the alveolar–capillary barrier, compared to oxygen, explains the preservation of a normal carbon dioxide level. This type of hypoxaemic respiratory failure, also called type I respiratory failure, may be caused by the following:

- Low ambient oxygen, *e.g*. high altitude
- Ventilation/perfusion mismatch: parts of the lung receive oxygen but not enough blood to absorb it, *e.g*. pulmonary embolism
- Shunt: oxygenated blood mixes with non-oxygenated blood from the venous system, *e.g*. right-to-left shunt
- Damage of the alveolar–capillary barrier, *e.g*. ILD, pulmonary oedema, acute respiratory distress syndrome and infection (pneumonia)

Key points

- Long-term oxygen therapy (LTOT) is the treatment of choice for chronic hypoxaemia (or type I respiratory failure).
- Mechanical ventilation is the treatment of choice for chronic hypercapnia (or type II respiratory failure).
- The main objective of oxygen therapy and mechanical ventilation is to restore normal nocturnal and daytime gas exchange and normal sleep quality.
- LTOT, NIV and invasive mechanical ventilation can be performed at home after appropriate training of the patient and family, and under adequate medical supervision.

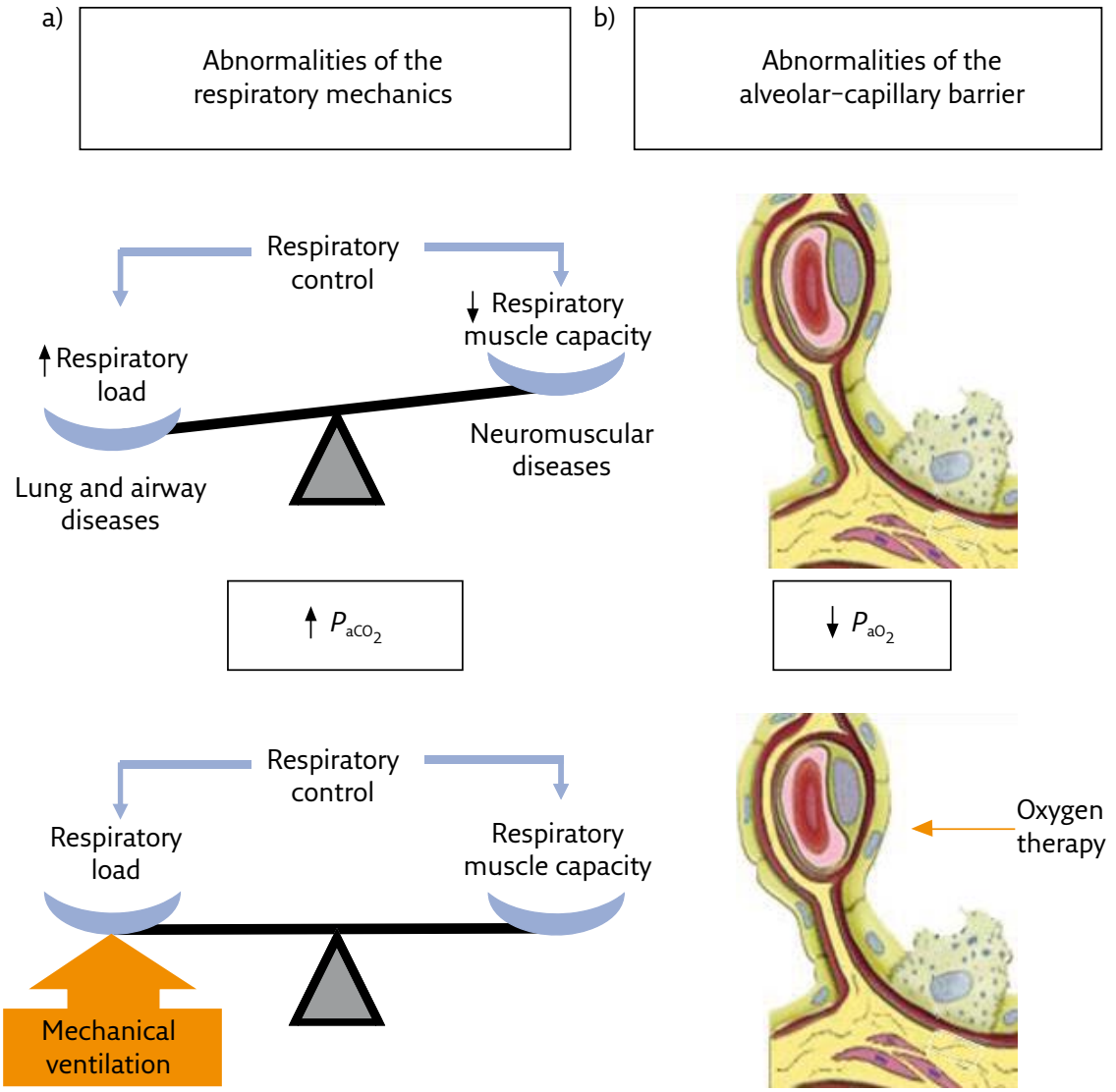

Figure 1. Schematic representation of the two types of respiratory failure. a) Type II: hypercapnic respiratory failure due to abnormalities of the respiratory mechanics. b) Type I: hypoxaemic respiratory failure due to abnormalities of the alveolar–capillary barrier.

Besides the treatment of the specific cause of lung disease, the treatment of hypoxaemic respiratory failure is oxygen therapy. An increase of oxygen content in the alveolar space increases the gradient between the alveoli and the capillary space and consequently elevates the oxygen content in the blood (figure 1).

Hypercapnic (type II) respiratory failure

Diseases that lead to a failure of the respiratory pump cause hypercapnia with normal or low oxygen levels. This type of hypercapnic respiratory failure is also called type II respiratory failure. In healthy subjects, the respiratory load (the effort needed for the subject to generate a breath) is low, the capacity of the respiratory muscles is normal, and the central drive appropriately commands the respiratory muscles. The contraction of the inspiratory muscles creates a negative intrathoracic pressure, which causes a volume of air (tidal volume (V_T)) to enter into the lungs through the airways. In disorders characterised by an increase in respiratory load, or by a weakness of the respiratory muscles, the central drive increases its demands of the respiratory muscles. However, when this imbalance exceeds a certain threshold, hypoventilation

(defined as V_T being too low) occurs, which causes retention of carbon dioxide in the blood. The diseases that may cause hypercapnic respiratory failure are:

- Severe upper airway obstruction, airway malacia, BPD or bronchiolitis obliterans, which may cause an excessive respiratory load
- Neuromuscular diseases that involve the motor neurons, the peripheral nerves, the neuromuscular junctions or the muscles, which may cause excessive respiratory muscle weakness
- Chest wall disorders, such as kyphoscoliosis, which may be associated with an increase in respiratory load and a dysfunction of the respiratory muscles due to a mechanical disadvantage
- Disorders of the central drive, which are rare and may be congenital, such as Ondine's curse (also called congenital central hypoventilation syndrome), or acquired due to drugs (*e.g.* opioids) or to compression or injury of the brainstem

In some disorders, concomitant involvement of several components of the respiratory system may lead to the pathogenesis of hypoventilation. For instance, upper airway obstruction and brain stem compression may both be present in diseases such as achondroplasia or mucopolysaccharidosis. As for type I respiratory failure, the first-line treatment targets the cause of the disease when possible (*e.g.* adenotonsillectomy in cases of OSA) but the main treatment of hypercapnic respiratory failure consists in mechanical ventilation, which aims to restore a normal respiratory balance (figure 1).

Combination respiratory failure

In other disorders, a combination of type I and II respiratory failure may be observed. The pathophysiology of CF may associate damage of lung tissue (causing hypoxaemia) with an increase in respiratory load (causing hypercapnia); the pathophysiology of obesity may associate an obstruction of the upper airways (causing OSA) with hypoventilation due to a restrictive component. An adequate deciphering of the pathophysiology of the disease and respiratory failure is thus mandatory for an appropriate treatment.

Oxygen therapy

The aim of long-term oxygen therapy (LTOT) is to prevent or correct the deleterious consequences of chronic hypoxaemia, such as pulmonary hypertension and heart failure. In the absence of validated markers of end-organ morbidity in children, the minimal level (and duration) of hypoxaemia that may be safely tolerated is not known. Moreover, it is probable that the consequences of chronic hypoxaemia vary according to age, with younger children being more susceptible, and according to the type of underlying disease.

In clinical practice, recommendations for LTOT target the normal S_{pO_2} values observed in healthy children. The oxygen flow should thus be adapted to reach this target, without any excessive correction in order to avoid the potential side-effects of hyperoxia. The harmful consequences of hyperoxia have been well documented in the premature child (retinopathy) but not in older children and in other diseases. In practice, a S_{pO_2} target between 94% and 96% seems safe and largely sufficient. Specific recommendations have been published for diseases such as chronic lung disease of prematurity, pulmonary hypertension, ILD and CF, taking into account the type of underlying disease, its pathophysiology, and the age of the patients.

The choice of the oxygen source depends on the oxygen flow and the daily duration of LTOT (during sleep only, or also during daily activities), the cost and local facilities. An oxygen concentrator is a cheap and safe source but is not possible for ambulation. When LTOT is required during daytime and daily activities, gaseous or liquid oxygen is preferred. The efficacy of LTOT should be checked by overnight gas recording for the S_{pO_2} but also by the carbon dioxide level, in order to detect hypercapnia, especially in patients with lung diseases. The appearance of hypercapnia during an optimal LTOT should lead to discussion of a switch to NIV.

Noninvasive ventilation

NIV comprises 1) CPAP, which is based on the delivery of a constant positive pressure in the airways, aiming to maintain airway patency throughout the entire breathing cycle, and 2) bilevel positive airway pressure (bilevel PAP), which aims to assist the breathing of the patient by delivering a supplemental higher positive pressure during each inspiration.

CPAP versus *bilevel PAP*

The choice of the type of NIV depends on the pathophysiology of the respiratory failure. CPAP is the simplest type of noninvasive respiratory support and is indicated in cases of "isolated" obstruction of the upper or lower airways. Indeed, in cases of airway obstruction, the other components of the respiratory balance (*i.e*. the respiratory muscles and the central drive) are normal and the restoration of a sufficient airway patency throughout the entire breathing cycle normalises breathing. Bilevel PAP is indicated when the two other components of the respiratory balance are impaired, *i.e*. the central drive and/or the respiratory muscles. In lung diseases associated with an increase in respiratory load (such as CF), the aim of NIV is to "unload" the respiratory muscles. As these patients have a normal central nervous system and a preserved respiratory muscle capacity, a ventilatory assistance that preserves the patient's own breathing pattern by allowing the patient to "trigger" assisted breaths, will be the most appropriate and comfortable. Conversely, in patients with weak respiratory muscles (neuromuscular disorders), the role of bilevel PAP will be to "replace" the respiratory muscles by delivering a positive pressure during inspiration. For these patients, the triggering of the ventilator may be difficult or impossible. A back-up rate (*i.e*. a minimal number of breaths delivered per minute by the ventilator) close to the normal respiratory rate during sleep for the patient's age is thus recommended. CPAP is thus clearly not the treatment of sleep disordered breathing in patients with neuromuscular disease. Finally, in the case of an abnormal central drive, the ventilator should be able to "take over" the command of the respiratory muscles with an appropriate back-up rate.

