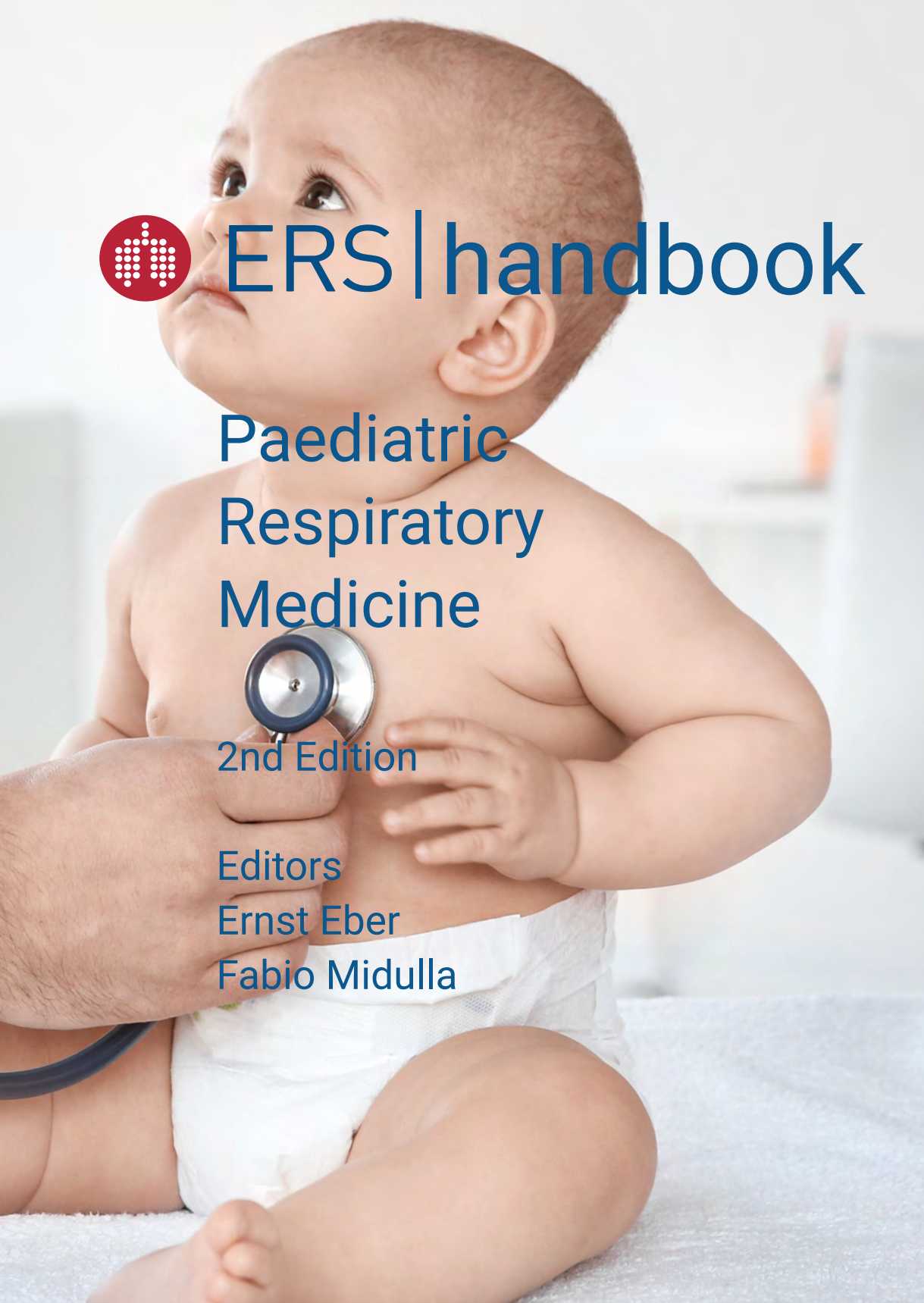

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Paediatric Respiratory Medicine

