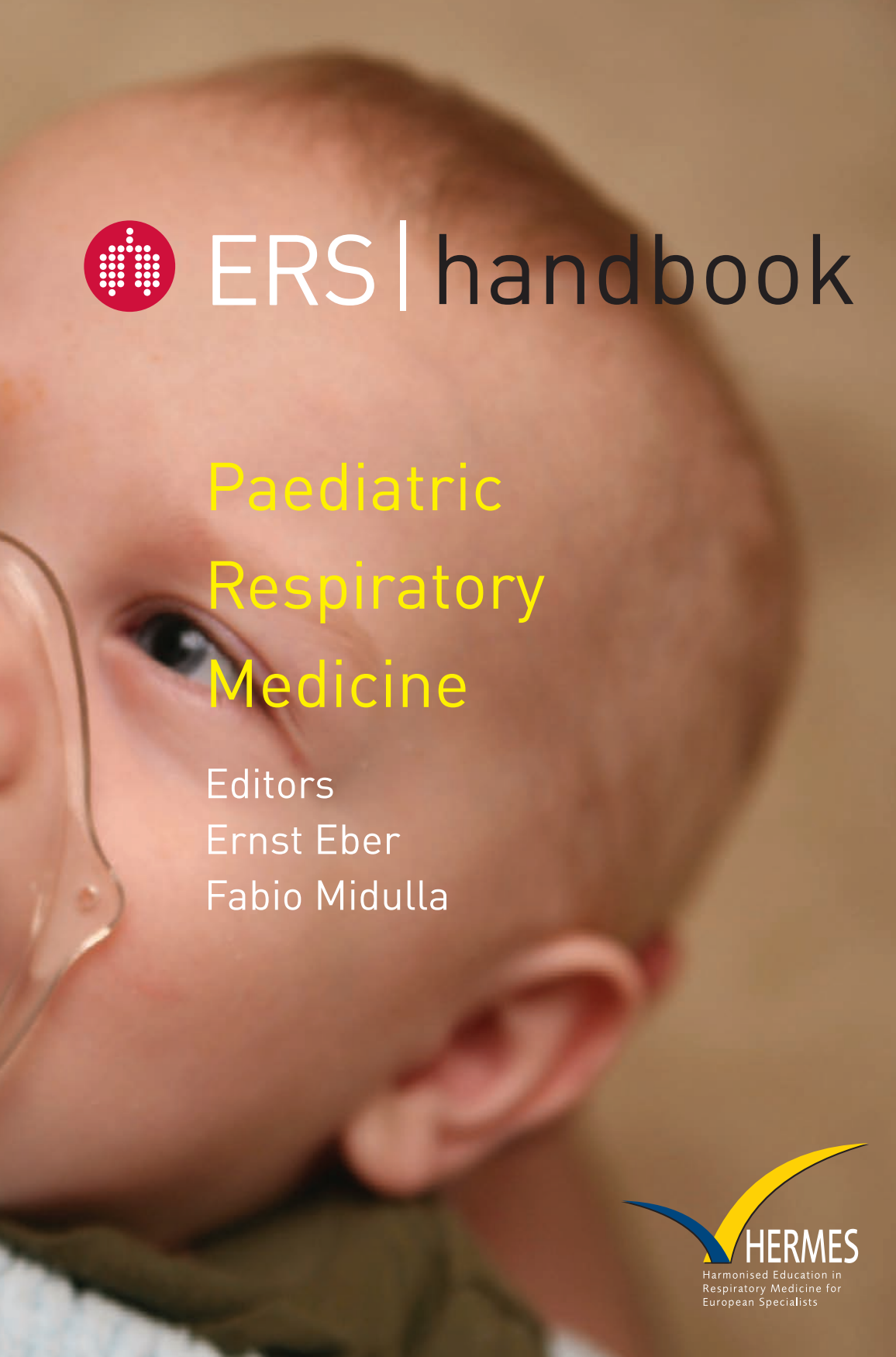

ERS | handbook

Paediatric Respiratory Medicine

Editors
Ernst Eber
Fabio Midulla

HERMES
Harmonised Education in Respiratory Medicine for European Specialists

ERS | handbook

Paediatric Respiratory Medicine

1st Edition

Editors
Ernst Eber
and Fabio Midulla

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Preface

"Tell me and I forget.
Teach me and I remember.
Involve me and I learn."
Benjamin Franklin

The dissemination of knowledge, and medical and public education constitute a fundamental objective of the ERS mission; and the ERS School 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, seven 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 *ERS Handbook of Respiratory Medicine* being the first textbook to be 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 paediatric HERMES project now well underway, it is an opportune time to publish an *ERS Handbook of Paediatric Respiratory Medicine* to provide a comprehensive update for specialists within this field of respiratory medicine. The content of this *Handbook* follows the HERMES syllabus and curriculum to provide a compact, state-of-the-art textbook, with each of the sections prepared by senior specialists and clinical experts in the field.

We hope that this *Handbook* will not only inform our trainees but also provide an easily accessible and comprehensive update for colleagues at all levels of seniority across paediatric respiratory medicine. Thus, this educational tool is intended to make a significant contribution to increasing the standards of training in paediatric respiratory medicine throughout Europe and, ultimately, to improving the care of children with respiratory disease.

We are indebted to the ERS School Committee and to the ERS staff who so thoroughly and thoughtfully curated this *Handbook*, and last, but not least, to all the contributors who have shared their knowledge and experience with the readers.

Ernst Eber and Fabio Midulla

Chief Editors

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By buying the *ERS Handbook of Paediatric Medicine*, you also gain access to the electronic version of the book, as well as an accredited online CME test.

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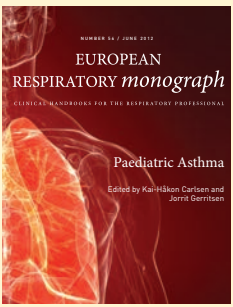
You'll also be able to take the online CME test. This *Handbook* has been accredited by the European Board for Accreditation in Pneumology (EBAP) for 18 CME credits.

Also available from the ERS



European Respiratory Monograph 56: Paediatric Asthma covers all aspects of paediatric asthma from birth through to the start of adulthood. It considers diagnostic problems in relation to the many phenotypes of asthma, covers the treatment of both mild-to-moderate and severe asthma, and discusses asthma exacerbations as well as exercise-induced asthma. The issue provides an update on the pathophysiology of asthma, the role of bacterial and viral infections, and the impact of environmental factors, allergy, genetics and epigenetics.

European Respiratory Monograph 47: Paediatric Lung Function offers a comprehensive review of the lung function techniques that are currently available in paediatric pulmonology. This field is developing rapidly and equipment and software can tell us more than ever about respiratory physiology in health and disease in children with various lung disorders. The issue provides a state-of-the-art review of the techniques, with a special focus on the clinical applications and usefulness in diagnosing and treating children with chronic lung disease.

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List of abbreviations

(C)HF	(Congestive) heart failure
AHI	Apnoea–hypopnoea index
AIDS	Acquired immunodeficiency syndrome
BMI	Body mass index
CF	Cystic fibrosis
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
FVC	Forced vital capacity
Hb	Haemoglobin
HIV	Human immunodeficiency virus
HRCT	High-resolution computed tomography
K_{CO}	Transfer coefficient of the lung for carbon monoxide
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
PCR	Polymerase chain reaction
P_{tcCO_2}	Transcutaneous carbon dioxide tension
S_{aO_2}	Arterial oxygen saturation
S_{pO_2}	Arterial oxygen saturation measured by pulse oximetry
TB	Tuberculosis
TLC	Total lung capacity
T_{LCO}	Transfer factor for the lung for carbon monoxide
V'_E	Minute ventilation

Anatomy and development of the respiratory system

Robert Dinwiddie

Anatomy of the lower respiratory tract

The lower respiratory tract consists of the trachea, hila of the lungs, large bronchial airways, small airways and alveoli. The larynx lies at the junction of the upper and lower respiratory tract and since it is a frequent source of pathology in children its anatomy will also be described. The mediastinum contains the heart and its related cardiac structures:

- thymus,
- trachea,
- thoracic lymph nodes,
- thoracic duct,
- vagus nerves,
- recurrent laryngeal nerves,
- autonomic nerve plexus.

Another important structure which passes through the thorax *via* the mediastinum is the oesophagus.

Key points

- The anatomy of the thorax can be divided into the lungs, heart, mediastinum, pleura, diaphragm and chest wall.
- The lungs can be further subdivided into the trachea, bronchi, hila, lobes and preacinar and acinar regions.
- The mediastinum contains the thymus, the heart and its associated structures, thoracic lymphatics, sympathetic and parasympathetic nerves and the oesophagus.

Larynx The larynx can be divided into three areas (fig. 1):

- supraglottis,
- glottis,
- subglottis.

It extends from the tip of the epiglottis to the lower border of the cricoid cartilage. In the neonatal period it lies at the level of cervical vertebrae C2–C3 and in adults at the level of C3–C6. It contains major cartilaginous structures including the epiglottic, thyroid and cricoid cartilages, and the paired arytenoid cartilages. The vocal apparatus is muscular and consists of the false vocal cords (vestibular folds) and the true vocal cords (folds). The true vocal cords are drawn together by adduction of the arytenoid cartilages. The larynx is bounded on each side by the aryepiglottic folds. These lie between the lateral borders of the epiglottis anteriorly and the upper edge of the arytenoid cartilages, which join posteriorly to form the interarytenoid cartilage. The larynx is chiefly innervated by branches of the vagus nerves. The subglottic area is supplied by the recurrent laryngeal nerves which also arise from the vagal nervous system. These supply the vocal cords and damage to them can result in unilateral or bilateral vocal cord paralysis.

Hila Each hilum forms the root of the lung joining it to the heart and the trachea. Structures that pass through this area on each side include the major bronchus, pulmonary artery, superior and inferior pulmonary veins, bronchial artery and vein, vagus nerves, pulmonary autonomic nerves and lymphatic vessels. Lymph nodes within each hilum are often directly involved in

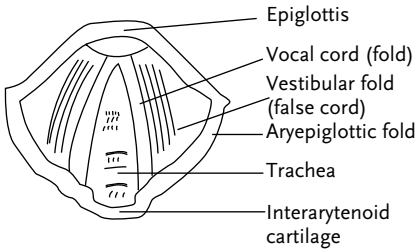

Figure 1. Laryngeal anatomy as seen from above.

disease processes spreading systemically from the lung parenchyme.

Trachea and bronchi The trachea is made up of anterolateral cartilaginous rings and a fibro-muscular posterior wall. The trachea divides into the right and left main bronchi (fig. 2). The right main bronchus is more vertically orientated than the left resulting in a greater percentage of inhaled foreign bodies entering that side. The right main bronchus gives off the right upper lobe bronchus and continues as the bronchus intermedius. This divides into the right middle and lower lobe bronchi. The right upper lobe bronchus divides into three segmental bronchi: apical, posterior and anterior. The right middle lobe bronchus divides into two: the medial and lateral segments of the middle lobe. The right lower lobe bronchus gives off a superior segmental branch and then medial, lateral, anterior and posterior segments. Segmental bronchi are particularly important to recognise during bronchoscopy. The left main bronchus divides into the left upper and lower lobe bronchi. The left upper lobe bronchus gives off the superior division supplying the apical, anterior and posterior branches of the left upper lobe. The inferior division of the left upper lobe supplies the superior and inferior segments of the lingua. The left lower lobe bronchus then descends laterally to give off a posteriorly located apical segment of the left lower lobe and then the antero-medial, lateral and posterior basal segmental bronchi. After dividing into segmental bronchi the airways further subdivide into subsegmental bronchi and then, from generation seventeen onwards, become bronchioles before finally becoming a terminal bronchiole (table 1). The portion of the respiratory tree from the trachea down to the terminal bronchioles is known as the preacinar region. The acinar region comprises the gas exchanging units and includes seven further branches of the distal lung made up of the respiratory bronchioles, alveolar ducts and the alveolar sacs.

The blood supply to the trachea and bronchi is principally *via* the bronchial arteries and the intercostal arteries, which arise *via* the systemic circulation from the aorta. The upper trachea is supplied by branches of the inferior thyroid arteries. The venous drainage from the trachea returns *via* the inferior thyroid venous plexus. The tracheal nerve supply is *via* the vagus nerves, the recurrent laryngeal nerves, supplying parasympathetic fibres and sympathetic nerves arising from the upper ganglia of the sympathetic trunks.