NIV equipment choice

NIV equipment comprises the device, a circuit and an interface. CPAP devices are the simplest devices; they have no or few alarms and no battery. All are able to deliver a constant CPAP. Some devices are able to deliver autotitrated CPAP, which is a mode during which the positive airway pressure is automatically adjusted between a minimum and a maximum airway pressure set by the prescriber, according to an analysis of the flow curve and airway resistance by the device software. More "complex" modes are also available, for example including a moderate decrease in airway pressure at the onset of expiration, or a variable increase in the airway pressure during inspiration. As all CPAP devices have been designed for adult

patients, manufacturers recommend a minimum patient weight, usually between 10 and 30 kg, for the use of these "complex" CPAP modes. The few studies that have compared "complex" CPAP modes with constant CPAP have not been able to demonstrate a superiority of these modes with regard to comfort or efficacy. Most bilevel PAP devices deliver a pressure-targeted ventilation, with the possibility of an inspiratory and expiratory trigger and a back-up rate. More recently, innovative modes, also called "hybrid modes", use "intelligent" algorithms to automatically adjust one or more settings to achieve predefined targets. These hybrid modes, also called volume-targeted pressure-controlled ventilation or average volume-assured pressure support, combine the characteristics of volume-targeted and pressure-targeted ventilation with the aim of overcoming the previous limitations. These modes provide a predetermined target volume while maintaining the physiological benefits of the pressure-targeted mode. The ventilator measures or estimates each consecutive expired volume and automatically adjusts inspiratory pressure within a predetermined range to ensure a stable target volume. These hybrid modes are increasingly used, despite the lack of validated studies in children.

Interfaces may cover the nose (nasal mask), the nose and mouth (nasobuccal mask), the face (total face mask) and, exceptionally, the mouth only (mouthpiece). Nasal pillows (or prongs or cannulas) are minimal-contact interfaces that are available for school-aged children and are very well tolerated. The choice of the interface is determined by the patient's age, weight, facial and skull anatomy (for the fitting of the headgear), nasal permeability and the eventual presence of mouth breathing, ventilatory mode (requiring a vented or non-vented interface), comfort and tolerance with the interface, and the patient's ability to remove the interface by themselves.

Challenges with NIV

NIV is a technically challenging treatment but the aim is for it to be performed at home. NIV is usually initiated in the hospital during a short hospital stay, in order to progressively acclimatise the patient to their treatment. As the treatment will be administered during sleep, an overnight monitoring of sleep with the optimal setting(s), at least with an assessment of overnight gas exchange, and ideally with polygraphy or PSG, is recommended before discharge. However, NIV may be also implemented in an outpatient or homecare setting, according to local resources, family capacity, patient stability and other socioeconomic factors. A sleep study with NIV is recommended but can be postponed until the patient is well adapted to the treatment and is able to sleep at least 6 h with the device. Training of the caregivers and of the patient is essential. The caregivers must not only be familiar with the putting on and taking off of the NIV interface and device, but also have training on the different problems that may occur at home. Careful checking of the caregiver competencies is mandatory. The availability of a trained homecare provider who is able to visit the patient at home on a regular and an as-needed basis is an important requisite of success of NIV. However, the large variability in availability and quality of homecare nursing to buttress parental care remains a limitation of home NIV in children.

Compliance with NIV is a major issue, as treatment efficiency is related to the length of nocturnal use. Most studies have reported relatively low compliance rates, with mean night use of between 3 and 5 h, but objective compliance levels close to the recommended sleep duration in children can be achieved by expert centres with a specific NIV therapeutic education programme.

There are no validated guidelines on the monitoring or long-term follow-up of children with NIV. The timing of the follow-up visits depends on the age and the medical condition of the child. Our practice consists of a sleep study 1 month after the initiation, and then every 2–6 months, with at least two check-ups per year including one full sleep study with NIV, but practice at other institutions and in other countries may vary, with no evidence for a superiority of one practice over another. Overnight S_{pO_2} with P_{tcCO_2} recording during NIV is recommended at each visit, as numerous asymptomatic patients remain hypercapnic during sleep with NIV, despite a normal overnight S_{pO_2} and normal daytime blood gases. This residual nocturnal hypercapnia can be easily corrected by simple measures such as changing the interface or the ventilator settings. Check-ups can also be performed at home after adequate training of staff. The simultaneous analysis of the in-built software of the ventilator and the overnight gas exchange gives useful information on important issues such as objective compliance, unintentional leaks, respiratory rate, airway pressure and respiratory events. However, as the majority of the devices are designed for adults, this information is not always reliable for children. Systematic polygraphic studies are recommended during NIV because residual respiratory events, such as patient–ventilator asynchronies, unintentional leaks, persistent obstructive events with or without reduction in central drive, and persistent central or mixed events, are common in stable asymptomatic children and may be accompanied by desaturations or arousals. Residual respiratory events are less common in stable asymptomatic children treated with CPAP.

Weaning from NIV

As opposed to the majority of adult patients, a significant number of children may be weaned from their ventilator support over time, either because of spontaneous improvement (in Pierre Robin sequence or BPD) or after upper airway, maxillofacial or neurosurgery (for tracheal or laryngeal stenosis, Treacher Collins syndrome or craniofaciostenosis). It is thus important to regularly evaluate the necessity to continue NIV by a sleep study during spontaneous breathing.

Invasive ventilation

A tracheostomy represents the treatment of last resort for severe airway obstruction that is not successfully relieved by CPAP or for children requiring permanent CPAP, which is difficult and associated with a limitation of social life. In cases of isolated upper airway obstruction without nocturnal hypoventilation, the patient will not need a simultaneous ventilatory assistance on their tracheostomy tube. A tracheostomy may also be proposed in children with persistent hypoventilation despite NIV, or when constant NIV is not possible or necessary, as in children with advanced neuromuscular disease or in very young infants. In cases of neuromuscular or lung disease, the patient will need a ventilatory assistance on the tracheostomy tube. In any case, a tracheostomy has to be prepared for and discussed thoroughly with the child and the parents. For further details, see chapter “Tracheostomy”.

Summary

In conclusion, LTOT, NIV and invasive mechanical ventilation can be performed at home after appropriate training of the patient and their family, and under adequate medical supervision.

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Tracheostomy

Colin Wallis and Joanne Cooke

A tracheostomy is an artificial opening in the trachea, usually between the second and fourth tracheal rings, into which a tube is inserted to facilitate breathing. The formation of a tracheostomy can be a lifesaving procedure but can also be life threatening if it is not cared for appropriately and kept clear from secretions and blockages 24 h a day.

Indications

In paediatrics, there is a wide range of indications for the insertion of a tracheostomy. The need for an artificial airway is broadly divided into four categories:

- Obstruction above the tracheostomy site
- Pathology below the tracheostomy site that can either be splinted by a tracheostomy tube or ameliorated by the introduction of positive pressure
- Acute and chronic lung conditions that will require prolonged ventilation
- A portal for long-term ventilator support in nonpulmonary conditions involving musculoskeletal abnormalities or loss of central respiratory drive

Some clinical examples are provided in table 1.

Types of tracheostomy tube

Paediatric tracheostomy tubes come in a range of neonatal and paediatric sizes. All have similar basic components:

- A means of securing the tube in place and accommodating the child's neck shape
- A universal 15 mm termination for connecting one-way valves and a heat and moisture exchanger (HME) or ventilator/resuscitation equipment
- The option of an extension to prevent occlusion from the patient's chin and allow some freedom to the tubing in long-term ventilation

Key points

- A tracheostomy can be lifesaving but also life threatening.
- A wide range of tubes is available to suit the needs of individual children.
- Consistent high-quality tracheostomy care must be delivered by all those caring for tracheostomy patients in the hospital, home and community.

- A single cannula (available on most tracheostomy tubes) to allow the maximum internal diameter (tubes are available with both an inner and outer cannula for teenagers); the cannula may be fenestrated
- A rigid introducer and round-ended tips for smoother insertion

There are also a number of useful additional options, including cuffed and fenestrated tubes and adjustable flanges.

Cuffed tubes

Principally, cuffed tubes are used when positive-pressure ventilation is required or to minimise aspiration of oral or gastric secretions. It should be noted that the cuffs are not an absolute barrier to aspirated secretions. Different types of cuff are available.

Air-filled cuffs are commonly used to support ventilation and prevent leaks. The inflation pressure can be measured with a manometer. Air leaks over time can be problematic. When inflated for long periods, the cuff may cause pressure necrosis of the tracheal mucosa. Cuffed tubes should be deflated at regular intervals.

The Bivona fome cuff is a self-inflating, foam, rubber-filled cuff that conforms to the dimensions of the trachea (figure 1a). It can be inflated permanently, and is useful in those children with chronic severe aspiration, when long-term protection of the airway is required. It adjusts to changes in pressure during the ventilation cycle while maintaining a low cuff-to-wall sealing pressure. A syringe and three-way tap should be available in the event of any tube change. It is essential to appreciate that, owing to the self-expanding nature of the foam, the cuff may be deflated somewhat using a syringe but will not fully collapse. This means that removal and/or reinsertion of this tube, particularly in a small child or in the context of a new stoma, may be difficult.

The Bivona TTS (tight-to-shaft) cuff is a high-pressure, low-volume cuff (figure 1b). The cuff is filled with sterile water. Care must be taken not to overfill the cuff as high pressure is exerted on the tracheal wall; the amount of water should be just enough to support artificial ventilation. The cuff may be inflated during meals and at night to protect the airway when aspiration is most likely, or during periods of ventilatory support (*e.g.* overnight). At other times, the cuff can be deflated completely to assume the profile of an uncuffed tube. This is useful at the time of insertion and when weaning from artificial ventilation, minimising trauma.

Table 1. Common indications for tracheostomy in children

Bypassing upper airway obstruction
Cystic hygroma and other upper airway tumours
Haemangioma
Severe laryngomalacia or laryngeal obstruction
Papillomatosis
Subglottic stenosis
Craniofacial abnormalities
Splinting lower airway pathology
Tracheomalacia
Direct trauma (*e.g.* burns, accidental alkali ingestion)
Portal for long-term respiratory support
Chronic lung disease
Neuromuscular conditions with weakness of respiratory muscles
Thoracic cage skeletal abnormalities
Central hypoventilation disorders

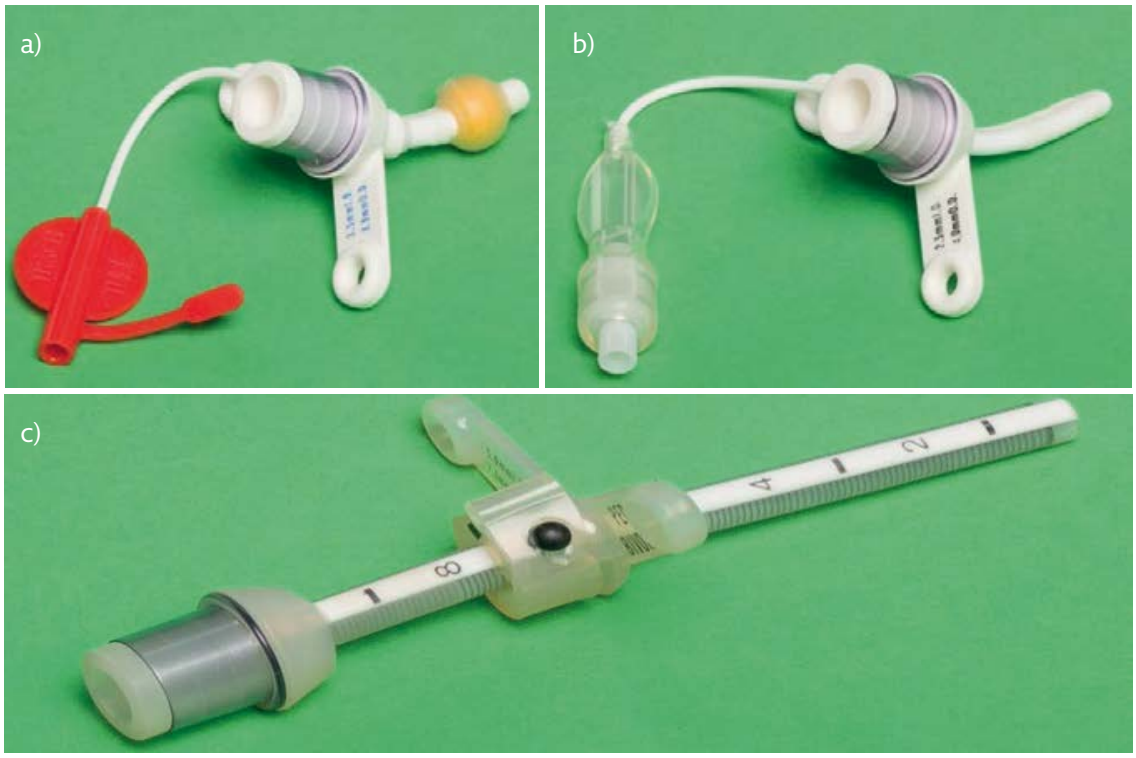

Figure 1. Examples of tracheostomy tubes. a) A Bivona fome cuff tube (low-pressure, self-inflating cuff with open red cap) requiring a syringe and three-way tap for deflation. b) A Bivona TTS (tight-to-shaft) cuff with a water-filled cuff (deflated in picture). c) A Bivona Hyperflex tube with adjustable flange.