2nd Edition

Editors
Ernst Eber
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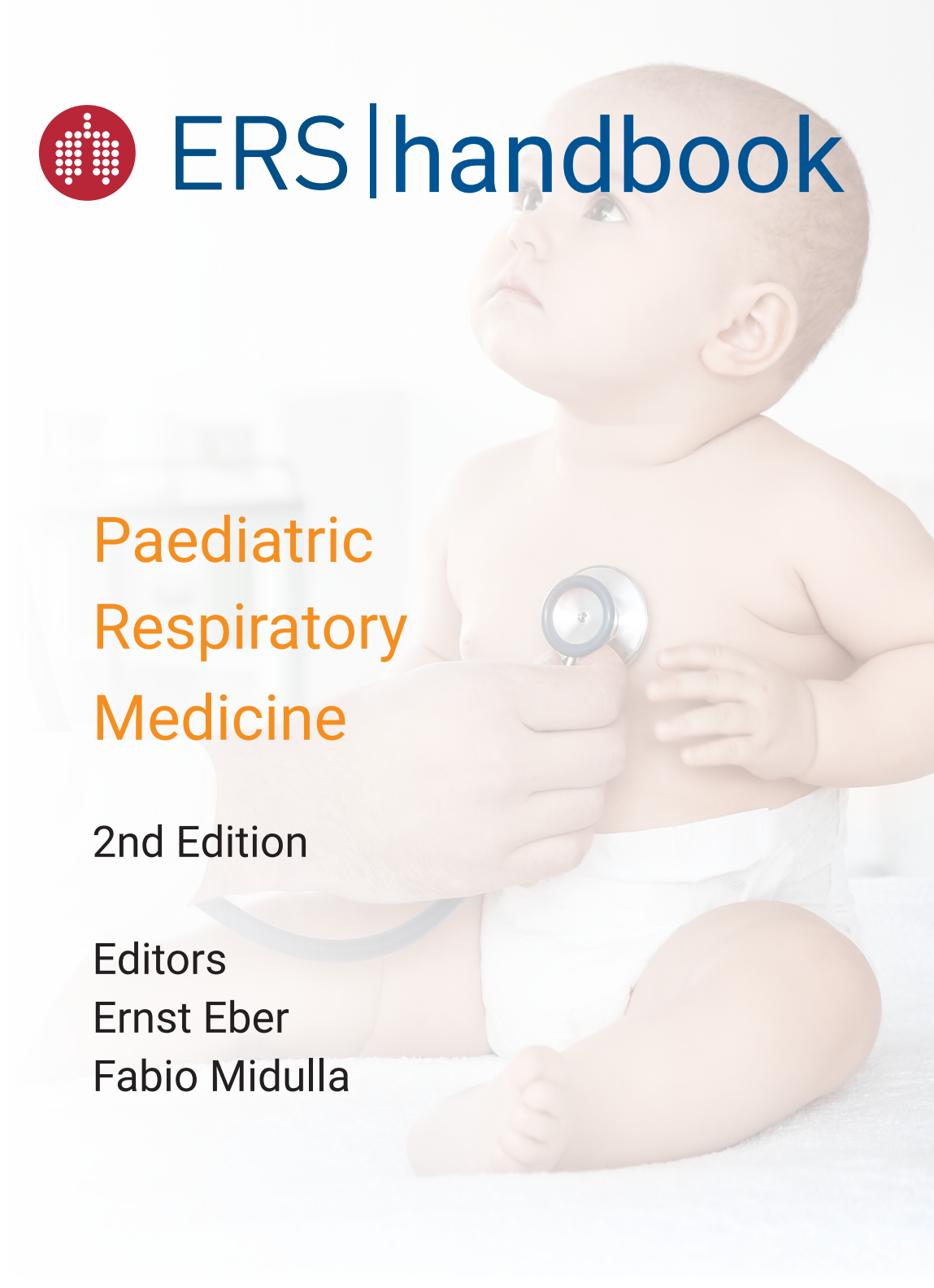