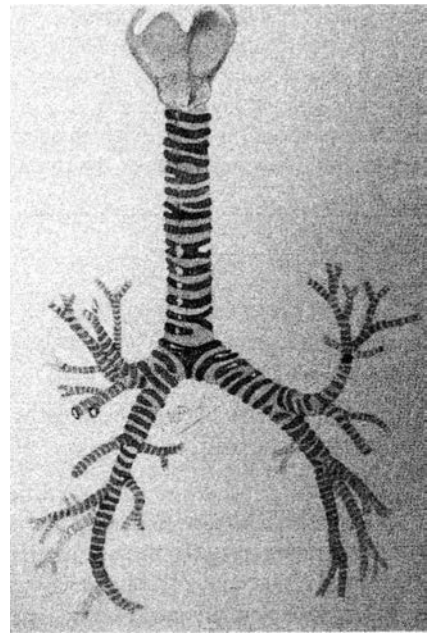

Figure 2. The trachea and bronchi. ©P.L. Shah.

Table 1. Anatomical subdivisions of the lung

Trachea	
Right main bronchus	**Left main bronchus**
Segmental bronchi right	**Segmental bronchi left**
Right upper lobe:	**Left upper lobe:**
Apical	Apical
Posterior	Posterior
Anterior	Anterior
Right middle lobe:	**Left middle lobe:**
Lateral	Superior
Medial	Inferior
Right lower lobe:	**Left lower lobe:**
Superior (apical)	Apical
Medial basal	Antero-medial basal
Anterior basal	Lateral basal
Lateral basal	Posterior basal
Posterior basal	

Pulmonary vasculature and lymphatic drainage The pulmonary artery carries deoxygenated blood to the lungs, thereafter subdividing and eventually becoming alveolar capillaries. Oxygenated blood then returns *via* the pulmonary capillary and venous circulation to the left atrium. The pulmonary arteries lie anterior to the carina and main bronchi. Each artery then enters the lung *via* the hilum. There are two pulmonary veins on each side (superior and inferior) that pass in front of and below the adjacent pulmonary artery and major bronchus.

The lymphatic drainage of the lungs, pleurae and mediastinum is *via* visceral lymph nodes. These are arranged along the bifurcation of the trachea, major bronchi and peripheral bronchi. Further nodes are situated in the mediastinum. The output of most of these vessels is into a bronchomediastinal trunk on each side of the trachea. Another major lymphatic vessel in the chest is the thoracic duct. This starts in the abdomen and enters the chest on the right side through the aortic hiatus of the diaphragm. It then ascends close to the aorta, subsequently crossing to the left side and runs alongside the oesophagus. It ends in the neck where it enters the left internal jugular vein. The right bronchomediastinal lymphatic trunk joins the right lymphatic duct and enters the venous circulation at the junction of the subclavian and internal jugular veins. Leakage of fluid from the thoracic duct is the primary cause of chylothorax in the paediatric age group.

Mediastinum The mediastinum is divided into superior, anterior, middle and posterior portions. It contains the thymus, which develops from the third branchial pouch and has two lobes located in the superior and anterior mediastinum. Its principle function is the programming of thymocytes. Thymocytes, which originate from bone marrow, mature into T-lymphocytes and have major immune functions, especially in relation to resistance to infection and the development of atopic status and allergy. T-helper (Th)-1 lymphocytes form part of the cellular immune system and are principally involved in the response to infection. Th-2 lymphocytes are part of the humoral immune system mainly involved in allergic

responses resulting in atopy and allergy-related diseases including anaphylaxis, asthma and allergic rhinitis.

The thymus gland is proportionately largest in infancy and early childhood; by adolescence it has begun to atrophy and greatly decreases in size.

Mediastinal lymph nodes are located in the pre-tracheal, paratracheal and subcarinal areas, as well as adjacent to the oesophagus.

Diaphragm The diaphragm is the principal muscle of respiration in childhood. It consists of a fibro-muscular sheet of tissue that separates the thorax from the abdomen. It is comprised of a central membranous tendon to which the muscles of the diaphragm are attached. These comprise muscles arising from the xiphoid process of the lower sternum, the lower six costal cartilages and the upper two to three lumbar vertebrae. Diaphragmatic muscles are more easily fatigued in infancy because they contain a smaller proportion of fatigue-resistant muscle fibres than in later life. The diaphragm is perforated by a number of hiatal openings through which important structures pass from the thorax to the abdomen. These include the oesophagus (oesophageal hiatus), the aorta (aortic hiatus) and the inferior vena cava (vena caval hiatus). The diaphragm is supplied by the right and left phrenic nerves arising through the cervical vertebrae C_3, C_4 and C_5.

Chest wall The chest wall includes the ribs and the intercostal muscles. The ribs initially develop as cartilage. The chest wall functions as a pump which performs the respiratory movements driving respiration itself. In the fetus the ribs are almost at right angles to the vertebral column and the muscles of the diaphragm are arranged more horizontally than in later life. Chest movements are therefore less efficient in early life than later life when the child adopts a more upright posture. The cartilaginous nature of the ribs also makes the chest wall less stiff, thus, resulting in the potential for paradoxical movements and indrawing of the thoracic cage during inspiration, especially in preterm infants. Intercostal muscles are also less active during rapid eye movement (REM) sleep which lasts twice as long in infancy as in later life. As the child matures and spends more time awake and in the vertical position, gravity acts on the ribs and intercostal muscles pulling them downwards. The chest also becomes less circular in shape and more ovoid, particularly in the preschool years. The rib cage becomes increasingly calcified with age and consequently stiffer which improves its mechanical efficiency.

Development of the lungs

Lung development starts very early in fetal life, just before 28 days of gestation, as an endodermal outgrowth of the fetal gut called the ventral diverticulum. Although almost all of the lung structure is in place by the time of birth the process continues throughout childhood into adolescence.

Intrauterine lung development Lung development *in utero* is divided into four periods.

- Embryonic: 3rd to 7th week of gestation.
- Pseudoglandular: 7th to 17th week.
- Canalicular: 17th to 27th week.
- Alveolar period: from 27th week to term.

Embryonic period (3–7 weeks): During this period the initial lung bud develops as an endodermal groove from the fetal foregut (respiratory diverticulum). The lining of the larynx, trachea, major airways and alveoli is endodermal in origin. The thyroid, cricoid and arytenoid cartilages and their associated muscles, originating from the mesoderm of the fourth and sixth branchial arches, also develop during this period. The developing tracheobronchial tree then subdivides into the major bronchi, lobar bronchi and peripheral airways. Other locally developing mesodermal tissues influence this branching pattern. At the end of this period the major subdivisions of lung anatomy have already formed and although the associated blood supply is not fully developed each lung bud is supplied *via* the pulmonary trunk, which appears at 5 weeks gestation from the sixth bronchial arch and divides into right and left branches. Each

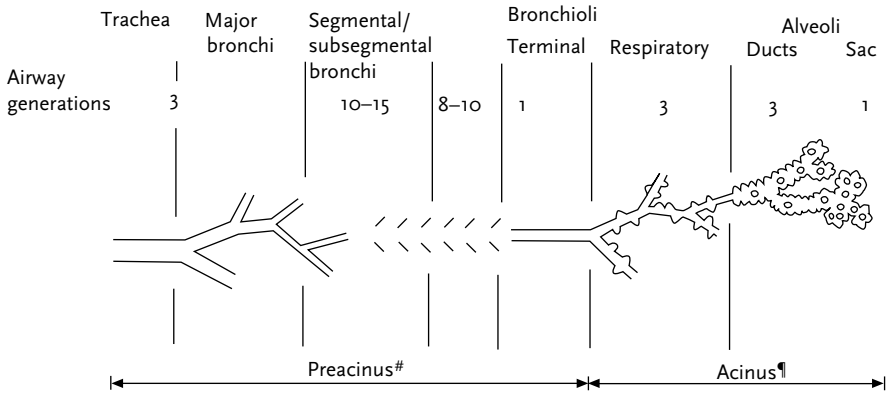

Figure 3. Anatomy of the tracheobronchial tree. #: this region comprises the conducting portion including trachea, bronchi and bronchioli to terminal bronchioles; ¶: this region comprises a gas exchanging unit (with alveoli) and includes respiratory bronchioli, alveolar ducts and alveolar sacs. Reproduced from Dinwiddie (1997), with permission from the publisher.

lung bud is also connected to the evolving left atrium by a pulmonary vein. The associated capillaries begin their development in the adjacent mesenchyme.

Pseudoglandular period (7–17 weeks): During this period there is further rapid branching of the airways. By 16 weeks the terminal bronchioles have developed and airway columnar and cuboidal lining cells have appeared. Fetal lung fluid develops and is propelled through the airways by fetal breathing movements first seen at around 10 weeks of gestation with important consequences for volume expansion of the fluid-filled lungs. Other specialised tissues develop including the cilia from 6 weeks, which becomes fully developed, including in the trachea, by 18 weeks. Cartilage and lymph vessels develop from 10 weeks onwards. These spread peripherally through the developing lungs. Goblet cells, mucus glands and airway muscles also first appear at this time and continue their development throughout prenatal and post-natal life. The main pulmonary arteries and veins develop further; the right pulmonary artery arises from the proximal part of the sixth right branchial arch following which the distal part degenerates. The left pulmonary artery arises from the sixth left aortic arch which gives off the main artery and then continues as the arterial duct (ductus arteriosus) and remains patent until the early period of adaptation to post-natal life. Bronchial arteries also develop directly from the aorta. The more distal preacinar arteries develop and are fully present by 16 weeks.

Canalicular period (17–27 weeks): At this stage the lungs develop their distal architecture. The peripheral airways elongate and the epithelial lining cells become cuboidal in shape in the lower airway generations. Mesodermal tissue thins out and the pulmonary microcirculation matures. Terminal bronchioles, respiratory bronchioles and distal alveolar sacs develop rapidly. The acinus, which forms the distal gas exchange unit of the lung, develops its final structure by 24 weeks; immediately before this time thin-walled saccules appear to develop into individual alveoli. The most peripheral pulmonary vascular structures develop as intimately associated alveolar capillary units to form a blood–gas barrier sufficient to maintain extrauterine life even at this gestation (fig. 3).

The alveolar lining cells subdivide into two types: Type I and Type II. Each is histologically distinguished by 24 weeks gestation. Type I (gas exchanging) cells occupy 95% of the alveolar lining. Primary surfactant production occurs in Type II cells.

Signalling pathways Overall, lung morphogenesis is under the control of a number of signalling pathways. These are primarily controlled by genetic factors, especially for the development of lung lobulation and the first 16 airway generations. These activities are mediated through a number of peptide growth factors and more distally by similar substances modified by local physical factors that regulate distal airway branching, development of the pulmonary vasculature and, ultimately, the alveoli. A number of polypeptides are known to be involved in this process including transforming growth factor (TGF)-β, bone morphogenic protein (BMP)-4, fibroblast growth factors (FGFs), platelet-derived growth factor (PDGF), epidermal growth factors (EGF)/TGFs, sonic hedgehog (SHH), vascular endothelial growth factor (VEGF), insulin-like growth factors (IGFs) and granulocyte-macrophage colony-stimulating factor (GM-CSF), as well as thyroid transcription factor (TTF)-1 protein.

Surfactant

Surfactant is produced in the Type II alveolar lining cells. It has a number of important functions. The primary role of surfactant is to promote and maintain lung volume and prevent alveolar collapse during expiration. Thus, surfactant decreases the mechanical work and energy expenditure of breathing, especially at birth. Surfactant also has an important role in host defence of the lungs against infection and in their response to tissue insults, such as barotrauma during treatment. Genetic defects in surfactant production are now known to be major aetiological factors in several chronic and potentially lethal lung diseases of infancy and childhood (table 2).

Type II alveolar lining cells are principally involved in the production, storage, secretion and recirculation of surfactant through the intracellular lamellar bodies. The principal surface active lipid in surfactant is phosphatidylcholine.

Four surfactant proteins have been identified. Surfactant protein (SP)-A is water soluble and acts mainly by decreasing protein-related inhibition of surfactant activity. It also has an important role in lung inflammation where it acts as part of the host defence mechanism. SP-A levels are responsive to pre-natal corticosteroid therapy. SP-B, which is hydrophobic, is an important component of lamellar bodies. It facilitates the reduction of alveolar surface tension when alveolar volume is reduced during expiration. SP-C, also hydrophobic, is another important protein component of lamellar bodies. It appears to function closely with SP-B in the spreading of surfactant onto the alveolar surface, thus, facilitating its surface tension reducing properties. SP-D is water soluble and not directly associated with the function of surfactant phospholipids. Its principal role appears to be as an innate immune system protein that acts as part of the host defence against infections, *e.g.* with common respiratory tract bacteria and viruses.