Fenestrated tubes

These tubes have an opening on the superior aspect, which allows air to pass up through the larynx, supporting speech and a more effective cough.

Adjustable flanges

Some tracheostomy tubes have an adjustable flange (*e.g.* FlexTend) and can be particularly useful in young children, for example in cases of a neonatal double chin or a very mobile child on long-term ventilation. Flange shapes vary: some practitioners favour straight flanges in children <1 year of age, as these tend to sit more comfortably in infants with short necks and overhanging chins. The "V" type is generally suited to older children.

Examples of commercially available tracheostomy tubes

Silicone tubes (Portex Bivona, TRACOE silcosoft)

The Bivona range is a commonly used tube favoured because of its comfort and versatility. It is made from opaque, white, siliconised polyvinyl chloride (PVC). It is latex free and hydrophobic, and hinders protein adhesion, thereby limiting secretion build-up and bacterial colonisation. These tubes can remain in place for up to 28 days and can be reused and sterilised up to five times. The silicone is reinforced with wire, producing a tube that is flexible and conforms to the shape of the trachea but resists kinking. There are two versions: paediatric (standard length) and neonatal (shorter length), with a range of inner diameters (2.5–5.5 mm and 2.5–4.0 mm, respectively).

Some Bivona tubes are not MRI compatible because of the wire coil in the shaft of the tube. New versions have the triangular MR-conditional symbol noted on the flange.

The tubes come in a variety of styles. Bivona FlexTend tubes have independent flexing proximal and distal shafts, which are beneficial for those requiring ventilation. For the Bivona Hyperflex version in paediatric sizes, the long shaft has an embedded stainless steel coil as an added safeguard against compression, and an adjustable flange (figure 1c). This permits alteration of the intratracheal tube length and is useful for children with unusual tracheal anatomy or pathology (such as distal tracheomalacia, granulations and abnormal tracheal length). Cuffed versions and contoured flange designs are also available.

A Portex Bivona customised tracheostomy tube service is available to address individual requirements of the patient, allowing adjustment of shaft style, curvature, length, diameter and flange position.

The TRACHOE silcosoft range for neonates and children has reinforced eyelets in the neck flange, and the cuff supply line is embedded in the material of the tube wall. The water cuff lies tight to the shaft when empty.

Shiley

This product range is manufactured from opaque, thermosensitive, latex-free PVC, with a thin-walled shaft, tapered tip and universal 15 mm connector. The tubes are available in neonatal, standard paediatric and long paediatric varieties, and in a longer paediatric tube (size 5.0–6.5) for those who require a tube midway between typical paediatric and adult lengths. Weekly tube changes are recommended for the PVC tubes.

Air-filled, cylindrical, low-pressure cuffed tubes are available. All Shiley tubes feature a recessed area behind the connector for increased comfort, and the neonatal tubes also have a lower flange for improved fit. Customisation services are also available and are single use only.

Smiths Portex

These tubes are made of a clear PVC material with a blue radiopaque line. Paediatric sizes have an internal diameter range of 3.0–7.0 mm. Cuffed and fenestrated (to facilitate vocalisation) versions are available. As with other PVC tubes, a weekly tube change is advocated.

Portex "555" series

The "555" tube is made from blue opaque PVC that is thermosensitive. It softens at body temperature, allowing it to conform to the shape of the child's trachea. This improves comfort and reduces the risk of mucosal damage. Like the Bivona range, the "555" has a contoured flange to secure the tube comfortably and with minimal movement. A 15 mm (universally compatible) clear plastic connector allows easy visualisation of any secretions and, like the FlexTend, makes occlusion by the chin less probable. These tubes are single use only and may require weekly changes because of the adherence of secretions.

Portex Blue Line

This range is manufactured from clear, thermosensitive PVC, allowing easy insertion and conformation to the trachea. The blue radiopaque strip running along the tube facilitates radiological assessment of its position. The product is available in a full range of paediatric and adult sizes, with or without connectors and/or fenestrations. It is designed for single use only.

Silver tubes

Silver tubes confer advantages over plastic varieties in certain circumstances. Most significantly, the tubes can be manufactured with very thin walls, permitting the use of an inner tube without compromising airflow. This can be removed and cleaned without taking out the whole tube. Silver tubes may remain *in situ* for up to 1 month. Silver tubes are rigid and do not conform to the trachea, which reduces comfort. Additionally, each tube is unique; the unit cost is high and the components are not interchangeable. Examples include the Sheffield, Negus and Chevalier Jackson tracheostomy tubes.

Montgomery Safe-T-Tube

The Montgomery Safe-T-Tube is suited to certain limited paediatric applications. It is a T-shaped silicone stent comprising a long principal lumen, with a shorter lumen projecting from its side at 75º or 90º. The limbs of the principal lumen can be trimmed: the lower limb of the stent can extend as far as necessary down the trachea towards the carina, while the upper limb can sit either below or above the glottis, depending on the clinical situation. The short limb is brought out through a tracheostomy and trimmed to a convenient length. The use and tailoring of a Safe-T-Tube is complex and typically individualised. It is generally well tolerated and can be left *in situ* for months at a time. It may have to be pulled out and replaced with a conventional tube in the unusual event of complete obstruction. The limitations of tube size (smallest outer diameter is 6 mm) and the associated significant risk of blockage forgo the use of Safe-T-Tubes in younger children.

Tracheostomy care

Consistent high-quality tracheostomy care must be delivered by all those caring for tracheostomy patients in both the hospital and the community.

Care of the new tracheostomy (<7 days)

The care of a newly formed tracheostomy differs from an established stoma. Displacement of the tracheostomy tube is a potentially fatal complication. To ensure a safe airway, the trachea is sometimes sutured to the skin at the time of surgery with tiny interrupted disposable maturation sutures. In addition, two long-looped "stay" sutures, attached to the tracheal wall, extend from inside the stoma and are taped to the chest. These assist with the opening of the stoma during the first week by raising the trachea to the surface of the skin and pulling the stoma apart so that a tube can be inserted. There is no consensus about the timing of the first tube change, but many would undertake the first tube change after 1 week, allowing the tract to form. A recent study suggested that the maturation sutures may allow an earlier first tube change (Woods *et al.*, 2019).

Stay sutures are removed after the first tube change. During this first week, children must receive continuous humidification. An HME should not be used during the first week.

Subsequent care

Following a multidisciplinary review of morbidity associated with paediatric tracheostomy by Hall *et al.* (2017), a TRACHE care bundle highlighted six main areas that should be addressed relating to tracheostomy care:

1) Pay attention to the tapes: ensure that the tension of the tapes is tight enough to support the tube; one finger should fit comfortably between the child's neck and the tapes.
2) Know the resuscitation process: if the tube is difficult to suction or is blocked, immediately change the tube and suction again.
3) Use the correct suction technique: if the suction length is too short, the patient is at risk of tube blockage, while if it is too long, it may lead to distal soft-tissue trauma and overgrowth; as a rough guide, the catheter size should be double the size of the tube (*e.g.* 8-French catheter for a 4.0 mm internal diameter tube).
4) Take care of the stoma and neck: clean daily.
5) Humidification: after the first week, warm humidification should be used as much as possible to counter thick secretions that can occlude the tracheostomy tube (*e.g*. an appropriately sized HME device); some ventilated children may require extra humidity, which can be delivered *via* a nebuliser or by a continuous warmed humidity system.
6) Have a well-equipped emergency box: this should contain a replacement tracheostomy tube (and one size smaller for the Shiley tubes), suction catheters, KY jelly, replacement tapes, round-ended scissors and gauze; this is not a box for general storage and no other items should be present.

Suctioning

A child with a tracheostomy may find it difficult to clear the airway, and suctioning is an essential aspect of their care. Suctioning should not occur distal to the tube tip. It is preferable to use suction catheters with graduations, so that practitioners can measure the exact depth to be suctioned. Catheters should only be inserted so that the distal hole sits at the end of the tube. This allows collection of secretions but no trauma to the distal tracheal mucosa. Suctioning is not a painful or distressing procedure; if the child becomes distressed during suctioning, the technique should be re-evaluated.

Humidification

The natural moistening of the air provided by the nasal passages and pharynx is bypassed by a tracheostomy. For children on a ventilator, warmed humidification is included in the circuitry. For children who are self-ventilating, the following HMEs are available:

- The Gibeck Humid-Vent Mini or "mini vent" is designed for neonates. It protrudes from the tracheostomy, preventing occlusion by the neck and provides a moisture output of >30 mg $H_2O \cdot L^{-1}$ at 20 mL tidal volume, with only 2.4 mL of added dead space. It is not possible to deliver oxygen through this device.
- The Thermovent T is suitable for spontaneously breathing tracheostomised patients >10 kg in weight. It has a low-profile design with minimal protrusion and maximum comfort. The high-performance, double-paper element makes it an efficient HME, with minimal resistance to flow.
- The TrachPhone is a lightweight HME intended for spontaneously breathing patients. It also has a valve for forced inspiration and expiration or suctioning, and a built-in oxygen port. It has a spring lid that can easily be occluded by a finger to facilitate speech. After releasing the finger, the lid falls forward automatically.

One-way valves

A one-way valve sits on the end of the tracheostomy tube. The valve opens as the patient breathes in and closes on exhalation, directing air up through the larynx. Not all children will tolerate a one-way ("speaking") valve, as a good air leak around and

above the tube is essential. The valve is not to be used while asleep or with a cuffed tracheostomy tube. Examples include the following:

- The Rüsch and Passy-Muir speaking valves. The Rüsch (and most other valves) are bias-open, closing only on expiration and open at all other times. The Passy-Muir valve is bias-closed and opens only for inspiration.
- The ProTrach DualCare valve. This combines a speaking valve with an HME. The switch between speaking mode and HME mode is achieved by twisting the lid of the speaking valve. On exhalation, the air is guided through the vocal folds and out through the mouth. When the ProTrach DualCare valve is in speaking mode, there is no HME effect.

Tracheostomy complications

Complications following formation of a tracheostomy include haemorrhage, tube blockage, accidental decannulation, infection and surgical emphysema. These are largely avoidable if the surgery is performed carefully, together with diligent and effective post-operative management during the first week and the use of maturation sutures. Common complications are listed in table 2.

Discharging a child with a tracheostomy

Prior to discharge home, the child's parents or main carers must be taught and be competent in the following:

- Tracheostomy tube changes (minimum of two)
- Tracheostomy tape changes
- Stoma care
- Suctioning
- Resuscitation skills/emergency care

In addition, the carer must do an overnight stay in the hospital with their child where they carry out all overnight care, and should feel confident about taking the child out of the hospital.

Planned decannulation

Decannulation can occur as a surgical procedure or within the ward setting over a period of 5 days.

Table 2. Common complications of paediatric tracheostomy

Early complications
Pneumothorax
Surgical emphysema
Tube displacement
Tube blockage
Bleeding
Later complications
Tube displacement
Accidental decannulation
Tube blockage
Skin breakdown
Infections (chest infections, at stoma site or tape related)
Granulation formation (at stomal site or tube tip)
Haemorrhage
Tracheal stenosis or tracheomalacia

Surgical decannulation

Surgical decannulation is carried out under a general anaesthetic and usually involves reconstruction of the upper airway or stomal area. The tracheostomy is removed at the time of surgery and the stoma closed surgically.