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Preface

"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

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

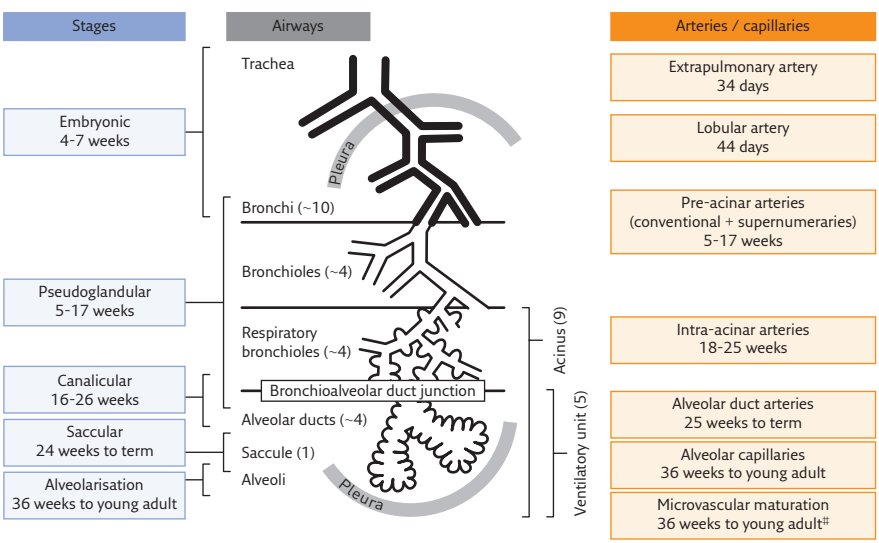

Figure 1. Layout of the bronchial tree and overview of lung development. The bronchial tree starts at the trachea, follows with the bronchi, bronchioles and alveolar ducts, and ends in the saccules. Gas exchange takes place in the alveoli, which completely cover the walls of the saccules and alveolar 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.

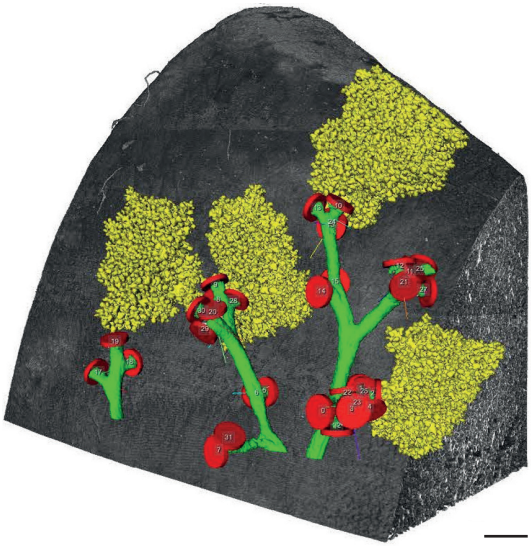

Figure 2. 3D-visualisation of rat acini/ventilatory units branching from terminal bronchioles. The conducting airways are drawn in green and the acini/ventilatory units in yellow, in a view looking from the outside onto the air–tissue surface. Hence, the ventilatory unit resembles the small tree of alveolar 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