Table 2. Components of surfactant

Phospholipids	78%
Dipalmitoylphosphatidylcholine	66%
Phosphatidylglycerol	4%
Phosphatidylethanol	5%
Sphingomyelin	3%
Cholesterol, glycerides and fatty acids	12%
Surfactant proteins A, B, C and D	10%

ABCA3 is another important substance related to surfactant function. It is an ATP binding cassette protein. Its precise function is not yet fully known but it has been shown to be widely present in Type II alveolar epithelial lining cells. Its most likely action is in the inward transport of lipids for surfactant production.

Surfactant secretion occurs by a process in which lamellar bodies are released from Type II lining cells within the alveoli. Phospholipids combine with SP-A, SP-B and SP-C. Secretion is stimulated by stretching of the lung parenchyma, as well as by extrinsically administered β-adrenergic

agonists. Surfactant lasts for approximately 5 h before being broken down. Approximately 50% of active surfactant is recycled through the lamellar bodies before being reused. When secreted into the alveoli and distal small airways, mature surfactant forms a structure (tubular myelin) that, along with other compounds, lines the alveolar surface. Fully functional surfactant secreted in normal amounts into the alveoli results in decreasing surface tension as the alveoli shrink in volume, preventing their collapse at the end of expiration. On inspiration surface tension rises.

At birth, even in the presence of surfactant, an initial opening pressure is required to establish a stable functional residual capacity (FRC) of ~30 $mL \cdot kg^{-1}$. This is in the order of 15 cmH_2O. In the surfactant-deficient pre-term infant, pressures twice as great may be needed just to initially open the alveoli with a tendency for recurrent collapse at end expiration. The presence of adequate amounts of active surfactant also results in the achievement of significantly greater lung volumes at full inspiration.

Several potentially severe conditions occur in young infants and children if abnormalities exist in the surfactant production or breakdown pathways. These include potentially lethal or severe lung disease in early life if there are genetic mutations of SP-B, SP-C, ABCA3 and TTF-1. These conditions are important causes of respiratory distress syndrome in full term, otherwise normal, babies. Another condition of variable severity, alveolar proteinosis, occurs in older children and adults when there is deficiency of GM-CSF, a substance which is vital for the breakdown of surfactant.

Surfactant proteins have important immunological functions. SP-A increases macrophage activity in the lung. It also facilitates the destruction of various microorganisms by other immune-modulated cells within the lung. The roles of SP-B and SP-C in lung inflammation have not yet been fully evaluated. SP-D stimulates the phagocytosis of several types of micro-organisms by alveolar macrophages. It also stimulates neutrophilic destruction of bacteria, including *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Escherichia coli*.

Exogenous surfactant is not only used in the treatment of preterm infants but also in a variety of diseases in older children.

During this pseudoglandular period the lungs reach a liquid-filled volume similar to the air filled FRC after birth of ~25–30 $mL \cdot kg^{-1}$. Fetal breathing movements at this gestation are especially important in the maintenance of the developing lung volumes.

In summary:

- Surfactant is predominantly composed of phospholipids, principally phosphatidylcholine.
- Surfactant contains four proteins A, B, C, and D.
- Surfactant proteins have important surface tension lowering functions and innate immune modulating properties.
- Genetic deficiencies of surfactant proteins cause serious, and potentially lethal, lung disease in neonates and infants.

Alveolar sac period (27 weeks to term)

This is the final stage of fetal lung development. It is at this stage of fetal life that the lungs are able to sustain independent breathing. The epithelial lining cells further differentiate and establish their intimate inter-relationship with the epithelial lining surface of the alveoli. Distal lung growth continues as the respiratory bronchioles subdivide into saccules, which then form their final specialised structure becoming alveoli. Alveoli are lined by two distinct types of cell. Type I alveolar lining cells cover 95% of the alveolar surface and have a thickness of 0.1–0.01 µm. Type II alveolar lining cells are thicker, with a diameter of 10 µm. Although covering only 5% of the alveolar surface, they play a vital role in surfactant production and metabolism.

During this period the pulmonary vasculature develops rapidly. The arterial

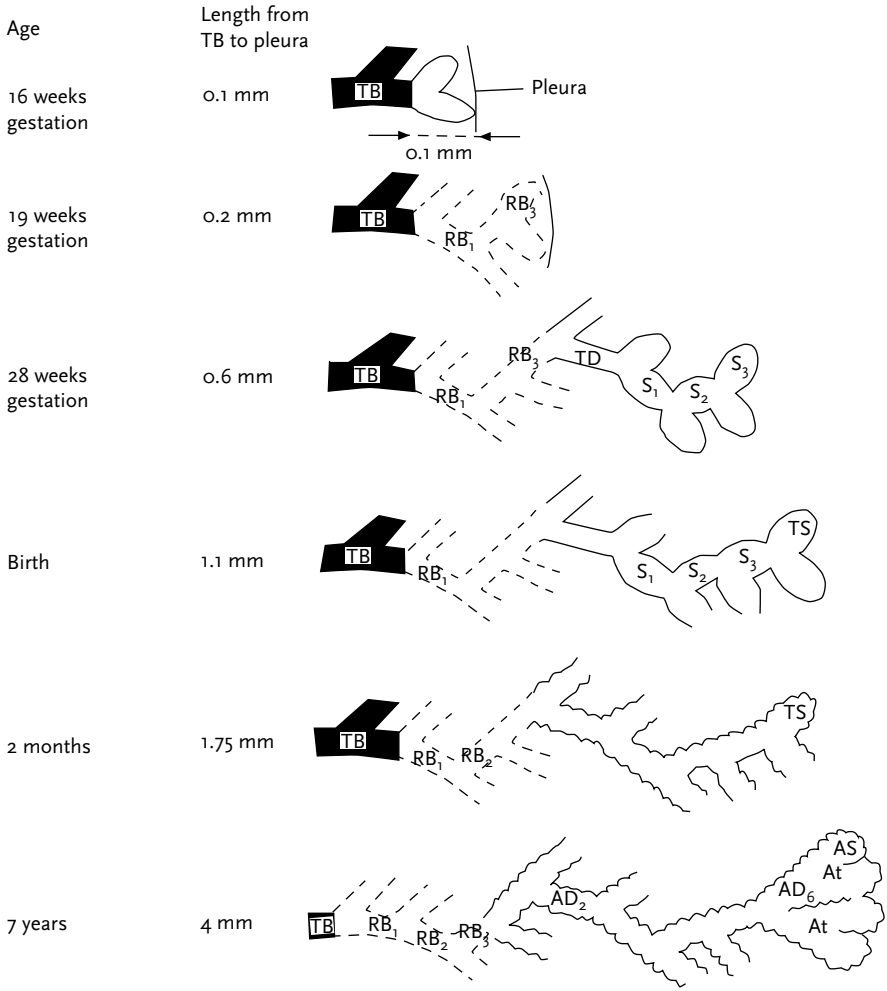

Figure 4. Development of the acinus. Stages of acinar development in fetal and post-natal life. TB: terminal bronchiole, RB: respiratory bronchiole; TD: terminal duct; S: saccule; AD: alveolar duct; At: atrium; AS: alveolar sac. Reproduced from Hislop (1974) with permission from the publisher.

muscle coat is proportionately thicker than in later life. This allows for intense vasoconstriction during periods of intrauterine hypoxia but is a major contributory factor to persistent pulmonary hypertension in the neonatal period (fig. 4).

Control of breathing

The development of control of breathing is a complex process beginning early in fetal life and is continuously changing throughout childhood. This is covered in detail in this *Handbook* in the Sleep-related Disorders section. Important reflexes that originate in the chest wall are the Hering–Breuer reflex and the Head's paradoxical reflex. The Hering–Breuer reflex is an inspiratory inhibitory response mediated through the vagal nerves. It is particularly active in the control of the rate and depth of breathing in the neonatal period and during the first 2 months of life. The Head's paradoxical

reflex is initiated by rapid lung inflation and precipitates an increase in respiratory effort. The increased compliance of the ribcage in the neonatal period can lead to distortion during REM sleep, resulting in respiratory irregularity and, in some cases, apnoea.

Post-natal lung development

After birth the alveoli become multilocular and progressively increase in size and numbers with further out budding of the alveolar saccules. By term, approximately one-third to one half of the adult alveolar numbers is present. Thereafter, alveoli continue to increase in number, especially during the first 2 years of life reaching 100–250 million by the end of this period. Adult numbers of alveoli, 300–400 million, are already present by the age of 2–3 years. Boys have more alveoli than girls. Alveolar multiplication continues at a reduced rate and is finally completed by 8–10 years of age. After this there is a continuing increase in diameter of the large airways and further remodelling of the alveoli until physical growth is complete. The peripheral airways increase in relative size and proportion compared to the central airways until the age of 5 years. Lung volumes increase throughout childhood. A final growth spurt occurs in adolescence associated with a parallel increase in lung volumes which lasts longer in boys than in girls. TLC at birth in a 3-kg newborn infant is, on average, 150 mL (50 $mL \cdot kg^{-1}$) increasing to 6.0 L (75 $mL \cdot kg^{-1}$) in adult males and 4.2 L (60 $mL \cdot kg^{-1}$) in adult females. During the first 10 years of life the rib cage gradually changes from a horizontal orientation to the downward (caudal) slope of the adult. Ossification of the ribs also progresses throughout childhood into early adult life reaching completion in the early 20s.

Factors affecting lung growth and development

A number of factors can adversely affect lung growth and development throughout both fetal and post-natal life; these are shown in table 3.

Table 3 Factors affecting lung growth and development

Abnormal embryonic and fetal development
Genetics
Hormones
Maternal and fetal malnutrition
Reduced fetal breathing movements
Reduced fetal lung fluid volumes
Inadequate size of thoracic cage
Impaired adaptation to post-natal life
Preterm birth and its treatment
Maternal smoking in pregnancy
Pre- and post-natal infection

Abnormalities of embryonic and fetal development, including congenital malformations, *e.g.* diaphragmatic hernia, can have profound effects on the growth and development of both the affected and also the contralateral lung, especially if it arises during the pseudoglandular period when airway generation is occurring at its maximum rate. Reduced alveolarisation is another associated complication. Genetic factors are particularly important and play a significant role in controlling various hormone-related influences, including thyroid hormones (TTF-1), FGF, PDGF, IGF-1 and TGF-β, as well as steroid hormones, specifically oestrogen α and β and androgen receptor hormones which are expressed in developing lung tissue. Maternal malnutrition results in low birth-weight babies as does placental insufficiency. These factors can lead to reduced lung growth for gestation. Severe maternal malnutrition, studied at the end of World War II, has been shown to result in an increase in COPD in adult life in affected offspring. Fetal breathing movements are first seen at 10 weeks gestation and are important for lung growth because of their role in the development and maintenance of lung volume. Lung cell proliferation is inhibited if fetal breathing movements are diminished. Absence of fetal breathing results in pulmonary hypoplasia including a decrease in distal lung airspaces. Hypoplastic lungs secondary to reduced fetal breathing movements have impaired synthesis and secretion of pulmonary

surfactants resulting in abnormal lung mechanics at birth. Reduced amniotic fluid volumes during pregnancy due to early rupture of the membranes or secondary to abnormal renal function, which results in oligohydramnios, can result in pulmonary hypoplasia. Intrauterine pleural effusions, such as congenital chylothorax, can result in inhibition of lung growth. Syndromes involving reduced thoracic cage development, for example Jeune's asphyxiating thoracic dystrophy, are associated with pulmonary hypoplasia and impaired surfactant secretion. Another cause of pulmonary hypoplasia relates to respiratory muscle weakness, such as occurs in congenital myopathies and neuropathies. Impaired adaptation to extrauterine life leading to chronic hypoxia or treatment-induced hyperoxia, with or without long-term ventilation resulting in barotrauma-induced lung injury, can also impair age-related lung growth and development. Maternal smoking in pregnancy is a well-described cause of impairment of small airway development with immediate and long-term consequences on small airway development and resultant hyperresponsiveness. Severe infections in early life, such as with adenovirus, can lead to obliterative bronchiolitis and impaired post-natal lung development.