Ward decannulation

Ward decannulation is the most common method to remove the tracheostomy tube. Endoscopic evaluation is required before decannulation to confirm patency at all levels and to exclude (and treat) peristomal complications such as granulation or collapse. Ward decannulation usually requires a 5-day admission, but this will vary according to the age of the patient and tube type:

- The tube is downsized until a size of 3.0 mm internal diameter is reached, allowing the stoma to shrink and the patient to adjust to breathing through the nose and mouth; for small infants/children weighing <12 kg, the tube is downsized to a 2.5 mm internal diameter or the tracheostomy tube is removed. This may take an extra day or two, depending on the size of the original tube.
- On the second day, if the patient is stable during the previous 24 h, the tracheostomy tube will be covered with a red "occlusion cap". The patient should be able to cough around the tube and clear secretions on their own.
- The tracheostomy tube is removed on day 3 and the stoma firmly dressed.
- Observation of the patient is carried out for a further day and night before discharge.

The dressing will need to be replaced as necessary. If the stoma has not closed after ~6 months, it will be closed surgically.

Further reading

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Epidemiology of lower respiratory tract infections

Hepsi Xavier and Steve Turner

The child's respiratory system is constantly exposed to infective agents, and acute lower respiratory tract infections are very common in children. The global burden of acute respiratory infections in children is huge: in 2016, 18% of all deaths in children under 5 years old were due to acute lower respiratory infections. The bacteria causing many respiratory infections are usually part of the normal upper airway flora and it is not fully understood what transforms them from commensal to pathogens. This chapter will describe the epidemiology and microbiology of acute and chronic lower respiratory tract infections. For the purpose of this chapter, croup, epiglottitis and tracheitis are considered upper airway infections and are not covered here, nor are TB or infections associated with CF (see chapters "Upper respiratory tract infections" and "Mycobacterial infection and disease" and section 9 of this *Handbook* "Cystic fibrosis"). The management of lower respiratory tract infections including pharmacology is covered elsewhere (see chapters "Acute lower respiratory tract infections", "Acute viral bronchiolitis", "Pleural infection, necrotising pneumonia and lung abscess" and "Protracted bacterial bronchitis and non-CF bronchiectasis").

Acute infections

Bronchiolitis

Definition

Bronchiolitis is an acute viral lower respiratory tract infection that occurs in infancy. Bronchiolitis is a clinical diagnosis based on history and examination, which has been defined by a Delphi consensus in the UK as "a seasonal viral illness characterised by fever, nasal discharge and dry, wheezy cough. On examination there are fine inspiratory crackles and/or high-pitched expiratory wheeze."

Key points

- Acute lung infections have a very high incidence in children.
- Chronic lung infections (*i.e.* lasting >4 weeks) are also common in children.
- Sex, age, geography and vaccinations are important determinants of lung infection incidence.
- The incidence for many infections changes over time, and this reflects changes in pathogen and/or host.

Infective agents

Approximately 75% of cases are associated with respiratory syncytial virus (RSV) infection and the remainder are associated with other viruses, including rhinovirus, human bocavirus, parainfluenza virus type 3, human metapneumovirus and adenovirus. Infection with more than one virus is increasingly recognised with the advent of more sensitive PCR testing. Bronchiolitis is considered a viral infection, but some infants develop a high fever (bronchiolitis is not commonly associated with a fever >38.5ºC) and features of shock, which respond to fluids and antibiotic treatment; a "secondary" bacterial lower respiratory tract infection can be associated with bronchiolitis.

Incidence

Approximately 20% of all infants develop bronchiolitis and 3% of all infants in Europe are admitted to hospital with bronchiolitis. The median age of admitted infants is 2–3 months, the age range is not normally distributed and very young infants are more commonly admitted than older infants. Bronchiolitis is a seasonal condition, and in the northern hemisphere the majority of cases occur between October and March with a peak in December (figure 1). In many European countries, there is evidence of alternating years of higher and lower incidence. An RSV vaccine is not available at present but may be introduced in the near future, and this is likely to change the epidemiology of bronchiolitis.

Risk factors

Young age, male sex, passive exposure to tobacco smoke and reduced lung function prior to onset of symptoms are associated with increased risk for bronchiolitis. More serious features of bronchiolitis are associated with prematurity (with or without BPD), haemodynamically significant heart disease and infection with RSV (compared with other viruses).

Prognosis

Bronchiolitis is a self-limiting condition that typically lasts for 2 weeks. Approximately 20% of infants with bronchiolitis have respiratory symptoms for >1 month during

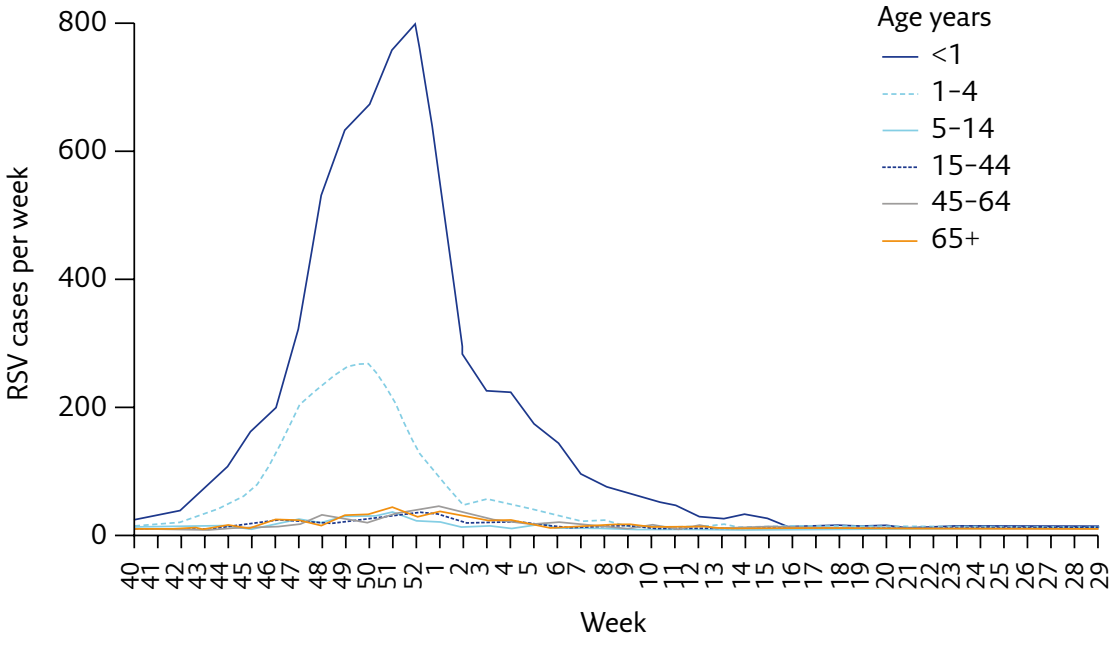

Figure 1. Laboratory reports of RSV cases by week of specimen and age in 2009–2010. Reproduced and modified from Salisbury et al. *(2013) with permission.*

convalescence. An association with increased risk for later asthma symptoms has been described, but this relationship is not straightforward. The association is seen more clearly in those who were hospitalised for bronchiolitis rather than those who were cared for in the community. The association usually becomes weaker as the children become older. One explanation for these observations is that a common airway abnormality or genetic predisposition may lead an individual to develop bronchiolitis in infancy and asthma in later childhood. Observations that infants with RSV bronchiolitis are less likely to develop asthma compared with those with non-RSV bronchiolitis suggest that RSV does not cause asthma.

Pneumonia

Definition

There are a number of definitions of pneumonia but no single gold standard definition. Pneumonia is a clinical diagnosis that is defined by the World Health Organization (WHO) as the presence of cough, fever and tachypnoea.

The broader term "acute lower respiratory tract infection" includes pneumonia, and for the purpose of this chapter is considered synonymous; both "pneumonia" and "lower respiratory tract infection" are clinical diagnoses.

There are a number of classifications of pneumonia, with typical community-acquired pneumonia (CAP) being by far the most common presentation. Classifications include:

- Typical/atypical: the symptoms of typical and atypical pneumonia are respiratory distress and hypoxia, but atypical pneumonia is also associated with headache, vomiting or diarrhoea. Different infective agents may be associated with typical (*e.g*. *Streptococcus pneumoniae*) and atypical (*e.g*. *Mycoplasma pneumoniae*) pneumonia so there is clinical merit in distinguishing between categories.
- CAP, hospital-acquired, tracheostomy- or ventilator-associated pneumonia: CAP is defined as the presence of signs and symptoms of pneumonia in a previously healthy child due to an infection which has been acquired outside hospital; hospital-acquired pneumonia is defined (in adults) as pneumonia that is acquired after ≥48 h of admission to hospital and is not incubating at the time of admission; tracheostomy- and ventilator-associated pneumonia are self-descriptive.
- Radiological: chest radiographs (taken for patients at high risk for severe illness or not recovering as expected) show patchy pneumonic changes in ~60% of cases, with lobar consolidation in ~20% and perihilar changes in a further 20%. Typical or atypical pneumonia is a clinical diagnosis and does not require imaging.

Infective agents

The challenge in obtaining a sample of lower airway secretions in a small and often unwell child means that until recently an infective agent was not identified in most cases of pneumonia. The recent introduction of PCR testing now means that infective viral agents can be identified in up to 85% of cases. Pneumonia can be caused by a number of bacteria and/or viruses (table 1), and approximately one-third of hospitalised children have both viral and bacterial infections identified. Viral identification is more common in younger children and is present in 80% of infants and 60% of 1–2-year-olds; typically, rhinovirus is identified, but other more "pathogenic" viruses can be present (table 1). Wheezing and conjunctivitis are more commonly associated with viral pneumonia compared with bacterial pneumonia. Typical pneumonias are usually caused by *S. pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*, while the most common agents causing atypical pneumonia in children are *Mycoplasma pneumoniae* and respiratory viruses. *Chlamydophila*

Table 1. Infective agents commonly associated with acute and chronic respiratory infection in children

	Bronchiolitis	Pneumonia	Empyema	Chronic bronchitis/ PBB
Respiratory viruses				
RSV	++++	++	–	
Parainfluenza virus	++	++	–	
Influenza virus	+	++	–	
Human metapneumovirus	++	++	–	
Rhinovirus	++	++		
Adenovirus		++		
Bacteria				
Streptococcus pneumoniae	–	+++	+++	++
Haemophilus influenzae	–	++	+	++
Streptococcus pyogenes	–	++	+	–
Moraxella catarrhalis	–	++	–	++
Mycoplasma pneumoniae	–	++	+	–
Staphylococcus aureus	–	+	+	–

More than one infective agent can be present at the same time for a single condition. PBB: protracted bacterial bronchitis; +++: very common pathogen; ++: moderately common pathogen; +: not commonly a pathogen; –: not thought to be a pathogen.

pneumoniae may also cause atypical pneumonia, and *Legionella pneumophila* can rarely be seen in immunocompetent children. Children with influenza virus infection are at increased risk for *Staphylococcus aureus* co-infection including pneumonia. Hospital-acquired and tracheostomy-/ventilator-associated pneumonias are often associated with methicillin-resistant *S. aureus* and *Pseudomonas* spp.

Traditionally, the lungs were thought to be sterile, but there is increasing recognition that there is a diverse commensal community of bacteria in healthy symptom-free children, and that the commensal bacterial species present include "pathogenic" bacteria, including *S. pneumoniae* and *H. influenzae*. Commensal bacteria are usually present at concentrations that are detectable using PCR but not by "traditional" culture techniques, and therefore a positive isolation on sputum culture is highly likely to indicate a truly "pathogenic" bacterium. In the presence of a tracheostomy, positive culture results are not necessarily indicative of infection and may indicate colonisation of the tracheostomy tube. In immunocompetent children, viruses are usually cleared within weeks, including viral DNA and RNA. The presence of RSV, human metapneumovirus, adenovirus or influenza virus is usually consistent with acute respiratory infection, but some other viruses may be present in the absence of symptoms (*e.g.* rhinovirus, coronavirus).