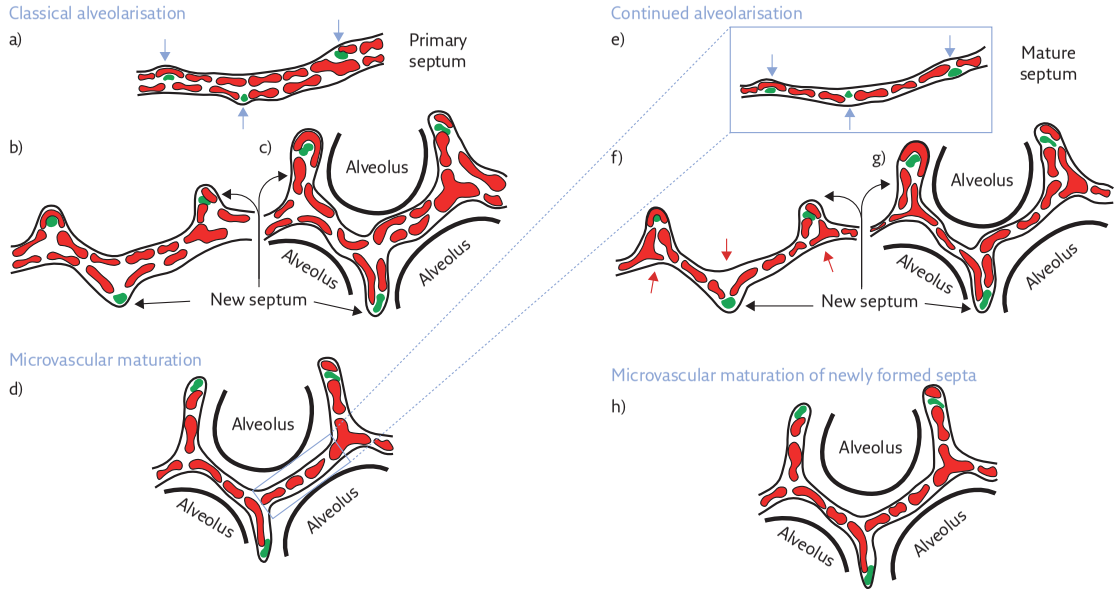

Figure 3. Classical and continued alveolarisation. The blue arrows indicate sites where new septa will be formed, where elastic fibres, collagen fibrils and PDGF-receptor-α-positive myofibroblasts (green) accumulate. Black arrows indicate folding to create new septa. a) At the beginning of classical 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.

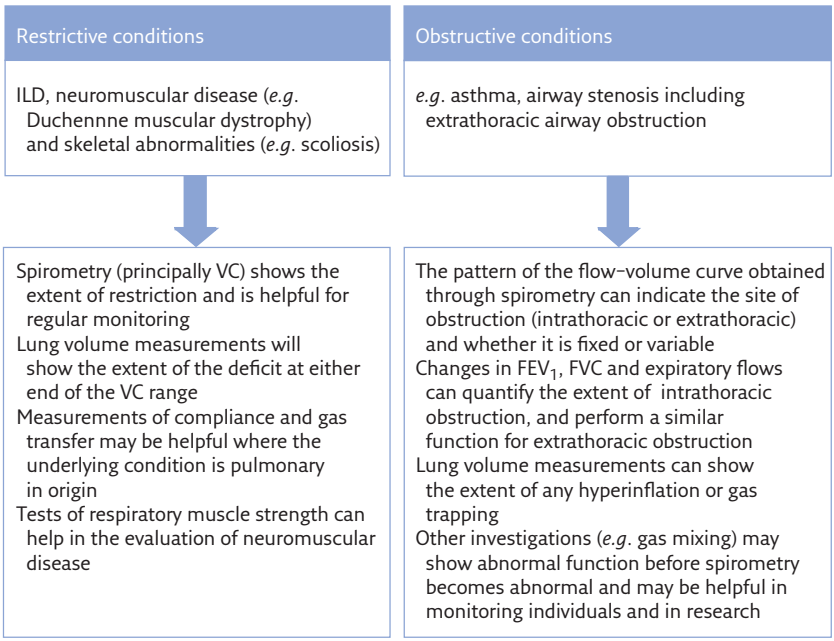

Figure 1. Consideration of abnormalities as either restrictive or obstructive in nature. These are not mutually exclusive, and individuals may show elements of both. VC: vital capacity.

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

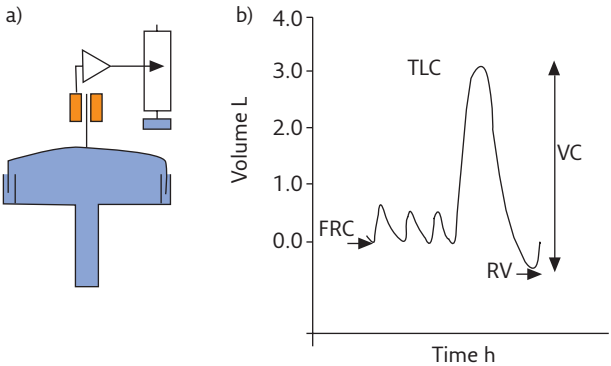

Figure 2. a) Original type of mechanical spirometer and b) associated recording of changes in volume. The recording shows three tidal breaths at FRC, followed by inspiration to TLC and expiration of VC to RV.