Thus, the growth and development of the lungs is a continuous process from early fetal life, throughout childhood and into early adulthood. The most important changes occur before birth and in early childhood. It is at these times that other adverse events, such as severe intercurrent infections, are most likely to have profound effects on future structure and function.

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Applied respiratory physiology

Caroline Beardsmore and Monika Gappa

Knowledge of respiratory physiology is essential for understanding the pathological changes in disease, and the application and interpretation of respiratory function tests. Pathological changes in lung physiology will vary according to disease or condition, 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 (fig. 1). Whatever condition is under consideration, spirometry remains a cornerstone of assessment, and measurement of lung volume is also vital for interpretation. This section will briefly summarise the underlying measurement principles and discuss how to approach clinical questions by applying available respiratory function tests. Before considering the applications of these measurements in a clinical context the underlying principles of the most commonly used measurements will be summarised.

Key points

- Distinguishing obstructive and restrictive disorders is simplistic but a helpful starting point.
- A combination of spirometry and body plethysmography is most useful.
- Visual inspection of the flow–volume loop, including the inspiratory limb, is essential.
- Assessment of inflammation is becoming increasingly recognised as an important part of the overall evaluation.

Spirometry and the flow–volume loop

Spirometry is the means of recording the volumes of inspired and expired air, and the maximum flows during the respiratory manoeuvres.

Equipment and procedure The original spirometers used from the inception of the technique until the 1980s were mechanical devices with a chamber from which the subject breathed in and out. The chamber incorporated a low-resistance movable section that accommodated the change in volume without any appreciable pressure change, and the movement was translated into a recording, either directly *via* a pen on a chart or *via* a transformer into a digital recording (fig. 2). These mechanical spirometers measured changes in volume directly, and flow was calculated secondarily. The historical devices have been superseded by electronic spirometers which have the advantages of portability, simplicity of cleaning and ease of use. The electronic spirometers usually incorporate a pneumotachograph or an ultrasonic flow-meter to measure flow, with volume subsequently being obtained by differentiation.

Children who are able to cooperate with testing will be asked to make an airtight seal around the mouthpiece, breathe steadily and then make maximum inspiratory and expiratory manoeuvres. 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 a flow–volume loop from the volume–time recording (the spirogram) is shown (fig. 3). The manoeuvres are repeated several times in order to achieve the best (highest) values and assess repeatability. Internationally accepted guidelines exist for the technical specifications and performance of spirometers, the conduct of the test, and quality control. Some modifications may be necessary for children, and the use of incentive spirometry may be particularly helpful in younger children.

Restrictive conditions: Interstitial lung disease, neuromuscular disease (*e.g.* Duchennne's muscular dystrophy) and skeletal abnormalities (*e.g.* scoliosis)	**Obstructive conditions:** *e.g.* asthma, including extrathoracic airway obstruction
Spirometry (principally VC) shows the extent of restriction and is helpful for regular monitoring. Lung volume measurements will show the extent of the deficit at either end of the VC range. Measurements of compliance and gas transfer may be helpful where the underlying condition is pulmonary in origin. Tests of respiratory muscle strength can help in the evaluation of neuromuscular disease.	The pattern of the flow–volume loop obtained through spirometry can indicate the site of obstruction (intrathoracic or extrathoracic) and whether it is fixed or variable. Changes in FEV_1,FVC and expiratory flows can quantify the extent of intrathoracic obstruction, and perform a similar function for extrathoracic obstruction. Lung volume measurements can show the extent of any hyperinflation or gas trapping. Other investigations (*e.g.* gas mixing) may show abnormal function before spirometry becomes abnormal and may be helpful in monitoring individuals and in research.

Figure 1. Consideration of abnormalities as either restrictive or obstructive in nature. These are not mutually exclusive and individuals frequently show elements of both.

Measurements of lung volume

The principal means of measuring absolute lung volumes are gas dilution (usually helium dilution), plethysmography and nitrogen washout, all of which measure functional residual capacity (FRC) and derived lung volumes (refer to the Pulmonary function testing and other diagnostic tests section in this *Handbook*). The underlying principle for plethysmography differs from the gas dilution or washout techniques, and this may be utilised to characterise the pathophysiology in different disease states.

Equipment and procedure *Whole body plethysmography* is used to measure (intra)thoracic gas volume. The principle of the measurement is such that it includes the volume of all the air in the chest, whether in communication with the airway and ventilated, or not. In contrast, FRC is generally taken to include the volume of the lungs in free communication with the airway opening and therefore ventilated. Nevertheless, the abbreviation FRC_P (FRC by plethysmography) has gained popularity and will be used hereafter. The measurement of FRC_P is based on Boyle's law. The subject is enclosed in a cabin, which is almost airtight, and breathes through a pneumotachograph that measures airflow. A shutter is closed in the device through which the subject is breathing, transiently occluding the external

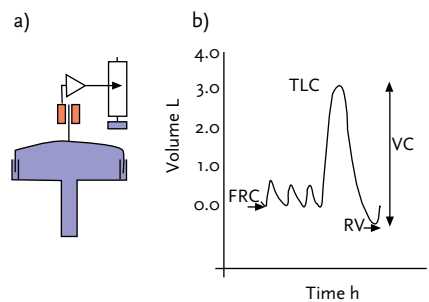

Figure 2. a) Original type of mechanical spirometer and b) associated recording of changes in volume. The recording shows three tidal breaths at FRC followed by inspiration to TLC, and expiration of VC to RV.

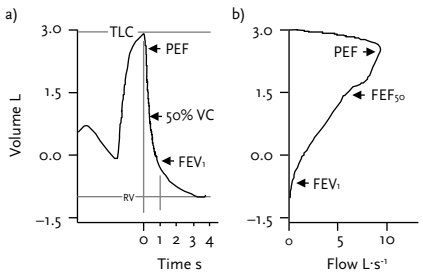

Figure 3. Relationship between a) spirogram and b) expiratory flow–volume curve, showing inspiration to TLC followed by forced expiration to RV. PEF occurs early in the manoeuvre, followed by smooth decline in flow to RV. Note that FEV_1 can only be derived from the spirogram.

airway. The subject makes a respiratory effort against the shutter and the alveolar pressure change is measured directly from the mouthpiece. The change in thoracic volume as the subject compresses or expands the chest is measured indirectly from the cabin pressure and used in the calculation.

Once FRC_P has been measured during the transient period of airway occlusion the subject continues to breathe through the mouthpiece and, after one or two breaths, makes a full inspiration and expiration so that the TLC and residual volume (RV) can be determined (refer to the Pulmonary function testing and other diagnostic tests section in this *Handbook*).

Nitrogen washout The principle behind this technique is to quantify the volume of nitrogen within the lungs and then, knowing the alveolar concentration of nitrogen, calculate lung volume. Therefore, the equipment combines a means of measuring volume, usually a pneumotachograph, and a nitrogen analyser or equivalent. The technical issues associated with nitrogen analysers mean that nitrogen is usually measured either by mass spectrometry or by quantification of other gases (oxygen and carbon dioxide) and subtracting these from 100%. The procedure requires the subject to breathe through a mouthpiece and, when steady respiration is established, the subject is switched to breathe 100% oxygen from either a reservoir or a bias flow. The expired nitrogen is quantified and the lung volume calculated. In simple terms, if the alveolar concentration of nitrogen was 80% and 2 L of nitrogen was exhaled during the test, the lung volume would be $2 \times 100/80$ L, or 2.5 L. The measurement is usually continued until the expired nitrogen is $<2.5\%$; continuation beyond this point results in significant amounts of nitrogen dissolved in the blood coming out of solution in the lungs and resulting in an artefactually high estimation of lung volume.

The principle behind the test is not restricted to nitrogen, and it is possible to use other tracer gases. These are first "washed in" to the lungs by giving the subject a pre-set concentration of inert, nonsoluble gas to breathe until alveolar (end-tidal) concentration is equal to the inspired concentration. One advantage of other gases can be the avoidance of breathing 100% oxygen, which can have undesired effects on pulmonary blood flow in certain patients (see chapter 3).

Helium dilution Measurement of lung volume by helium dilution requires a mechanical spirometer which, at the start of the measurement, is set to a known volume and contains a known concentration of helium (typically 10%). The subject is connected to breathe tidally from the spirometer, with carbon dioxide being absorbed in order not to provoke hyperventilation. Oxygen is titrated into the system in order to maintain a stable baseline volume and prevent onset of hypoxia. As the air in the lungs mixes and equilibrates with that in the spirometer, a new, lower concentration of helium is established. When this is stable, the FRC can be calculated as follows:

$$V_1C_1 = V_2C_2$$

where C_1 and C_2 are the initial and final concentrations of helium, V_1 is the starting volume of the spirometer and V_2 is the final volume, *i.e.* spirometer and lung volume combined. Rearranging:

$$V_2 = V_1C_1/C_2$$

and

$$FRC = V_2 - V_1$$

The calculated value of FRC is likely to need some small adjustment for the dead space of the mouthpiece and any connections to the spirometer. The spirometer will be at room temperature, but (by convention) lung volume is expressed at BTPS (body temperature, ambient pressure, saturated with water vapour). Most modern equipment will have the corrections within the software so that the measurement shown will be accurate. Usually three determinations are made and a mean value reported.

Which measurement of lung volume is most appropriate? The measurement of choice will depend on why the measurement is being taken, *i.e.* what is the question to be answered. Measurements based on dilution or washout measure the volume of lung that is being ventilated, *i.e.* functional, 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 changes in pressure and volume that are used in the calculation. In healthy individuals the differences in FRC may be slight but in others they can differ considerably, and the size of the difference may be informative. Therefore, in some patients with complex conditions, it may be helpful to include different methods to assess lung volumes in the evaluation. Measurements based on dilution or washouts have the advantage that the time taken to complete the measurements can be informative. Where pulmonary function is good, equilibration of gas or the ease with which a gas is washed out is rapid. More accurately, the amount of ventilation required to achieve equilibration or washout is less in a healthy individual than in a subject with deranged function, and assessment of this adds valuable information. This change in ventilation can be quantified by parameters of ventilation inhomogeneity such as the Lung Clearance Index (LCI) and other indices which have been shown to be much more sensitive to early changes within the small airways than parameters obtained using full forced expiratory manoeuvres.

Assessment of obstruction

Patients with obstructive disorders form the largest component of the workload of the respiratory paediatrician, with diseases involving the small airways (mainly asthma and CF) being the most common. Spirometry continues to be an essential part of assessment and monitoring, demonstrating deviation from predicted values and changes over time or in response to treatment. The typical patient with obstructive respiratory disease will have an expiratory flow–volume loop that shows a distinct concave shape, such that flows at high lung volumes (peak expiratory flow (PEF) and forced expiratory flow at 25% of FVC (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 loop is an essential part of the evaluation. During the course of expiration, the site of flow limitation moves progressively down the bronchial tree into ever smaller airways, where the extent of any airway narrowing (*e.g.* caused by oedema of the airway epithelium mucosa) has a greater effect.

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 usually reduced and this can be helpful in interpreting spirometry. However, FEV_1/FVC should not be considered in isolation, because it cannot convey whether either or both component parts are within normal limits or not. For example, when assessing response to bronchodilator in an asthmatic patient, there may be a significant improvement in both FEV_1 and FVC, but little change in FEV_1/FVC. When assessing changes in response to treatment it is helpful to take account of changes in the shape of the flow–volume curve, since it is not uncommon to measure a significant improvement in FEV_1 (usually an increase of $\geqslant$12%), but for the patient to still have a significant degree of obstruction so that the

expiratory flow–volume curve continues to show marked concavity. *Vice versa*, a change in the flow–volume loop from concave to linear or convex may be the sole indicator of bronchial reversibility in patients with asthma, even if the parameters are within the normal range.

The shape of the flow–volume loop can also help with the diagnosis of obstruction in the large airways. With a fixed obstruction, such as a subglottic stenosis, the maximum flow that can be achieved will be determined by the physical dimensions of the airway at its narrowest point. 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 fairly constant from one year to the next, with progressive worsening of the flows as related to predicted values. The flow–volume curve will appear flattened on both the inspiratory and expiratory limbs, with a loss of a well-defined peak flow and no significant response to bronchodilator (fig. 4).