Incidence

Age and geography are major determinants of the annual incidence of pneumonia in children. In developed countries, there are up to 4 million cases per annum in children <5 years and 152 million cases in developing countries. Thus, in developed countries

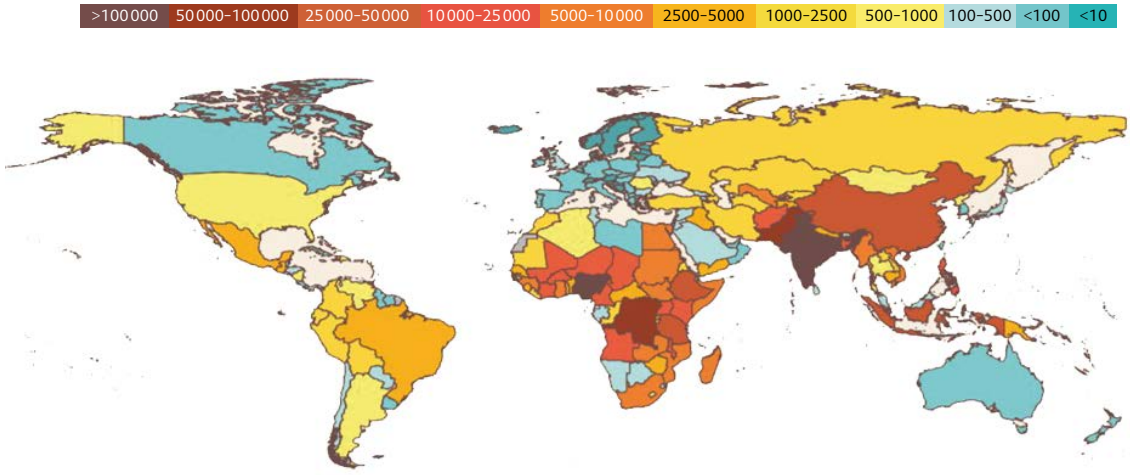

Figure 2. Pneumonia deaths for children aged <5 years at the country level in 2013. Reproduced and modified from the Institute for Health Metrics and Evaluation (2014) with permission.

the number of episodes per child-year is <0.1, while for developing countries, the WHO Child Health Epidemiology Reference Group cites a median of 0.28 episodes per child-year but with an interquartile range of 0.21–0.71. Figure 2 highlights the higher burden of pneumonia deaths in sub-Saharan Africa and the Indian subcontinent relative to Europe and North America. Pneumonia is responsible for 18% of all deaths of children aged <5 years in developing countries. Pneumonia prevalence is highest in South Asia and sub-Saharan Africa. Globally, pneumonia-specific mortality among children <5 years decreased by 55% from 13.6 per 1000 livebirths (95% CI 12.9–15.4) in 2000 to 6.6 per 1000 livebirths (95% CI 5.8–8.0) in 2015.

Risk factors

Pneumonia is a seasonal disease with peak presentations occurring at the same time as bronchiolitis, *i.e.* December and January in the northern hemisphere. Boys are at increased risk for pneumonia compared with girls, and this sex difference is not fully understood but is likely to be due to a combination of "host factors" such as a relative reduction in lung function for boys compared with age-matched girls. Abnormal lung function in early infancy and exposure to tobacco smoke are associated with a higher risk of later radiologically confirmed pneumonia. The risk for pneumonia is reduced in cases who consult with their primary care physician early in the illness and in those who have the pneumococcal vaccine. Additional risk factors for pneumonia include being immunocompromised (including HIV infection) and malnourishment.

Prognosis

Complete resolution is the usual outcome for childhood pneumonia, although a small proportion (<0.1%) of children develop bronchiectasis.

Empyema

Definition

Empyema is thought to complicate 1% of childhood bacterial pneumonias and can be defined as a parapneumonic effusion, *i.e.* a collection of fluid within the pleural cavity. There is a continuum of parapneumonic effusion from a reactive (exudative) effusion to purulent effusion (empyema) and then to organised effusion (a "skin" or "rind" restricting inflation of the underlying lung). Bilateral empyema is very uncommon. Rarely, empyema may be associated with no preceding febrile illness and a lack of elevated inflammatory markers and this should raise suspicion of underlying malignancy.

Infective agents

The same infective agents associated with bacterial pneumonia are implicated in empyema causation (table1). Bacteria are identified in pleural fluid and/or blood culture in approximately five times as many cases when PCR is used compared with standard bacterial culture, but even with PCR no infective agent is identified in ≥25% of cases. Where bacteria are identified, *S. pneumoniae* is present in 50–70% of cases, and a study from Australia reported that 97% of *S. pneumoniae* were nonvaccine-related serotypes; this demonstrates the efficacy of pneumococcal vaccination but also the ability for "new" serotypes to fill the void left by vaccination.

Incidence

The incidence of empyema is currently approximately three cases per 100 000 children. Figure 3 demonstrates how the incidence increased in Scotland, UK, during the early 2000s and then fell after the introduction of the 13-valent pneumococcal vaccination. The incidence of empyema continued to rise after the introduction of the seven-valent pneumococcal vaccine (PCV-7) and this is thought to have been due to "serotype replacement", *i.e.* the pneumococcal serotypes associated with empyema were not included in PCV-7 and replaced the serotypes that were included in PCV-7, resulting in more serious pneumonia.

Risk factors

The mean age of children presenting with empyema is 4–5 years, which is unexpected given the higher burden of pneumonia among infants compared with older children; a lower threshold for treatment with antibiotics in younger children may partly explain

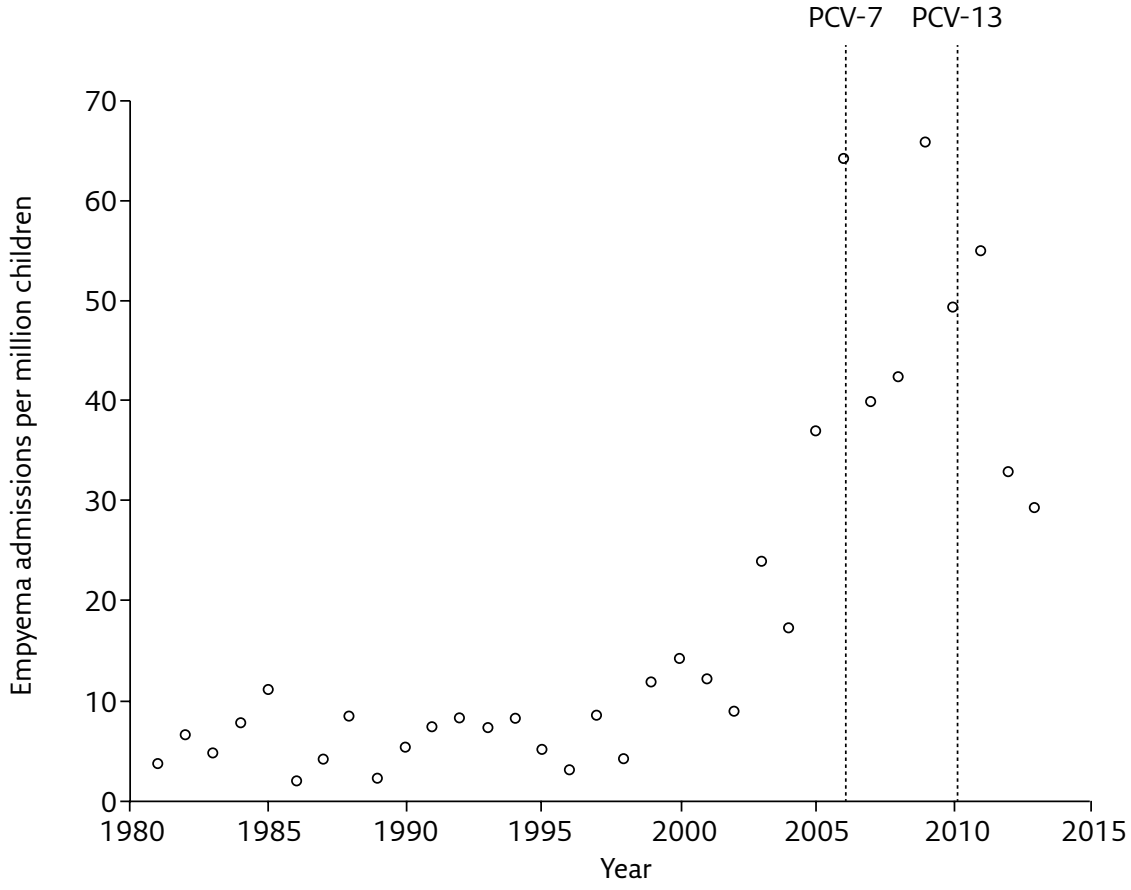

Figure 3. Empyema admissions per million children per year in Scotland, UK, between January 1981 and December 2013. PCV-7: seven-valent pneumococcal vaccine; PCV-13: 13-valent pneumococcal vaccine. Reproduced from Nath et al. *(2015) with permission.*

this apparent inconsistency. There is evidence that the prevalence in 1–4-year-olds is increasing. Boys account for 70% of cases. Prior treatment with antibiotics and pneumococcal vaccination are associated with a reduced risk for empyema.

Prognosis

Empyema is a serious and potentially life-threatening infection, but most children survive the initial illness and their long-term prognosis is usually excellent. Chest radiography changes may persist for ≥12 months and there is a theoretical but seemingly very small risk of bronchiectasis.

Chronic infections

Chronic or protracted bacterial bronchitis

Definition

Chronic bronchitis, or protracted bacterial bronchitis (PBB), is not described in many text books but has recently been the subject of a European Respiratory Society task force, which recommends that the following three criteria should be met for diagnosis: 1) the presence of continuous chronic (>4 weeks' duration) wet or productive cough, 2) the absence of symptoms or signs (*i.e.* specific cough pointers) suggestive of other causes of wet or productive cough, and 3) cough resolved following a 2–4-week course of an appropriate oral antibiotic. Chronic bronchitis is often associated with coarse, loud "rattly" respiratory sounds that can wrongly be interpreted as wheeze and the child will be incorrectly diagnosed with asthma. The differential diagnosis for PBB includes foreign body aspiration, CF, immune deficiency and pertussis.

Infective agents

H. influenzae is the most common causative organism, found in 28–58% of children. *S. pneumoniae* is the second most common cause and is present in 13–58% of children, followed by *M. catarrhalis*, which affects 17–59% of children. Respiratory viruses are likely to be important precipitants in some cases, but their role is not currently fully understood.

Incidence

Different definitions of chronic bronchitis (or cough) have been used in epidemiological studies making the incidence difficult to estimate. The incidence of chronic bronchitis is highest in children aged 1–2 years. As many as 20% of preschool children may have a cough that lasts for >1 month.

Risk factors

Assuming that other alternative diagnoses for chronic cough are excluded, the main risk factor is young age and being exposed to other preschool children. There is no evidence of an immune deficiency, but absence of evidence is not the same as evidence of absence. Some studies report a male predominance with PBB (there is no clear reason why there should be a difference in prevalence between sexes). The age range for the occurrence of PBB is usually 10 months–5 years.

Prognosis

The long-term outcome is usually very good. This condition is characterised by relapse and remission, and up to 76% of children will have further episodes, but these eventually cease. PBB is much less common in children aged >5 years and the outcome may not be as positive in this age range as for younger children. There is a possibility that recurrent infection leads to progressive airway damage (a "vicious cycle hypothesis") and in some cases to bronchiectasis. While bronchiectasis is an

important differential diagnosis for PBB, it remains to be determined whether PBB may precede bronchiectasis.