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

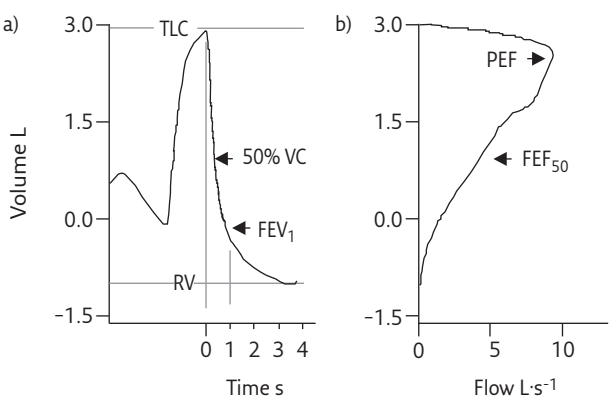

Figure 3. Relationship between a) a spirogram and b) an expiratory flow–volume curve, showing inspiration to TLC, followed by forced expiration to RV. Peak expiratory flow (PEF) occurs early in the manoeuvre, followed by a smooth decline in flow to RV. Note that FEV_1 or any other timed volume can only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

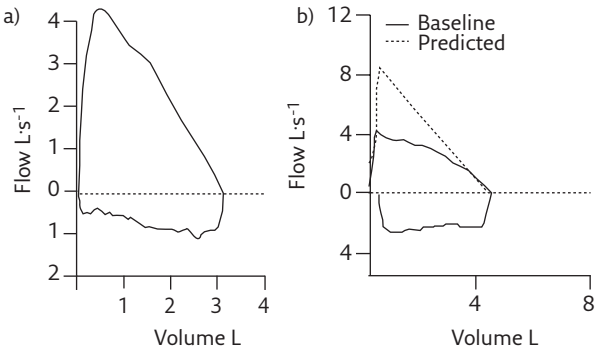

Figure 4. a) Variable upper airway obstruction (laryngeal polyp), illustrating reduced flow through inspiration but a normal pattern for the expiratory curve. b) Fixed obstruction (tracheal stenosis), with flattening of both the inspiratory and expiratory curves. On expiration, the flow is reduced primarily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

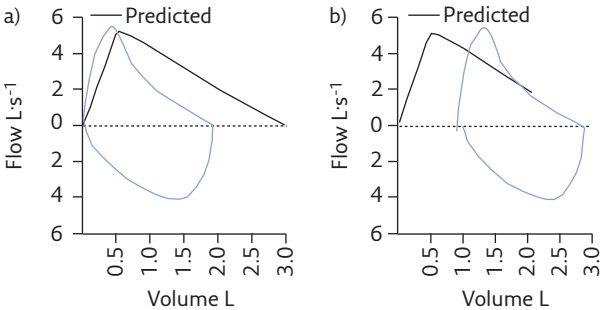

Figure 5. Flow–volume curve from a child with restrictive disorder, including a schematic of the predicted expiratory flow–volume curve with a VC of 3.0 L predicted. a) The actual flow–volume curve aligned with the schematic at TLC. The expiratory flow appears to be substantially below the predicted 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.