Where there is an extrathoracic variable obstruction, the abnormality will be evident on the inspiratory limb of the flow–volume loop (fig. 4), and expiration may be unaffected. During expiration the positive-pressure gradient extending from the lung down to the airway opening will tend to

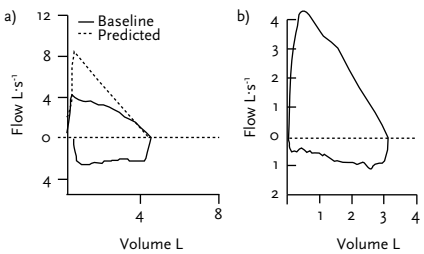

Figure 4. a) Fixed obstruction (tracheal stenosis), with flattening of both inspiratory and expiratory curves. On expiration, flow is reduced primarily at high lung volume, with normal flow in the last quarter of VC. b) Variable upper airway obstruction (laryngeal polyp), illustrating reduced flow through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

dilate the extrathoracic airway, 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. The inspiratory flow will be low and may be variable. During performance of the test it may be noticeable that the patient takes a long time to inspire fully to TLC; a technician or physiologist with experience of observing and coaching children can confirm whether the test is indicative of extrathoracic obstruction or not.

In cases where there is severe obstruction of the small airways (*e.g.* an exacerbation of asthma or advanced CF), the distribution of lung volumes may become abnormal. During the course of expiration the airways become narrower as 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 an early stage in the manoeuvre. When this happens, RV is increased and vital capacity (VC) is reduced. Since the range of prediction for RV is fairly wide, the RV/TLC ratio is a useful indicator of early airway closure. If airway narrowing becomes more marked, so that airway closure begins within the normal tidal breathing range, the patient will adopt a pattern of breathing which involves breathing at an elevated FRC in order to maintain airway patency. If this becomes a frequent or extended event, such that the inspiratory muscles become trained, it is possible that the TLC (which is dependent, in part, on respiratory muscle strength) may increase. A reduction in VC should be an indicator for measurement of absolute lung volumes in such patients. The technique of choice for this should be plethysmography, since this technique can quantify trapped gas. In the most extreme cases, where patients have extensive airflow obstruction and uneven distribution of pressure changes within the chest, the assumptions underpinning plethysmography may no longer be valid but in these individuals there is usually clear clinical evidence of hyperinflation.

Assessment of restriction

Restrictive diseases are characterised by a reduction in TLC, leading to restriction in lung expansion. 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 shortness of breath 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, since the range of predicted value is wide. Serial measurements are more informative, for example in the early stages of Guillain–Barré syndrome as a pointer to probable need for mechanical ventilation, or to monitor the progression of scoliosis.

The shape of the expiratory flow–volume loop 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. Most spirometers will display the flow–volume loop together with a schematic of the predicted loop, and almost invariably the loops will be aligned at TLC (fig. 5). To the uninitiated, this will 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 (PEF and FEF_{25}) are reduced in restrictive disease, not because of airway obstruction but because the volumes at which they are measured are constrained. Alignment of the recorded flow–volume loop with the predicted loop at TLC will further compound the impression that flows are reduced; alignment at RV may be helpful in these cases.

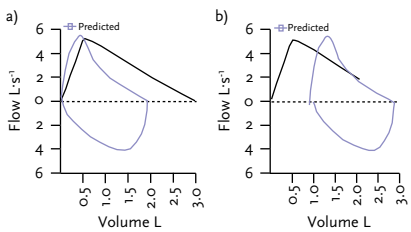

Figure 5. Flow–volume loop from a child with restrictive disorder, including a schematic of the predicted expiratory flow–volume loop with a VC of 3.0 L predicted. a) The actual flow–volume loop aligned with the schematic at TLC. It appears as if the expiratory flows are substantially below the predicted flows. b) The actual flow–volume loop aligned at RV, showing that measured expiratory flows coincide with predicted flows over much of the VC. Note that the precise positioning of the actual loop 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 also increased, as may happen in skeletal abnormalities. RV may also be elevated in severe obstructive disease, but changes in spirometry will usually distinguish between the two. Measurements of absolute lung volumes are all based on determination of FRC, which may be influenced by the posture of the subject. The number of individual measurements performed may also affect the accuracy, and is generally higher for plethysmography than other techniques where a maximum of three determinations is usual. In contrast, the within-test repeatability of spirometry is generally good, making VC the index of choice for monitoring changes in restrictive disease. Where the restriction is due to a neuromuscular condition, spirometry may be more variable and the flow–volume loop 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 unnecessary and fruitless 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 to 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 impossible to make an accurate measurement of body height, as is often the case in nonambulant 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. An alternative approach is to measure maximum inspiratory and expiratory pressures directly, which has the advantage that predicted values can be related to age rather than height.

Interstitial lung diseases 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, a situation that can also arise in children treated with certain medications for cancer**.** Assessment of *T*LCO, from its components *K*CO and alveolar volume (*V*A), can be informative in children able to perform the necessary manoeuvre. The most common technique is the single-breath method. In brief, the subject breathes out to RV, 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 and a slow, 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 the transfer factor cannot be measured in very young children, but it may be possible in some as young as 6 years of age. From a practical perspective, pulse oximetry at rest and during exercise is easy to apply and informative when abnormal; a finding of normal saturation is reassuring but can disguise the presence of significant lung disease.

Assessment of inflammation

Applied respiratory physiology has historically been mainly limited to studies of pulmonary mechanics and gas exchange, but should properly be extended to peripheral lung function. In the clinical setting this should include an assessment of the degree of inflammation, particularly in asthma. The most common means of assessment is measurement of the exhaled nitric oxide fraction (*F*eNO). Measurement of nitric oxide is also relevant in screening for primary ciliary dyskinesia, because levels of nasal *F*eNO are lower than in healthy individuals. Equipment for measuring *F*eNO ranges from laboratory-based analysers using a chemiluminescence technique to hand-held, portable devices that incorporate an electrochemical sensor. The measurement of *F*eNO requires that the subject maintains a steady expiratory flow for a minimum period of 4 s, which is usually achieved by having the subject breathe out against a resistance, with the value of *F*eNO (expressed in parts per billion) being available within approximately 2 min. A detailed review of the technical aspects and clinical applications is available (see chapter 3). The measurement of *F*eNO may contribute to confirming a diagnosis of asthma, but has a greater role in assessing response to steroids. 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.

Measurement of *F*eNO can be considered a marker of inflammation, but in this regard it may be of most help in asthma. In CF (where airway inflammation is a feature) values of *F*eNO are normal or even low. In situations where *F*eNO may not be useful, looking at the profile of inflammatory cells or other biomarkers in sputum may be informative (see chapter 3) but the value of various biomarkers is still being evaluated. Sputum may be produced spontaneously,

particularly in patients with CF, but can be otherwise obtained by sputum induction with hypertonic saline. In children where this is not possible, bronchoalveolar lavage can be used to obtain the sample in those individuals where the importance of the sample merits the invasiveness of the procedure.

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Immunology and defence mechanisms

Diana Rädler 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 of immune defence, namely the innate and the adaptive immune system, also designated as the first- and second-line 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.

Key points

- Innate immune mechanisms comprise a mechanical, physical and chemical barrier, which act together in the defence against invading microorganisms.
- 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 system.
- Interaction of innate and adaptive immune regulation is required for specific defence against respiratory diseases, involving prenatal and postnatal factors.

Innate defence mechanisms

Innate immunity of the lung The lung is exposed to a multitude of airborne pathogens while only very few cause respiratory infections. This observation is proof of the efficiency of the lungs' defence system. The innate immune system is composed of a mechanical, physical and chemical barrier, which act together in the defence against invading microorganisms (fig. 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 the:

- nasal hairs,
- nasopharynx channels,
- glottis,
- trachea,
- small branches of the bronchi and bronchioles.

The surface of the airways is covered with mucins and glycoproteins which trap microorganisms. This complex is then cleared by cilliary movement of the mucus to the oropharynx.

Cell types participating in innate immunity Several cell types participate in initiating and maintaining the innate immune response and link the innate and adaptive part of the immune defence (fig. 1). Macrophages engulf and digest pathogens by phagocytosis and initiate the adaptive immune system. Dendritic cells are a link between the innate and adaptive immunity,

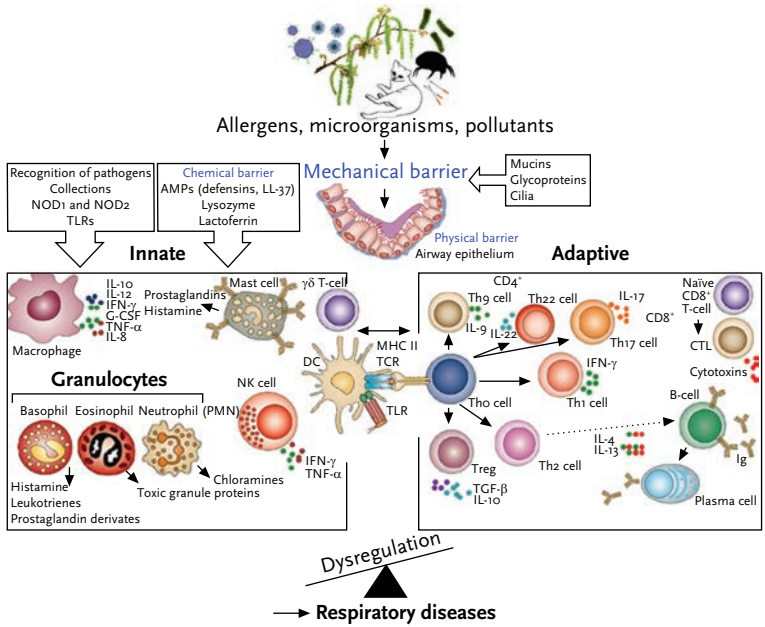

Figure 1. Overview of the initiation and interaction of the innate and adaptive immune system. LL-37: cathelicidin; IL: interleukin; G-CSF: granulocyte colony-stimulating factor; DC: dendritic cell; NK: natural killer cell; Th: T-helper cell; TGF-β: transforming growth factor-β; CTL: cytotoxic T-cell.

as they ingest, process and present antigens to further cell types of the immune system. Granulocytes are a group of white blood cells containing cytoplasmatic granules. They are divided into three types, namely neutrophils, eosinophils and basophils. Neutrophils participate in phagocytosis and immediate killing of microorganisms, independent of previous exposure, whereas basophils are highly specialised in the synthesis and secretion of several pharmacologically active products such as histamine, proteases, leukotrienes or prostaglandin derivates. Eosinophils are recruited to the site of inflammation during a T-helper (Th)-2 type immune response, where they produce a variety of cytokines and lipid mediators and release their toxic granule proteins.

Additionally, natural killer cells are a type of cytotoxic lymphocyte, which are involved in a fast immune reaction and killing of cells in the absence of antibodies and major histocompatibility complexes (MHCs) on their surface. The γδT-cells are a small subset of T-cells which have a T-cell receptor (TCR) composed of a γ- and δ-chain instead of the more frequent occurring α- and β-chain. These cells are thought to play an important role in the recognition of lipid antigens. Due to their complex biology, *i.e.* exhibiting characteristics of the innate and the adaptive immune system, they are thought to be involved in both systems.

Mast cells participate in inflammatory processes by releasing characteristic granules and hormonal mediators upon activation. For example, they produce histamine and prostaglandins.

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

Recognition of pathogens by the airway epithelium The airway epithelium is the point of contact for smaller inhaled

substances like allergens, microorganisms or pollutants. It presents the interface between external environment and internal milieu. This epithelium forms a physical barrier and, moreover, contributes to the host defence in several ways, including production of chemokines, cytokines and antimicrobial peptides (AMPs), as well as proteinase inhibitors and surfactant proteins as chemical barrier.