Pertussis

Definition

Pertussis (or whooping cough) is characterised by paroxysms of coughing that can last for ≥4 months. There are three stages to the infection:

- Initial catarrhal phase, lasting for 1–2 weeks and characterised by a runny nose and nonspecific cough
- Subsequent paroxysmal phase, lasting for 1 month and characterised by paroxysmal cough and often also an inspiratory whoop and vomit at the end of paroxysms
- Convalescent phase, lasting for up to 3 months and characterised by paroxysms of shorter and less frequent duration

The catarrhal and early paroxysmal phases are when the individual is highly infectious. Inspiratory whoop and post-tussive vomiting are not necessarily specific for pertussis. In one community study of children aged <3 years, these symptoms were present in 50% and 70%, respectively, of cases of pertussis and in 25% and 40%, respectively, of cases with chronic cough but not pertussis. In older children with pertussis who had been vaccinated, <15% of cases had whoop or vomiting, and generally those children who have been vaccinated and have pertussis have a less severe illness.

Infective agent

Bordetella pertussis usually causes pertussis, but *Bordetella parapertussis* and RSV can also cause a pertussis-like illness.

Incidence

As in all respiratory infections, incidence is age dependent; a survey of cases across Europe reported an overall incidence of 10 cases per 100 000 children but this was 100 cases per 100 000 among infants and one case per 100 000 among older teenagers. Over all ages, there are approximately 200 million cases of pertussis each year, and in 2014 there were 24.1 million cases of pertussis globally in children <5 years old, leading to 160 700 deaths in 2014. There are peaks (epidemics) every 4 years.

Risk factors

The major risk factor for pertussis is not being vaccinated (*i.e.* very young infants and older children who have not been vaccinated). Prior vaccination does not protect all individuals against pertussis but is associated with less severe symptoms if these develop. The vaccination has been offered to pregnant mothers between 16 and 32 weeks of pregnancy to provide the unborn infant with protection since 2010 in Belgium and since 2012 in the UK.

Prognosis

Pertussis remains a serious condition on a worldwide scale and is associated with 200 000 deaths per year, predominantly in infants. Once paroxysms fully resolve, most children make a complete recovery, although some may develop bronchiectasis.

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Impact of indoor and outdoor pollution on respiratory health

Norrice Liu and Jonathan Grigg

Each day, 93% of the world's children breathe in polluted air that is damaging to their health. Globally, the World Health Organization (WHO) estimates that 600 000 paediatric deaths annually are related to acute lower respiratory infections secondary to air pollution. In European cities, >80% of the population are exposed to pollution levels over the limits set by the WHO air quality guidelines (World Health Organization, 2013). Air pollution adversely affects every stage of the life course, impacting on the respiratory, cardiovascular (in adults), endocrine and neurological systems. Children are a vulnerable group: not only are their immune systems immature but inhaled pollutants also have the potential to suppress the normal development of organs, especially the lung. Not unsurprisingly, children with existing respiratory disease are especially vulnerable. The data underpinning our understanding of the adverse effects of air pollution come from epidemiological studies. For many of the associations, the data are robust, with effects reported across countries and using different methods of exposure assessment. Some of these adverse effects, such as increased risk of asthma exacerbations, are associated with short-term exposure, whereas other effects, such as the development of asthma, are associated with exposures over longer time periods. It is important to note that the air pollutants described in this chapter are highly correlated owing to the similarity of their sources, typically from fossil fuel combustion; it is therefore challenging to pinpoint one culprit for any particular health effect.

Key points

- Globally, air pollution is associated with high morbidity in children. It has adverse effects impacting across the life course, and children with chronic respiratory illnesses are most vulnerable.
- The air pollutant mix is changing with modern human technologies, living behaviours and modes of transport. Key components of this mix are oxides of nitrogen and particulate matter.
- There may be ways that children with chronic respiratory diseases can reduce personal exposure to air pollution, but more data are needed for these to be evidence based.

Outdoor air pollutants and their sources

Particulate matter

Particulate matter (PM) is composed of solid and liquid organic and inorganic particles suspended in air. For regulatory purposes, inhalable PM is categorised into PM_{10} and $PM_{2.5}$, *i.e.* PM <10 and <2.5 µm in aerodynamic diameter, respectively. Above this 10 µm cut-off, PM is increasingly likely to be removed in the upper airway. It is reasonable to assume that the smaller size fractions of inhalable PM are more harmful to health, as alveolar penetration is increased and the smallest PM has the potential to cross into the systemic circulation. As PM_{10} and $PM_{2.5}$ tend to be highly correlated, the assumption of differential PM toxicity has been difficult to establish in epidemiological studies.

"Primary" PM is the component that is emitted directly to the atmosphere. This component includes anthropogenic (caused or influenced by humans) sources such as traffic-related air pollution (TRAP) from gasoline- and diesel-powered engines, and includes PM from tyres and brake abrasion. Black carbon is a component of engine emissions, and this is the fraction of PM that most strongly absorbs light, commonly known as "soot". Power stations, factories, construction and agriculture as well as combustion of coal, oil, biomass and wood are other sources of anthropogenic primary PM. There are, however, nonanthropogenic sources of PM including dust, sea spray, pollen and soil particles. "Secondary" PM is formed by chemical reactions of other pollutants (*e.g.* ammonia, sulfur dioxide, nitrogen oxides) in ambient air.

Nitrogen oxides

Nitrogen monoxide (NO) and nitrogen dioxide (NO_2) are nitrogen oxides (NO_x). NO_x are formed when nitrogen reacts with oxygen during combustion, and are commonly generated during the burning of fossil fuels but also during natural occurrences such as lightning and microbial processes. NO_x are a component in the formation of secondary PM, ozone, smog and acid rain. Artificial emissions (vehicle engines, power plants, industrial and domestic combustion) are major culprits in the developed world, with road transport alone being responsible for 40% of total NO_x emission in Europe (European Environment Agency, 2013).

Volatile organic compounds

Volatile organic compounds (VOCs) are chemicals that readily evaporate. They are emitted when fossil fuels are burned; other sources include domestic and industrial work (evaporation of solvents, cleaning products and paints), cigarettes and vegetation.

Ozone

Ozone (O_3) is produced from chemical reactions between VOCs and NO_x under strong UV light. Its levels are therefore the highest on hot, sunny, windless days. O_3 is able to travel far and accumulate in the atmosphere distant from its source.

Sulfur dioxide

Sulfur dioxide (SO_2) is a colourless acidic gas formed when sulfur-containing fuels (*e.g.* coal, heavy oils) are burned. The largest contributor of SO_2 in the developed world is power generation. Other sources include commercial and residential fuel burning. SO_2 combines with water to form sulfuric acid, which is the major component of acid rain.

Carbon monoxide

Carbon monoxide (CO) is generated by incomplete combustion of carbon-containing fuels (*i.e.* with insufficient oxygen, not all carbon atoms are converted into carbon dioxide). Motor transport is the most significant source of CO, and industrial and residential fuel combustion are among other contributors.

Indoor air pollutants and their sources

Globally, indoor air pollution is associated with 3.8 million deaths a year worldwide. Indeed, WHO estimates that household air pollution doubles the risk of childhood pneumonia and, mainly in low- and middle-income countries, is accountable for 45% of worldwide childhood pneumonia deaths under the age of 5 years. Indoor air pollution can be generated both from indoor sources and from ingress of outdoor pollutants. In low- and middle-income countries, indoor pollution includes smoke from inefficient fuel combustion during cooking and heating (generating NO_2 and PM). In high-income countries, children tend to remain indoors for long periods of time. This behaviour increases the potential for relatively low concentrations of indoor air pollutants to impact on their health. A significant fraction of indoor-generated air pollution (carbonaceous PM, CO, NO_2 and VOCs) is from heating, cooking and chemical emissions from building and furnishing materials, as well as from cleaning and personal products, insecticides, dust, mould and cigarette smoke. A focus on energy conservation may result in insufficient ventilation, which in turn increases exposure to indoor-generated pollutants. Ingress of fossil-fuel-generated PM and gases into buildings is a major issue where homes and schools are situated near busy roads. Indeed, outdoor NO_2 and the air tightness of the building structure account for 84% of the variation of indoor NO_2 among classrooms in some urban areas. There is currently limited information on indoor air-quality standards; the WHO provides recommendations on household fuel combustion emission rates for $PM_{2.5}$ and CO (World Health Organization, 2014). Compliance with these emission rates will result in homes meeting the WHO air quality guideline for annual $PM_{2.5}$ and 24 h CO (table 1). The American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE) also provides standards and guidance on indoor air quality testing and improvement.

International and European outdoor air pollution limits and guidelines

The European Union (EU) sets legal standards and objectives for ambient air quality (Directive 2008/50/EC). These limits aim to avoid or reduce harmful effects on human health and the environment. The EU limits apply over different periods of time because the health impacts associated with the pollutants occur over different periods of exposure. Short averaging periods aim to protect the population from acute health effects, whereas longer averaging periods aim to protect against long-term, potentially irreversible, health effects. The WHO also provides guidelines on limits of major air pollutants, and these tend to be lower than the EU legal limits (table 1). Furthermore, national and other international guidelines may have different pollutant limits and standards because of the use of different risk assessment tools and the adoption of different acceptable risks to their target populations based on differences in social standards, background air pollution severity and the feasibility of risk adversity.

Exposure of children to outdoor (ambient) air pollution

Children living in urban areas in high-income countries are often exposed to the highest levels of air pollution during their commute to/from school, albeit for only

Table 1. EU limits, WHO guidelines and main sources of ambient (outdoor) air pollutants

Pollutant	EU legal limits $\mu g \cdot m^{-3}$ (averaging period)	WHO guidelines (averaging period)	Main sources
PM_{10}	50 $\mu g \cdot m^{-3}$ (24 h) 40 $\mu g \cdot m^{-3}$ (1 year)	50 $\mu g \cdot m^{-3}$ (24 h) 20 $\mu g \cdot m^{-3}$ (1 year)	Transport (exhaust, tyre, brake wear), combustion, industrial processes and construction
$PM_{2.5}$	25 $\mu g \cdot m^{-3}$ (1 year)	25 $\mu g \cdot m^{-3}$ (24 h) 10 $\mu g \cdot m^{-3}$ (1 year)	
NO_2	200 $\mu g \cdot m^{-3}$ (1 h) 40 $\mu g \cdot m^{-3}$ (1 year)	200 $\mu g \cdot m^{-3}$ (1 h) 40 $\mu g \cdot m^{-3}$ (1 year)	Transport, combustion
O_3	120 $\mu g \cdot m^{-3}$ (8 h)	100 $\mu g \cdot m^{-3}$ (8 h)	Reaction of hydrocarbons, NO_x and VOCs in sunlight
CO	10 $mg \cdot m^{-3}$ (8 h)	100 $mg \cdot m^{-3}$ (15 min) 35 $mg \cdot m^{-3}$ (1 h) 10 $mg \cdot m^{-3}$ (8 h) 7 $g \cdot m^{-3}$ (24 h)	Transport, combustion
SO_2	350 $\mu g \cdot m^{-3}$ (1 h) 125 $\mu g \cdot m^{-3}$ (24 h)	500 $\mu g \cdot m^{-3}$ (10 min) 20 $\mu g \cdot m^{-3}$ (24 h)	Coal combustion and road transport

Data from the European Commission air quality standards (2017), the WHO fact sheet on ambient (outdoor) air quality and health (2016), and the Institute for Public Policy Research report "Lethal and illegal: solving London's air pollution crisis" (2016).

relatively short periods each day (figure 1 and table 2). Morbidity associated with outdoor air pollution is mostly related to exposure to PM and NO_2 in epidemiological studies, although common outdoor air pollutants include PM, NO_x, O_3, SO_2, CO and hydrocarbons. The major sources of outdoor air pollution are fossil-fuel-powered engines (PM, NO_x) in motor vehicles, trains and ships, power plants, coal combustion and biomass burning (PM, NO_x, SO_2).