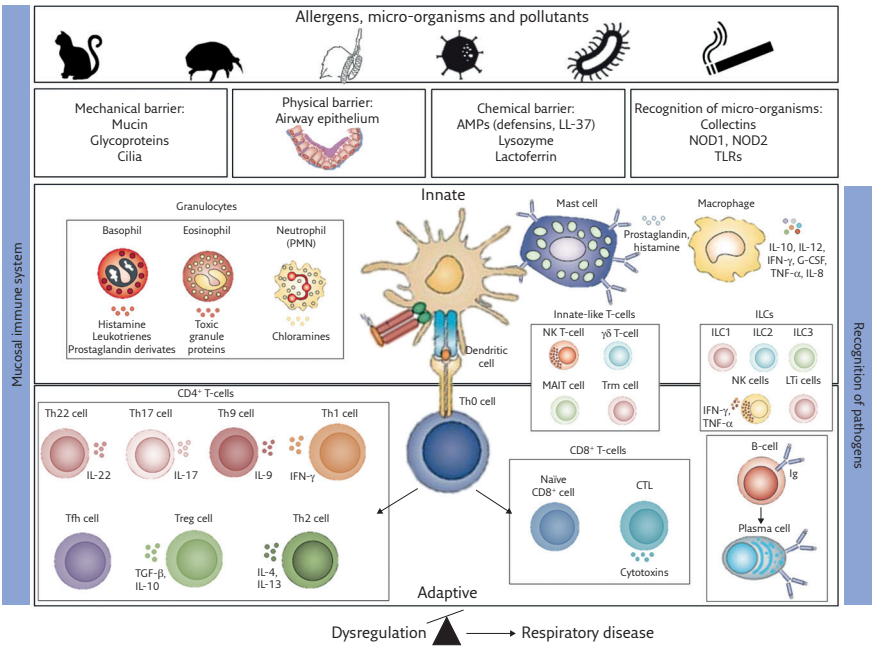

Figure 1. Overview of the initiation and interaction of the innate and adaptive immune systems. AMP: antimicrobial peptide; LL-37: cathelicidin; NOD: nucleotide-binding oligomerisation domain; TLR: Toll-like receptor; PMN: polymorphonuclear neutrophil; IL: interleukin; IFN: interferon; G-CSF: granulocyte 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

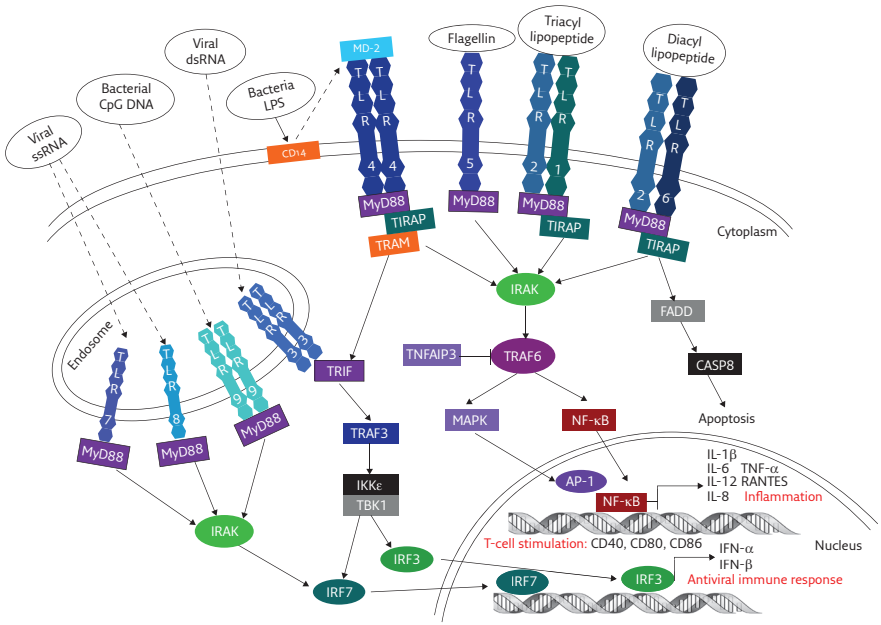

Figure 2. TLR signalling cascade. The myeloid differentiation primary response gene 88 (MyD88)-dependent pathway can be used by all TLRs except TLR3. The MyD88-independent pathway is utilised by TLR3 and TLR4. ssRNA: single-stranded RNA; dsRNA: double-stranded RNA; LPS: lipopolysaccharide; MD-2: myeloid 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 (plexímeter). 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 >180°.

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).

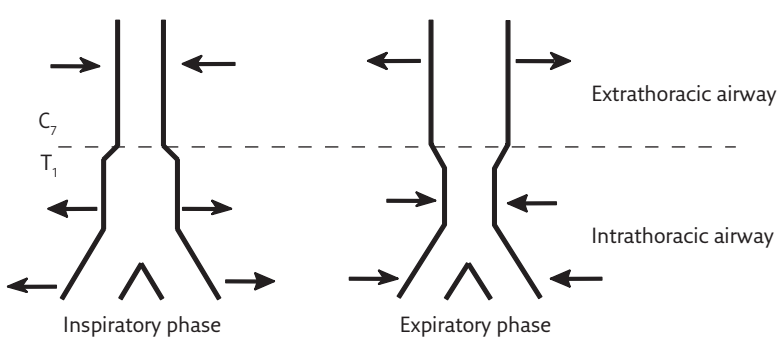

Figure 1. During inhalation, a negative intraluminal pressure (relative to that of the atmosphere) is generated in the extrathoracic airways. This results in a minimal collapse, which, in normal individuals, is not clinically relevant. Exhalation induces a positive intraluminal pressure, which tends 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

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