As a response to pathogenic exposure, the innate immune system releases antimicrobial peptides 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 introduce the aforementioned cascade, microorganisms need to be recognised first. Microorganisms have characteristic conserved molecules on their surface, the pathogen-associated molecular patterns (PAMPs), which can be recognised by pattern recognition receptors (PRR). These receptors comprise soluble forms, such as collectins. Eight collectins have been identified so far, including the mannan-binding lectin (MBL) or the surfactant proteins (SP)-A and SP-D. Collectins play a key role in the first line of defence by binding to invading microorganisms and thereby enhancing phagocytosis by macrophages. The other groups of PRRs are the intracellular nucleotide-binding oligomerisation domain (NOD) proteins NOD1 and NOD2, which are involved in peptidoglycan recognition, and the transmembrane molecules, such as Toll-like receptors (TLRs), which directly mediate a cellular response after microbial exposure. The TLR signalling cascade is shown in figure 2. TLRs are the homolog to the Toll receptor in Drosophila flies. In total, 13 TLRs have been identified in mammals so far 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 (ROS). 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. The 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 interleukin (IL)-1 receptor-associated kinases (IRAK)1 and IRAK4 and the tumour necrosis factor (TNF) receptor-associated factor (TRAF)-6. This leads to activation of NF-κB and MAPK (JNK and p38), followed by the translocation of NF-κB and activator protein 1 to the nucleus and the upregulation of proinflammatory 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 interferon (IFN)-γ), is utilised by TLR3 and TLR4. TRIF forms a complex with TRAF-3 and subsequently activates the interferon regulatory factors (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, respectively. The dimers have different ligand specificity. Moreover, additional co-receptor molecules increase ligand sensitivity. Four different adaptor molecules exist: MyD88, TIRAP, TRIF and TRAM. This variety of adaptor molecules might allow

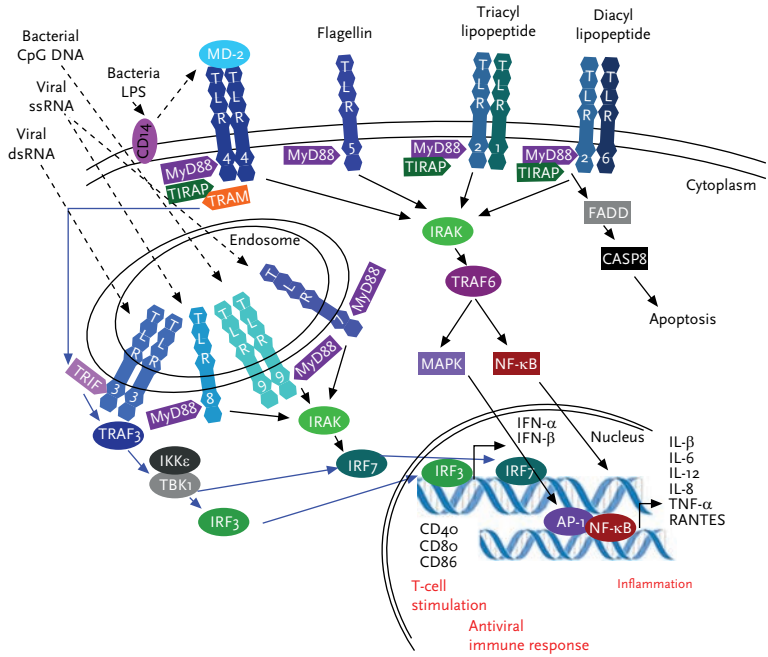

Figure 2. TLR signalling cascade. The myeloid differentiation primary response gene 88 (MyD88)-dependent pathway can be used by all TLRs except TLR3 (black arrows). The MyD88-independent pathway is utilised by TLR3 and TLR4 (blue arrows). RANTES: regulated on activation, normal T-Cell expressed and secreted; IRF: interferon regulatory factors; AP-1: activator protein-1; MAPK: mitogen-activated protein kinase; IKKε: IκB kinase-ε; TBK: TANK-binding kinase; FADD: Fas-associated death domain; CASP: caspase 8, apoptosis-related cysteine peptidase.

them to recruit different transducers, resulting in specific downstream signalling. For TLR4 signalling, CD14 faciliates the presentation of lipopolysaccharide (LPS) to MD-2, a co-receptor required for LPS recognition by TLR4.

The most studied TLR, TLR4, is the central component in response to LPS, a unit of the outer membrane of Gram-negative bacteria. TLR2 recognises a wide array of bacterial and fungal substances. Recently, TLR2 was described to also be 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 thought 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.

Antimicrobial factors Airway epithelial cells secrete large numbers of different molecules, which are involved in inflammatory processes. These molecules kill microorganisms, induce wound healing and angiogenesis, and orchestrate the adaptive immune response (fig. 1). The term AMP summarises a class of innate effector molecules of the lung, 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, whereas defensins and cathelicidins are the principal families found in the respiratory tract.

Defensins are highly structured compact peptides, classified into α- and β- subgroups depending on their folding. The α-defensin human neutrophil peptides (HNP)-1 to HNP4 are present on neutrophils and have a non-oxidative microbicidal activity. The β-defensins are widely expressed throughout the epithelia in order to avoid microbial colonisation. In general, defensins induce proliferation of the airway epithelial cells and are involved in wound repair. Cathelicidin, also called LL-37, displays a similar activity as defensins and attracts neutrophils, monocytes, activated mast cells and $CD4^+$ T-cells. 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 as a lytic to bacterial membranes whereas the antibacterial activity of lactoferrin is mediated by their iron-binding property. It holds iron, an element necessary for growth, away from the bacterial metabolism. The function of these antimicrobial substances in host defence has been proven in several animal experiments. For example, mice deleted in the LL-37 homologue CRAMP (cathelicidin antimicrobial peptide) showed an impaired defence against invasive bacterial infections. Moreover, AMPs play an important role in several lung diseases, such as pneumonia, chronic bronchitis or CF. In CF patients, AMPs might become inactivated as a result of the high salt concentration in the epithelial lining fluid. Moreover, AMPs show a concentration-dependent toxicity towards eukaryotic cells. In high concentrations, which have been described in CF and chronic bronchitis patients, AMPs contribute to exuberant inflammation, potentially through lysis of lung epithelial cells, induction of IL-8 production and restriction of defensin-induced cytotoxicity.

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.

The communication of alveolar macrophages with other immune cells is of great importance in order to launch an efficient immune response (fig. 1). Cytokines play a major role in pulmonary host defence, especially IL-10, IL-12, IFN-γ, granulocyte colony-stimulating factor (G-CSF) and TNF-α, the key mediator in recruiting polymorphonuclear leukocytes (PMLs) into the lung. Microorganisms that are resistant to the microbicidal activity require 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.

Neutrophil recruitment and enhancement of phagocytic defence The PMLs represent the largest population of intravascular phagocytes with greater phagocytic activity than alveolar macrophages. In response to inflammatory stimuli like 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 azurophil granules with the phagolysosome generates highly toxic antimicrobial compounds like chloramines and defensins, 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 (MIP)-2.

In summary, the innate immune system is crucial for an immediate defence against infection. However, this part of the immune system does not contain an immunological memory, which allows a fast and specific response in the case of a reinfection with familiar agents. This immunological memory is a key feature of the second, adaptive, part of the immune defence.

Adaptive defence mechanisms

Basic principles of adaptive immune defence 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 several respiratory tract infections. Besides T-cell mediated immune responses, the humoral and the mucosal immune system play a prominent role in the adaptive immune defence.

T-cell mediated immune response After T-cell 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 CCL21 (ligand) 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* MHCII (to the TCR), the co-stimulatory 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 for the induction of efficient immune responses. Subsequently, T-cell differentiation into effector T-cells and proliferation takes place. These effector cells operate with other cells, not with the pathogen itself.

T-cells can be roughly classified into the subpopulations of $CD4^+$ and $CD8^+$ T-cells. The $CD4^+$ T-cells consists of Th1, Th2, Tregs and the recently described subgroups Th17, Th22 and Th9 (fig. 1). Th1 effector cells support activation of macrophages and express cytokines, which induce a class switching to specific antibody classes. Th2 cells express B-cell activating effector proteins and secrete cytokines, regulating the class-switching which is responsible for anti-parasitic and allergic immune responses.

Tregs are relevant for keeping 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 hitherto known, and are essential for acute inflammatory processes through activating or recruiting neutrophils to the local infection. Th9 cells, previously 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 (fig. 1). The cytotoxic CD8 T-cells recognise and eliminate virus-infected cells by secreting cytotoxins such as perforin, granulysin and granzymes.

The humoral immune system response to infections consists of production of antibodies through plasma cells, which derive from B-lymphocytes, binding of the antibody to the pathogen and elimination through phagocytosis and molecules of the humoral immune system. For production of the antibodies, antigen-specific Th cells are important. B-cell proliferation and differentiation takes place in the T-/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 through the "heavy chains" of the isotype and antibody classes.

The secretory Ig, i.e. 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 Ig can be detected. Newborns already have a large amount of secretory (s)IgM and sIgA, directed against bacterial and viral pathogens and also against antigens, *e.g.* for anti-casein.

This antigen sensitisation takes place during intrauterine development, as there is no passage over the placenta. sIgA is the main Ig in the respiratory tract, while sIgM decreases during maturation. While IgM can efficiently agglutinate particulated antigens and make microbes more susceptible to phagocytosis, IgA is essential for binding of antigens without activating an inflammatory response. IgA (two subclasses: IgA1 (80% in the respiratory tract) and IgA2) protects against viruses and bacteria by inhibiting bacterial adherence, blocking toxins and neutralising viruses. The former is sensitive to bacterial proteases (*Streptococcus pneumoniae, Haemophilus influenzae* and *Neisseria meningitidis*). By binding IgA to antigens before transcytosis, it can additionally activate cells through binding to the Fc receptors. Two major mechanisms of IgA response exist, an innate, T cell-independent mechanism, which provides a first line of protection, and a T cell-dependent adaptive response, which takes longer to develop the high affinity antibodies. IgG is locally produced, binds subephithelial 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 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 through 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 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 function (*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. Thus, it is not surprising that the majority of severe infections worldwide are caused by invasion of pathogens through the mucosa. Approximately 4 million people worldwide die of acute respiratory infections every year. Besides pathogens, foreign, non-pathogenic antigens can invade, *e.g.* food proteins in the gastrointestinal tract.

The mucosal immune system probably contains 75% of all lymphocytes of the body and produces the majority of Ig in healthy individuals. Specific features of the mucosal immune systems are as follows.

- Anatomical: the interaction between mucosa-epithelium and lymphatic tissue, particularly components of the lymphatic tissue.
- Modulated effector-cell mechanisms: activated or memory-cells exist also without prior infection and nonspecific natural effector T-cells and Tregs are present.
- Immune regulation: an actively downregulated immune response, inhibitory macrophages and tolerance-inducing dendritic cells are present.

Some immune responses to antigen overload occur in the mucosa, induced by particular compartments of the mucosal immune system. Antigen intake and presentation, Microfold cells and especially dendritic cells are involved, while special "homing receptors" are relevant.

Pathogenic microorganisms use different strategies to invade the body, *e.g.* 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 of common airway microorganisms. As bacterial colonisation generally exerts a positive effect on humans,

there has to be ''coexisting, non-harmful'' 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 co-stimulation. Mostly, differentiation of Tregs occurs, which guarantees a healthy immune regulation. If pathogens invade, an inflammatory response is induced, activation of antigen presentation and co-stimulation 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 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 intrauterine development, is responsible for whether a child develops asthma or transient wheezing or stays healthy.

The most convincing results originate from epidemiological studies. Multiple cross-sectional and longitudinal studies have replicated the finding 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 the innate TLR-receptors, activation of Tregs seems to be essential as an important adaptive defence mechanism.

A further example is respiratory infections early in life, which can lead to subsequent protection or, conversely, 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 mechanism Defence against potentially harmful substances and pathogens is crucial for healthy development. As the development of the immune system occurs during the prenatal stage, the specific defence mechanisms of the lung are most probably already developed.

Prenatal period Prenatal 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 or 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 their interactions seem to influence this early immune response.

Regarding modulatory mechanisms of intrauterine 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 gestational age. 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

allo-antigens 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 the 15th and 20th week of gestation and can be antigen specific.

Post-natal period During this period, similar influences as 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 change 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 in the lymph nodes.

Regarding dendritic cells, age-dependent immaturity is associated with a decreased ability to react to inflammatory conditions. In children 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 occur depending on the type of infection, as other infections are rather protective against development of allergic airway inflammation.

In summary, early exposure to infections seems to influence 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.

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 these influences can occur prenatally and are the key for later immune and, potentially, disease development.

Taken together, the innate and adaptive immune system need to work efficiently individually, being closely connected to each other in order to provide 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 like allergies.

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Environmental determinants of childhood respiratory health and disease

Erik Melén and Matthew S. Perzanowski

Worldwide, exposure to second-hand smoke is one of the most common indoor pollutants and as many as 40% of children are regularly exposed. Adverse effects of long-term exposure to anthropogenic ambient air pollution on children's respiratory health are also well described, particularly in relation to asthma and lung function. In developing countries, biomass smoke from domestic fires for cooking and warmth constitutes a major source of air pollutants. Children are known to be more susceptible to hazardous airborne substances compared to adults, possibly because of their growing organs and tissues. In addition, children have higher ventilation per minute in relation to body size and often have higher physical activity compared to adults, which leads to relatively higher exposure. However, protective environmental factors have also been identified, such as farming and rural environments. Large individual variability in response to environmental factors exists, especially for allergen exposure, and genetic susceptibility may partly account for this (termed gene–environment interaction). This chapter will discuss the role of these major environmental determinants of respiratory health in children.