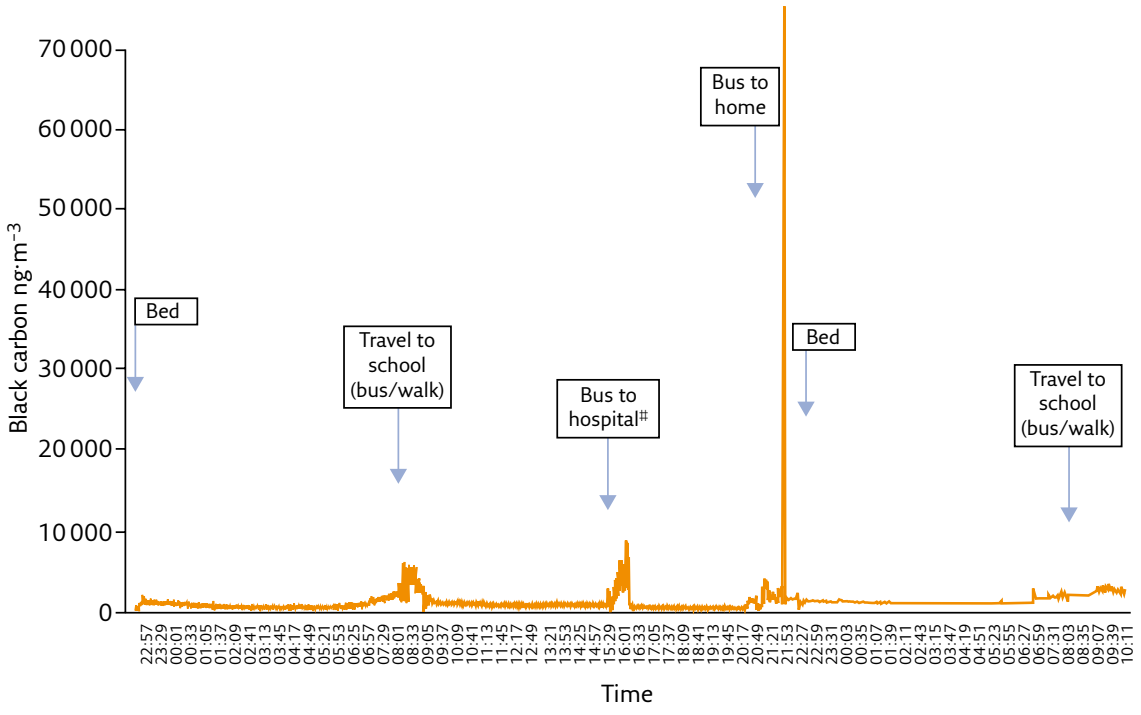

Figure 1. Black carbon readings from an aethalometer carried by a child in London, UK, on a typical school day. #: daily journey to hospital to visit sibling with chronic illness.

Table 2. Average time spent in different micro-environments, and average black carbon exposure in each environment, from six children in London

	Home	Commute	School	Outdoor	Indoor
Average time spent in each micro-environment %	57.53	6.79	32.26	1.27	2.14
Average total black carbon exposure in each micro-environment %	37.56	15.06	43.85	1.39	2.14

Data from the UNICEF report "The toxic school run" (2018).

Immune response to air pollutants

As described earlier, there is strong epidemiological evidence linking air pollution to adverse health effects. Apart from effects on the respiratory system (the first line of defence against inhaled pollutants), robust effects on the cardiovascular system are reported in adults, with emerging evidence for effects on the neurological and endocrine systems in both children and adults. A biologically plausible mechanism for adverse effects on both the respiratory system and remote organs is that phagocytosis of inhaled PM by alveolar macrophages (figure 2) stimulates the release of pro-inflammatory cytokines such as interleukin-6, interleukin-8 and tumour necrosis factor, which directly affect other lung cells and, by crossing into the systemic circulation, affect distant organs. Another putative mechanism is oxidative stress due to PM impacting directly on nonphagocytic cells. An impaired capacity of alveolar macrophages to phagocytose PM, as observed in severe asthma, increases the risk that inhaled PM will impact on other lung cells, as well as move into the systemic circulation and lodge in distant organs.

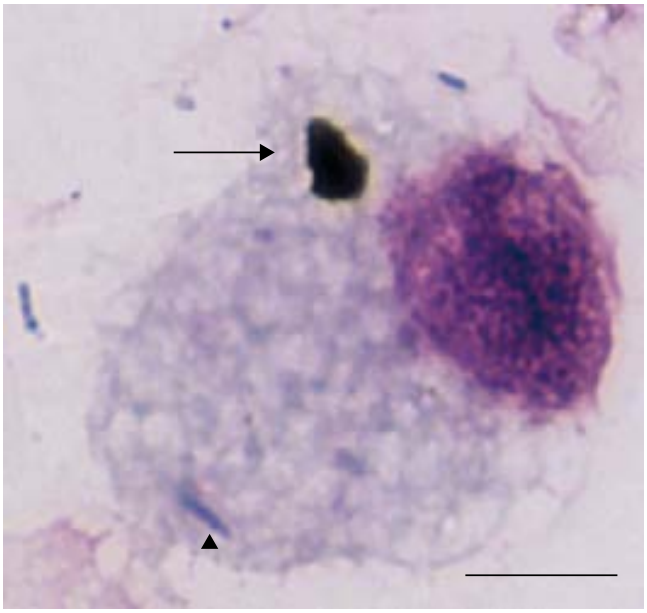

Figure 2. Phagocytosed carbonaceous PM (arrow) within an airway macrophage from a healthy child living in a UK city. The cell was obtained by sputum induction. Rod-shaped bacteria (arrowhead) are seen within the cytoplasm. Scale bar = 10 µm.

Health effects of outdoor and indoor air pollution

Particulate matter

Both short- and long-term exposure to PM are associated with respiratory morbidity and mortality. First, there is an independent association between maternal exposure to PM from TRAP and adverse fetal outcomes, such as low birthweight at term and premature birth; such associations have been reported with PM exposures below the current EU recommended limit. Second, children's lung function growth is suppressed by exposure to increased concentrations of PM. For example, in southern California, children (aged 10–18 years) living within 500 m of a motorway had significant FEV_1 growth deficits (–81 mL) compared with those living more than 1500 m from a motorway (Gauderman *et al.*, 2007). A follow-up study showed that reductions in PM_{10} and $PM_{2.5}$ led to improvements in FEV_1 and FVC growth in adolescents: the mean 4-year growth in FEV_1 increased by 65.5 mL per 8.7 $\mu g \cdot m^{-3}$ of PM_{10} reduction, and 65.5 mL per 12.6 $\mu g \cdot m^{-3}$ of $PM_{2.5}$ reduction, with comparable findings in FVC (Gauderman *et al.*, 2015). PM exposure is also associated with both new-onset preschool wheeze and school-age asthma. Indeed, a study reported that global exposure to TRAP is associated with 4 million cases of new-onset paediatric asthma per year. Increased levels of $PM_{2.5}$ are also associated with increased risk of asthma exacerbations. Interactions between PM and airborne allergens may also increase the risk of asthma exacerbations in sensitised children. The wide range of adverse health effects of PM across the life course is summarised in table 3.

Nitrogen oxides

All forms of NO_x have the potential to cause adverse health effects, with NO_2 of particular concern in urban areas. First, maternal exposure to NO_2 is associated with reduced FEV_1 later in childhood, and NO_x exposure during childhood is associated

Table 3. Adverse health effects of PM across the life course

Life stage	Health effects of PM
Fetal	Reduced fetal growth Premature birth Low birthweight at term
Infancy	Infant mortality Risk of respiratory distress and pulmonary infections
Preschool age	Suppressed lung function growth Preschool wheeze
School age	Suppressed lung function growth School-age asthma Exacerbation of asthma Cognitive deficits
Adulthood	New-onset asthma Accelerated lung function decline Exacerbation of asthma Lung cancer New-onset type 2 diabetes Accelerated cognitive decline Exacerbation of existing cardiovascular disease

Information from the report of a working party by the Royal College of Physician and Royal College of Paediatrics and Child Health, "Every breath we take: the lifelong impact of air pollution" (2016).

with reduced lung function (FVC and FEV_1). There is also evidence to support a link between long-term exposure to NO_2 and new-onset asthma, and between short-term exposure and asthma exacerbations. Second, exposure to high levels of NO_2 is also associated with airway irritation and inflammation, and increased susceptibility to respiratory infections. There is, however, an ongoing debate on how many of the adverse health effects associated with NO_2 are due to NO_2 *per se* and how many are due to exposure to other components of TRAP. Although an independent effect of NO_2 in vulnerable children (*e.g.* those with asthma) is highly likely, it should also be regarded as a marker for the toxic TRAP mix in epidemiological studies.

Volatile organic compounds

VOCs are irritants to the eyes and the respiratory tract, causing breathing difficulties. Some VOCs are associated with central nervous system damage and cancer.

Ozone

O_3 is another eye and respiratory irritant. Short-term exposure to high levels of O_3 may lead to airway inflammation. It can also reduce lung function and cause asthma exacerbations.

Sulfur dioxide

SO_2 causes bronchoconstriction; in children with asthma and chronic respiratory problems, SO_2 will therefore predispose them to exacerbations, as well as increase their susceptibility to pulmonary infections.

Carbon monoxide

CO reduces the blood capacity to carry oxygen to tissues. It is not a clinically important component of TRAP, although clearly it can cause acute poisoning when children are exposed to vehicle exhaust in confined areas.

Methods to reduce children's exposure to air pollution

With the major sources of air pollution coming from motorised engines, power plants and burning of fossil fuels, the chief responsibility to reduce ambient air pollution lies with policy makers. However, there are various measures that can be taken to reduce an individual's exposure to air pollution. For example, plants such as trees and hedges can act as a physical barrier to intercept PM and absorb gaseous pollutants, and this can be applied to schools, playgrounds and parks.

Table 4. Advice from the British Lung Foundation on measures to take according to different air pollution levels

Pollution level	Measures
Low	Avoid spending long periods of time along busy roads
Moderate	Reduce or avoid strenuous outdoor activities
High	Reduce or avoid strenuous outdoor activities Avoid pollution hotspots Avoid rush hours; travel earlier before pollution levels build up Use less polluted routes when cycling, walking or running Use reliever inhaler if pollution is a trigger to asthma symptoms ± Seek medical attention

Indoor air purification is a modern way of tackling indoor air pollution, most of which can achieve >90% efficiency in removing air pollutants, but all systems have their limitations. Mechanical air filtration works by capturing air pollutants using a filter. The most commonly used HEPA (high-efficiency particulate air) filters are efficient in removing pollution particles but require regular replacement. Electronic air filtration is effective but can be affected by humidity in the ambient air, and may generate charged particles that are hazardous. Adsorption is a technique using adsorbents to remove gaseous pollutants; however, adsorbents have short lifespans and humidity can affect their performance. UV radiation can destroy indoor airborne pollutants but with subsequent generation of O_3 and radicals.

At an individual level, walking along quieter roads, cycling or scooting, using public transport and carpooling are simple ways to reduce exposure to air pollution. However, these require long-term compliance in order to achieve adequate exposure reduction with positive health impacts. National and international resources on various measures on high pollution days are available (table 4).

Further reading

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Prevention and cessation of smoking

Giuliana Ferrante, Giovanna Cilluffo and Stefania La Grutta

Active and passive smoking in childhood: overview of the current evidence

Tobacco smoke is the main source of preventable morbidity and mortality, causing almost 6 million deaths each year, of which 166 000 are in children. Children and adolescents are particularly susceptible to developing smoke-related adverse health effects, such as sudden infant death syndrome, asthma and allergies, and infections such as pneumonia, ear infections and meningitis. Exposure to second-hand smoke (SHS) in childhood also causes cardiovascular and neurocognitive problems, as well as nicotine addiction symptoms, which can develop even in those who have never smoked. Moreover, it has been demonstrated that exposure to passive smoking during pregnancy is a risk factor for stillbirth, preterm birth, low birth weight, congenital malformations and onset of respiratory disorders in the first years of life. In children with chronic respiratory diseases, exposure to passive smoke often results in poor lung function, increased exacerbations, emergency department visits and hospitalisations. The World Health Organization (WHO) estimates that ~40% of children worldwide are exposed to passive smoke, especially between 3 and 11 years of age. In particular, children growing up in low-income families have a higher risk of being exposed than those living in higher socioeconomic conditions. These disparities are probably due to the lack of awareness of the damage caused by passive smoking, as well as to the inadequate application of the current anti-smoking legislation.