Key points

- Exposure to ETS, ambient air pollutants and biomass smoke increases the risk of respiratory disease (*e.g.* asthma and pneumonia) in children.
- Protective effects of certain exposures, such as farming lifestyle and some microbes, on asthma and allergy have been observed.
- Genetic susceptibility and co-exposure to several environmental factors contribute to an overall complex relationship between inhalant allergens and disease development.

Adverse effects of environmental exposures

Environmental tobacco smoke (ETS) There is ample evidence from both epidemiological and experimental studies that ETS has many negative effects on several organs in the body, including the respiratory system, through induction of oxidative stress, inflammation and tissue damage. If a child's mother smokes during pregnancy, the fetus is exposed to nicotine, carcinogens and other toxic substances that pass the placental barrier. Solely prenatal exposure, without subsequent post-natal exposure, is associated with a 60–70% increased risk of asthma in pre-school children, which underlines the importance of targeted preventive efforts. Post-natal ETS exposure has been convincingly associated with asthma and lung function deterioration in many studies.

Data from the World Health Organization (WHO) show that, on average, 40% of children aged 0–14 years are regularly exposed to ETS, with the lowest exposure in central and southern Africa (12%) and highest exposure in East Asia (67%). Children are considered to be at increased vulnerability to ETS-related health effects relative to adults because of heavy exposure

in the home by family members that is difficult to avoid. The global disease burden of ETS exposure in children is immense and the importance of preventive measures to reduce this exposure cannot be stressed enough. It has been estimated that 165 000 children aged <5 years die every year from lower respiratory infections caused by ETS exposure.

Anthropogenic air pollution Combustion of fossil fuels contributes both particulate matter (PM) (*e.g.* soot, non-volatile polycyclic aromatic hydrocarbons (PAHs)) and gases (primarily NO, NO_2, CO_2, SO_2, ozone, volatile PAHs) to indoor and outdoor air. PM_{10} and $PM_{2.5}$ (particles with a 50% cut-off aerodynamic diameter of 10 and 2.5 µm, respectively) constitute inhalable particulates and these are commonly measured in studies on respiratory effects from pollutants. Automobile exhaust (gases in particular), combustion processes and road dust (particulates) are the main sources of pollutants of interest for the respiratory system. Other chemical agents, such as phthalates commonly used in consumer products, can evaporate into food or the air and exposure to these agents has also been associated with respiratory symptoms.

Similar to ETS, ambient air pollutants may induce airway inflammation, increased airway responsiveness and lung damage, partly due to oxidative stress mechanisms. Both short- and long-term exposure has been associated with an increasing range of adverse respiratory outcomes, and air pollutants are well-known triggers for asthma exacerbations. Exposure to particles from diesel exhaust have also been linked to atopy, and experimental data support adjuvant effects of particles on IgE synthesis. However, conflicting evidence for air pollution being causative in the development of asthma and allergy persists.

There is evidence that adverse long-term effects of air pollution occur on lung function growth. A US study from California showed that children who lived within 500 m of a motorway had ~3% lower lung function, measured as FEV_1, compared to children living >1500 m from the motorway. Whether this growth deficit persists into later adulthood is not known. Exposure *in utero* and during infancy appears particularly harmful and studies report negative effects on lung function in infants, as well as in school-age children. Also in areas with relatively low air pollution levels such as Stockholm, Sweden, remarkably strong effects are seen in that children with the highest exposure during the first year of life are four to five times more likely to have poor lung function at school-age compared to low-exposed children, further supporting the relevance of air pollution to impaired lung development.

Biomass smoke Open domestic fires for biomass burning (wood, charcoal, crop residues, *etc.*) for cooking and heating are main sources of air pollutants in certain parts of the world (fig. 1). More than 2 billion people live in households in which biomass fuels are used regularly. Several studies show positive associations between asthma prevalence and biomass cooking indoors, but a recent meta-analysis did not provide reliable evidence of overall increased risk of asthma in children. However, many studies on biomass smoke effects suffer from limitations in study design, confounding control and low power, and further research in this area is warranted.

Figure 1. Open domestic fire for cooking and heating (image courtesy of J. Thacher, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; personal communication).

In contrast to effects on asthma, there is rather strong evidence that exposure to indoor air pollutants from cooking or heating is associated with pneumonia and acute lower respiratory infections in young children. A recent WHO meta-analysis concluded that indoor exposure increased the risk of pneumonia almost two-fold. From a population point of view, this is of utmost importance since pneumonias can be attributed to around half of all deaths occurring worldwide in children <5 years of age.

Allergens The role of inhalant allergen exposure in the aetiology of asthma and allergic sensitisation is complex, and our understanding of these processes has changed markedly during the last 30 years. It is now acknowledged that asthma and allergy are heterogeneous diseases and that overall, wide-spread generalisation about allergen exposure and disease development cannot be made. It is likely that genetics, phenotype diversity and large variations in the intensity and pattern of allergen exposure contribute to this complex picture. Nevertheless, sensitisation remains an important risk factor for asthma exacerbations and development of severe symptoms. In combination with an upper respiratory infection, exposure to a certain allergen in sensitised individuals may have detrimental effects. Asthma is rather common in urban, low socioeconomic families, and for "inner-city asthma", exposure to cockroach and dust mite allergens have more convincingly been associated with disease. A recent trial of anti-IgE among inner-city children in the USA found a decrease in seasonal exacerbation peaks (autumn and winter) typically associated with viruses, suggesting a complex relationship between allergic sensitisation, viruses and asthma exacerbations.

Role of protective environmental factors

The hygiene hypothesis Almost 25 years ago, the so called "hygiene hypothesis" was introduced suggesting that the decrease in infectious burden and microbial exposure during early life may have led to increased predisposition to allergy and asthma. Presence of older siblings in the home, day care attendance and certain infections (*e.g.* herpes or Epstein–Barr virus) early in life were reported to protect against the development of asthma in school-age children. From an immunological point of view, reduced activity of T-regulatory cells, which may lead to reduced immune suppression, has been emphasised as a basis for the mechanisms behind the hypothesis. As of today, recent data indicate, however, that the hygiene hypothesis only partly holds true, and that aetiological mechanisms are, after all, rather unclear.

Farming lifestyle One key component of the hygiene hypothesis, farming lifestyle, has consistently been associated with low prevalence of asthma and allergy in both low-income and high-income countries. Early animal contact at the farm and consumption of unpasteurised milk seem to be particularly important for the protective effect. In addition, children living on farms are exposed to a greater variety of environmental microorganisms (certain bacteria and fungi) compared to non-farming children and this diversity is inversely related to the risk of asthma. Visible mould and dampness in the home are, however, associated with increased risks of asthma and allergy.

The link between environmental exposure and genetic factors

Although smoking and exposure to certain air pollutants are established risk factors for respiratory diseases, not all individuals who are highly exposed develop diseases such as asthma. Thus, large individual variability in response to environmental factors exists, and genetic susceptibility (and epigenetics) may partly account for this. In this context, genes involved in the anti-oxidative system, inflammation and innate immunity have been a particular focus in studies of respiratory diseases. Variants in *IL13, GSTP1* and *TNF* have been shown to modulate the adverse effects of ETS on asthma risk and pulmonary function, and *CD14* variants are related to the risk for allergy related to domestic dust mite allergen exposure.

In addition, gene–environment interactions have been reported with both protective and adverse effects observed. For example, the dose-response to developing sensitisation to cockroach with increasing cockroach allergen exposure was observed to be greatest among children exposed to higher levels of PAHs and those with a deletion of *GSTM1* (involved in detoxification of PAH). However, convincing and reproducible interaction effects have been difficult to identify in large, well-characterised data sets, especially if genome-wide association study (GWAS) data were used. Further research is warranted in this area before we better understand the complex interplay between genes and the environment and certainly before clinical applications can be implemented.

Conclusion

There is good evidence that exposure to pollutants such as ETS, ambient air pollutants and biomass smoke increase the risk of respiratory disease in children. Protective effects of certain exposures, such as farming lifestyle and microbes, on asthma and allergy are also well described. Genetic susceptibility and co-exposure to several environmental factors contribute to an overall complex relationship between inhalant allergen exposure and disease development.

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History and physical examination

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Respiratory medicine, particularly in 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 proper history and physical examination. This section discusses basic issues of paediatric medical history and physical examination of the respiratory system, and briefly addresses the pathogenesis of physical findings. Lung sounds and specific signs and symptoms are addressed in separate sections of this chapter.

Key points

- Patient history is focused on the respiratory system and is adapted to patient circumstances (emergency situation, chief complaint, chronic problem, age, *etc.*); however, other pertinent organ systems should not be neglected and structure is important in order to avoid missing helpful clues.
- Respiratory physical examination of the chest includes inspection, palpation, percussion and auscultation. Nomenclature of lung sounds is a subject of considerable confusion.
- A structured physical examination of the chest, applied with flexibility in paediatric patients, including the upper respiratory system, evaluation of cyanosis, the digits and other pertinent organ systems, is fundamental to the evaluation of the respiratory patient.

Medical history

Patient history in 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 further obscured. The chaotic use of terms for respiratory signs and symptoms, such as "wheezing", adds to the confusion. Nevertheless, useful information may be obtained from children as young as 3 years of age and 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 (Bickley *et al.*, 2013).

The physician should ask open-ended questions and, depending on the complaint, further questioning will focus on and expand specific points. Still, a general structure of the required information needs to be kept in mind in order to cover all the issues relevant to the presenting illness. Such structure should include the major concern that prompted consultation (chief complaint) and a chronological description of the problem. Clarification of its onset, frequency, timing, duration and severity, relation to specific circumstances, and response to medication already used should be sought. Other relevant signs and symptoms need to be investigated and previous assessments and laboratory results reviewed. Past medical history, especially that of the respiratory system, is important. Recurring or persistent respiratory problems, emergency visits,

hospitalisations, surgery, vaccination status, and pre-, peri- and neonatal circumstances including prematurity, mode of delivery, birth weight, *etc.* 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 aforementioned issues.

Chief complaint and past medical history 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 expression "not all that wheezes is asthma" holds true, but then again, "not all that wheezes is a wheeze". Regarding cough, it is important to clarify whether it is dry and irritating, or whether it sounds wet (or productive, if the child can produce sputum); also, if it is often accompanied by wheeze. Cough-variant asthma, if existent, is unusual and chronic (>4 weeks duration) wet cough is the most common presentation of persistent (protracted) bacterial bronchitis, an "out-of-fashion paediatric diagnosis revisited" that may require more extensive investigation.

In the case of diagnosed asthma, a questionnaire-based clinical scoring system such as the Children's Asthma Control Test (C-ACT), which has been validated for children aged 4–11 years, is useful in the evaluation of asthma control. C-ACT uses information from the child (four questions, including a visual scale) and the parents (three questions); the score is based on daytime asthma symptoms such as cough and wheeze (also during exercise and play), night awakenings due to asthma, and parental report of disease activity during the last 4 weeks.

If a diagnosis of asthma cannot be made with reasonable certainty, further probing may be in order. What was the reason that prompted specialist consultation? Was the onset of wheeze and/or cough acute or progressive? Was it related to viral cold (coryza) or a sudden episode of choking while eating or playing with small objects, thus suggestive of aspiration?

Viral infections in young children are the most common cause/trigger of such symptoms; six to eight colds per year, mostly during the colder 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, if so, in what respect. In addition, what is its duration and that of similar previous episodes? Are they only triggered by colds (viral wheeze) or are there other triggers such as laughter, exercise, strong odours, aeroallergens, *etc.* (multiple-trigger wheeze)?

Cough and wheeze after exercise are associated with airway hyperresponsiveness; intolerance to exercise, poor feeding and oedema are consistent with CHF.

Do the episodes occur during night sleep and, if so, do they wake up the child? Seasonality of symptoms (viral or pollen season) and evidence of eczema, allergic rhinitis and/or allergic sensitisation should be addressed.

Does the child vomit and does vomiting always come after coughing, or is it related to meals and the recumbent position (*i.e.* reminiscent of gastro-oesophageal reflux)?

Have inhaled medications been used and does any medical (or other) intervention appear helpful? If the patient is already on medications, their compliance should be evaluated. 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 these, information on stool consistency should be sought and the diagnosis of CF considered.