Key points

- Tobacco smoke is the main source of preventable morbidity and mortality, and children are particularly susceptible to developing smoke-related adverse health effects.
- Interventions for prevention and cessation of smoking can be performed at both population and individual levels.
- Preventing exposure to second-hand smoke should begin before childbirth and continue throughout childhood, as no level of exposure to tobacco smoke is risk free.
- Paediatric practitioners must take an active role in smoking prevention and cessation.

Besides the well-known route of exposure represented by SHS, a mixture consisting of the smoke emitted from a burning cigarette (side-stream smoke) and the smoke exhaled from the smoker (main-stream smoke), a new way of exposure was recently identified, called "third-hand smoke" (THS). THS is a mixture of pollutants that, once the cigarette has been consumed, are deposited on surfaces and in dust or react with other compounds to form secondary pollutants, which may have harmful effects for the health of exposed subjects. SHS exposure results from the involuntary inhalation of side-stream and main-stream smoke, while THS exposure is derived from the involuntary inhalation, ingestion or dermal uptake of pollutants present in air, in dust and on surfaces. Whereas SHS is removed through ventilation, THS pollutants may persist in indoor environments for as long as several days or months after tobacco products have been smoked. Moreover, domestic smoking may affect children's respiratory health through prolonged exposure to higher levels of particulate matter and toxic chemical agents produced by pyro-synthesis or during cigarette combustion and released in indoor environments.

Children of smoking parents are at increased risk of becoming smokers in later life, and earlier parental quitting is associated with a lower risk of smoking in adolescence. Adolescents are uniquely vulnerable to smoking initiation, as the first use of tobacco typically occurs in this age group. In this context, the increasing use of electronic cigarettes (e-cigarettes) or other tobacco-based products, which are supposed to be less harmful than the traditional cigarette, may contribute to this concerning trend. Candy- or fruit-flavoured e-cigarettes are appealing for children and adolescents, inducing a large spread among youths in some parts of the world. However, it should be emphasised that the use of e-cigarettes does not prevent smoking. Indeed, e-cigarette users are more likely to initiate use of any combustible product, such as cigarettes, a hookah, cigars or pipes. Therefore, e-cigarette use may increase cigarette smoking initiation, and smoking e-cigarettes should be strongly discouraged among young people. To date, information regarding the adverse health impact of e-cigarette use is scanty. The most frequently reported acute effects include systemic and respiratory effects such as increased heart rate, platelet dysfunction, throat irritation, cough/phlegm, bronchitis, airway obstruction and asthma exacerbations. E-cigarette exposure has also been shown to cause alterations in gene expression *in vitro*.

Interventions for the prevention and cessation of smoking

Interventions for the prevention and cessation of smoking can be performed at both population and individual levels (table 1).

WHO recommends the implementation of smoke-free legislation that prohibits smoking in public indoor spaces, including workplaces and places of social gathering. In recent decades, efforts to reduce passive smoke exposure have resulted in smoking ban laws for workplaces and public places across many countries. Such legislation has reduced tobacco smoke exposure and has encouraged people to quit smoking, with improved health outcomes. However, >80% of the world's population is currently unprotected by smoke-free laws, so exposure to passive smoke remains a global public health priority. It is noteworthy that children's exposure patterns differ from those of adults, as they usually spend more time in the home and in other potentially unregulated places such as cars. Recent evidence shows that children experience health benefits through reduced exposure to passive smoke during pregnancy and in the home environment. As homes are places where children can be dangerously exposed to passive smoking, public health policies should also focus on smoking cessation at home.

Table 1. Interventions for the prevention and cessation of smoking

Population level
Laws banning smoking in workplaces and public places
High cigarette prices
Enforcement of minimum age of purchase
Banning of tobacco advertising
Health warnings on cigarette packs
Social media campaigns
Free national smoking cessation services
Individual level
Face-to-face or telephone counselling
Minimal level of advice
Educational material
Mobile phone-based applications
Educational home visits
School-based policies
Prescriptions for tobacco-dependence treatment (*e.g.* nicotine replacement therapy)
Referral to available cessation services or to toll-free quitlines
Multicomponent counselling-based actions

Countries with strong tobacco control strategies, such as high cigarette prices, enforcement of minimum age of purchase and free national smoking cessation services, have achieved an impressive decline in smoking prevalence, even among adolescents and people on low incomes. Implementation of comprehensive strategies that also include actions such as the banning of tobacco advertising, the use of health warnings on cigarette packets and social media campaigns should result in improved health for the general population, as well as for people with chronic respiratory diseases. Educational campaigns supporting the creation of "smoke-free" environments for children and strategies for sustaining parents in the decision to stop smoking may contribute to this goal. Educating parents about the benefits that can derive from raising their children in a smoke-free environment and inviting them to avoid smoking inside homes and cars are actions that can help in drastically reducing exposure to SHS, particularly in a vulnerable population such as children.

Preventing exposure to SHS should begin before childbirth and continue throughout childhood. The American Academy of Pediatrics recommends that paediatricians and healthcare providers inquire about tobacco use and tobacco smoke exposure, advise about the health effects of active and passive smoking, and address the tobacco dependence of adolescents and/or parents/caregivers as part of routine care. Recently, a position statement of the Forum of International Respiratory Societies emphasised that initiation of e-cigarette use is associated with the subsequent initiation of combustible tobacco product use among adolescents. Therefore, surveillance surveys concerning combustible and e-cigarette use among youths should be carried out in different countries and regions of the world.

Convincing parents to quit smoking and at the same time helping adolescents before it is too late are therefore two preventative interventions in which the paediatrician can play a pivotal role. Indeed, the paediatrician represents a central figure for the family, especially in the first years of a child's life, and children represent the most powerful motivator for parents in choosing to stop smoking. Interventions may include face-to-face interactions, use of educational material and mobile-phone-based applications to prevent initiation of tobacco use. Paediatricians should also

support parents in quitting through counselling, recommendations and prescriptions for tobacco-dependence treatment (*e.g*. nicotine replacement therapy); they should also refer caregivers who smoke to available cessation services or to toll-free quitlines. However, paediatricians rarely devote themselves to anti-smoking screening and counselling in the context of their clinical activity, for reasons ranging from lack of time to the absence of *ad hoc* training. The simple brief advice of quitting smoking has been shown to be effective, and effectiveness consistently increases if the clinician devotes more time to this activity. Studies showing a significant effect in reducing childhood exposure to environmental tobacco smoke have covered a wide range of interventions, such as in-person or telephone counselling, family- and school-based strategies, and multicomponent counselling-based actions. Interestingly, the effectiveness of one particular intervention over others is still unclear, given the low quality of evidence. More high-quality and larger studies are needed in order to draw definitive conclusions.

Summary

Preventing exposure to smoke in childhood might significantly improve children's health worldwide. The evidence of persistent use of tobacco by parents/caregivers together with the emergent epidemic of alternative tobacco products, especially among adolescents, suggest that the fight against smoke is far from over. Therefore, paediatric practitioners must take an active role in smoking prevention and cessation. To this purpose, guidelines aimed at increasing provider compliance with smoking cessation promotion are needed. Moreover, gaining the trust of parents and children is a prerequisite for establishing a good relationship of care. Training on communication techniques is therefore essential to improve the effectiveness of the clinician's educational interventions.

The best measure to improve health globally and to protect children is to reduce tobacco use and exposure to passive smoke, as no level of exposure to tobacco smoke is risk free. The WHO Framework Convention on Tobacco Control endorses calls to action, advocating effective policies to reduce tobacco consumption through the implementation of the MPOWER technical package, which combines policy change with increased public awareness in order to set out the path to protect present and future generations from the hazardous effects of tobacco smoke.

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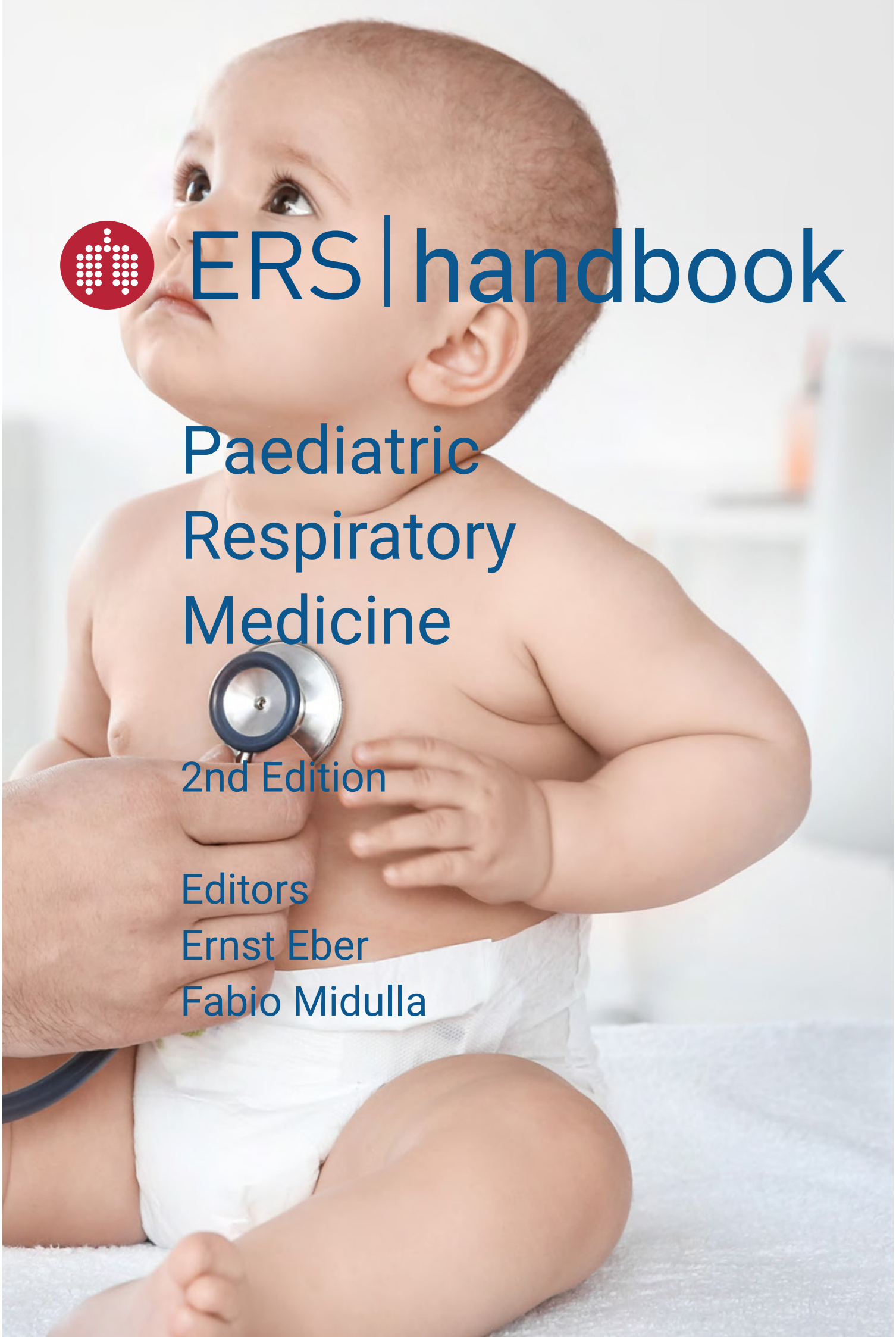

ERS | handbook

Paediatric Respiratory Medicine

2nd Edition

Editors
Ernst Eber
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The 19 sections of this second edition of the *ERS Handbook of Paediatric Respiratory Medicine* cover the whole spectrum of paediatric respiratory medicine, from anatomy and development to disease, rehabilitation and treatment. The editors have brought together leading clinicians to produce a thorough and easy-to-read reference tool. The *Handbook* is structured to accompany the paediatric HERMES syllabus, making it an essential resource for anyone interested in this field and an ideal educational training guide.

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