Knowledge of the duration of pregnancy is important, as are the circumstances at birth (including birth weight and Apgar scores) and during the neonatal period. History of prematurity, intubation, mechanical ventilation, or prolonged oxygen dependence and corrected oesophageal atresia with or without a tracheo-oesophageal fistula is crucial for interpreting the child's respiratory symptoms in later years; the diagnoses of chronic lung disease of prematurity, subglottic stenosis, tracheomalacia and gastro-oesophageal reflux need to be considered accordingly. History and duration of breastfeeding, gastro-oesophageal reflux, and problems of poor feeding or failure to thrive should be addressed.

Chief complaints such as cyanotic episodes, hoarseness, stridor, snoring and/or apnoea, haemoptysis, chest pain, *etc.* will require further specific probing by the respiratory specialist (see the relevant sections of this chapter).

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 positivity or TB.

Environmental history can be quite revealing. Exposure to indoor tobacco smoke, wood stove heating or gas cooking can trigger asthma exacerbations and predispose to poor respiratory health. Questions should address exposure to other inhaled irritants and the presence of pets and indoor plants. Wall-to-wall carpets, an aged dwelling environment or renovation may be important contributors to the child's symptoms. This also holds true for exposure to outdoor air pollution.

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

Physical examination

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

The issue of allergy often arises in the presence of airway disease (*e.g.* asthma). 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, a constantly open mouth – often associated with a history of snoring and, in more severe cases, with sleep apnoea – and a high arched palate identify children with upper airway obstruction (rhinitis and enlarged lymphoid tissue) but not necessarily of allergic aetiology. Evidence or history of eczema is also helpful.

Chest The patient's chest should be exposed and inspected for congenital or acquired deformities (*e.g.* pectus excavatum, pectus carinatum, kyphoscoliosis). During inspection – indeed, throughout the entire physical examination – the two sides of the chest are compared. Hyperinflation of the thorax (*e.g.* air trapping due to asthma or

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 also 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 (see Tachypnoea, dyspnoea, respiratory distress and chest pain). In chronic obstruction, the Hoover sign may be observed. It consists of (untoward) indrawing of the lateral chest during inspiration at the level where the diaphragm attaches to the ribcage. It is associated with an outward movement of the lateral ribs caudally to this level and is caused by the reduction of the zone of diaphragm–chest wall apposition. It may be associated with the loss of the bucket-handle movement of the ribs of the barrel-shaped chest and with the exaggeration of pump-handle movement about the longitudinal axis of the body. However, it does not reliably reflect the degree of obstruction.

Palpation of the chest usually follows that of the head and neck. It 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 can be evaluated and asymmetrical movement can be identified by placing the palms of both (warm) hands in a manner ''wrapping'' the child's chest symmetrically, with the thumbs placed posteriorly and the rest of the fingers anterior. The physician ''follows'' the chest excursions during breathing with his hands, comparing the two sides by observing the movement of the thumbs away from the midline.

Vibrations generated by the voice and felt with the palm of the hands or the base of the fingers, *i.e.* tactile fremitus, 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'' (equivalent vocalisations should be used in other languages), rather loudly will result in increased tactile fremitus in the case of parenchymal consolidation (*e.g.* pneumonia) and attenuation of the tactile fremitus in the case of pneumothorax and pulmonary distension (air trapping). Pleural friction rubs may also be noted.

Since its initial description two and a half 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 materials such as tissues. Thus, by interpreting the acoustic result of an impulse, one can draw conclusions about the bordering 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 small 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. Between these two extremes are the characteristics of the sound produced by chest percussion over normal lung parenchyma. Most paediatricians use the indirect method of percussion, whereby they tap lightly, vertical to the surface, with the long finger of one hand (plexor), two or three times in each position, on the terminal phalanx of the middle finger of their other hand (pleximeter), which is placed over an intercostal space. The chest is percussed symmetrically.

Since the respiratory system is the most frequently affected organ system in paediatric practice, 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.

To have infants assume a straight position and young children cooperate for proper auscultation is an art; still, it may not always be possible to listen adequately over all 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.

To date there is no definitive nomenclature of lung sounds. In this section, the terminology of the CORSA (Computerized Respiratory Sound Analysis) guidelines is adopted (Sovijärvi *et al*., 2000); terms used by other authorities or popular among physicians are also mentioned.

Respiratory sounds are related to chest air movement, either 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 (or otherwise detected) over the chest.

(Normal) breath sounds are respiratory sounds that arise from breathing, excluding adventitious sounds. They consist of the following.

- Vesicular breath sound (a misnomer, as it does not originate in vesicles, *i.e.* the alveoli) is a quiet, low-frequency, nonmusical sound. Its energy peaks below 100 Hz and decreases rapidly between 100 and 200 Hz, but is still audible above 1000 Hz. It is auscultated over the chest during inspiration and hardly audible during normal expiration.
- Bronchial sound is auscultated over the upper anterior chest wall, of higher frequency and intensity than vesicular sound and of approximately equal duration in inspiration and expiration.

Normal breath sounds are characterised by a broad frequency spectrum that ranges according to the location of auscultation. Tracheal sounds are heard over the extrathoracic trachea. They are broad-spectrum noises with frequency spectra from $<$100 to $>$1500 Hz and a rapid power decrease at ~800 Hz. They have a short inspiratory and long expiratory duration. Muscle sounds are low-frequency ($<$20 Hz), low-intensity sounds related to the contraction force of thoracic skeletal muscles that mesh into the normal breath sound spectrum. Often, the terms ''respiratory sounds'', ''breath sounds'' and ''lung sounds'' are used interchangeably. This is also the case with the terms ''vesicular sound'' and ''normal breath sound'', and with the terms ''bronchial sound'' and ''tracheal sound''. In fact, the sound described here as ''bronchial'' is termed ''bronchovesicular'' (intermediate between tracheal and vesicular) in certain textbooks (Brown *et al*. 2008; Bickley *et al*., 2013), while the terms ''tracheal sound'' and ''bronchial sound'' are used interchangeably.

Adventitious sounds are additional sounds superimposed on normal breath sounds; they are usually associated with pulmonary disorders. Adventitious sounds are primarily divided into continuous (musical or wheezes) and discontinuous (nonmusical or crackle) sounds.

Wheeze is the respiratory sound term most widely used by physicians and the general public, albeit with dismal specificity. It is characterised by periodic waveforms (continuous, of musical quality) with a dominant frequency $>$100 Hz (range $<$100 to $>$1000 Hz) and duration $\geqslant$100 ms. However, the term usually implies a dominant frequency of $>$300 to 400 Hz. Lower-frequency wheezes have different

pathogenesis and are often termed rhonchi (see later). In general, wheezes are louder than breath sounds and may be audible at the patient's mouth or at a distance. They are better transmitted through the airways rather than through the lung to the thoracic surface and their higher frequencies (approximately >700 Hz) are better or solely transmitted over the trachea. Wheeze is of great clinical value as it is usually associated with airway obstruction due to various mechanisms (*e.g.* bronchoconstriction, airway wall oedema, intraluminal obstruction such as a foreign body, external compression or dynamic airway collapse). Prediction models (the fluid dynamic flutter theory) have shown that expiratory wheeze always signifies flow limitation, while its absence does not preclude flow limitation (Grotberg *et al.*, 1989). Healthy subjects can wheeze during forced expiration, probably due to the aforementioned mechanism. However, the mechanism of generation of inspiratory wheezes, which are often associated with more pronounced obstruction, is not clear. In addition, wheeze may be produced by turbulent flow-induced airway wall vibration, without flow limitation (Pasterkamp *et al.*, 1997). Notably, there is a loose correlation between the proportion of wheeze detected throughout the respiratory cycle and the severity of obstruction, but there is no correlation between wheeze intensity and the degree of obstruction. It should be remembered that wheezing is not a parameter of the clinical scores of asthma, croup or bronchiolitis. The classification of wheeze into mono- and polyphonic is addressed in a separate section of this chapter, as is stridor, which is a loud, usually inspiratory, continuous sound that, other than being heard at the mouth or at a distance, can be auscultated over the chest wall.

Rhonchus (plural: rhonchi) is a low-pitched, continuous (musical) sound that consists of rapidly dampened sinusoids (frequency <300 Hz, duration >100 ms). Rhonchi are generated by intraluminal secretions and collapse of large airways. However, the term 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", see below).

Crackles (other terms in use are "crepitations" or "rales") are adventitious, discontinuous (nonmusical) sounds, usually auscultated during inspiration, that represent local phenomena. Crackles are classified according to their waveform, duration and timing in the respiratory cycle. Fine crackles (subcrepitant crackles) are characterised by high pitch, low intensity and short duration (two-cycle duration (2CD) <10 ms). They are caused by the explosive opening of small airways collapsed by surface forces (increased elastic lung recoil pressure or inflammation/oedema in the lung); they are gravity dependent and the sound is rarely transmitted to the mouth. Fine, late inspiratory crackles are typical of interstitial/fibrotic lung disease. However, they may also be present in normal subjects who inhale slowly from their residual lung volume, which can be explained by the mechanism already described. Coarse crackles (crepitant crackles) are low-pitched, higher intensity and longer duration sounds (2CD >10 ms); they are more scant, gravity independent and usually audible at the mouth. They are generated by a different mechanism to that of fine crackles, *i.e.* movement of thin secretions in the bronchi or the bronchioles. They start early and continue until mid-inspiration but may be heard during expiration. A typical example of coarse crackles can be heard in bronchiectasis and chronic airway obstruction (*e.g.* CF). Similar auscultatory findings can be found focally early in pneumonia but shift into more end-inspiratory crackles of variable duration that progress to fine crackles during recovery. Acoustic analysis has characterised the crackles of cardiac failure as coarse, of long duration during inspiration and appearing late in the course of the disease (Brown *et al.*, 2008; Pasterkamp *et al.*, 2012).

Other adventitious sounds are squawk and the pleural friction sound. A squawk (sometimes classified as a type of wheeze)

is a ''composite'', short (50–400 ms), inspiratory adventitious sound with a musical character (short inspiratory wheeze) that is preceded by a crackle. It is not associated with airway obstruction but rather with pulmonary fibrosing (restrictive) disease. It is thought to result from the vibrations set in motion by the sudden opening of a collapsed airway. Pleural friction sound (or friction rub) is coarse crackles (often described as ''leathery'') produced by inflamed parietal and visceral pleura that cause vibration of the chest wall and local pulmonary parenchyma. It can be auscultated during inspiration or in both phases of breathing. Pleural friction precedes pleural effusion and disappears when fluid is formed. The ''rub'' is synchronous with breathing and does not disappear with cough, but is modified by the breathing pattern and posture (Brown *et al*., 2008; Bickley *et al*., 2013).

Voice transmission is filtered by normal lung parenchyma so that speech becomes indistinct (*i.e.* perceived as an incomprehensible mumble) when auscultating the chest. When there is underlying consolidation or compression, higher frequencies are effectively transmitted. Thus, normally spoken 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'' sounds to ''A''. Whispered pectoriloquy is an unusually clear transmission of whispered sounds during auscultation in the case of severe consolidation or compression.

Cyanosis and clubbing Examination of organ systems beyond the respiratory system should be performed as deemed necessary. Inspection of the skin and mucosa for cyanosis is obviously important, and the fingers should be evaluated for digital clubbing.

Cyanosis is the bluish-purple discoloration of the skin or the mucosa caused by high concentrations of reduced Hb in the capillary bed and the subcapillary venous plexus. Ideally, cyanosis should be evaluated in daylight in a comfortably warm environment. The peripheral perfusion of the patient should be taken into account. The detection of cyanosis is influenced by various factors such as type and intensity of light, skin pigmentation, and ambient temperature. Central cyanosis is sought at the ear lobes, the mucous membranes (buccal, tongue and nasal) and the retina. It is considered to be reliable evidence of hypoxaemia. Peripheral cyanosis or acrocyanosis (circumoral, or in the distal phalanges of fingers and toes) is more common and, especially in case of cold extremities, does not necessarily imply hypoxaemia. Tissues with increased oxygen consumption or reduced blood flow (increased arteriovenous oxygen difference) are prone to high concentrations of reduced Hb; hence, the poor clinical value of peripheral cyanosis in evaluating arterial oxygen content (Stack, 2005).

The value of reduced Hb in the capillary bed required for cyanosis is 4–6 $g \cdot dL^{-1}$, which corresponds to 3 $g \cdot dL^{-1}$ of reduced Hb in arterial blood. Capillary blood oxygen content is postulated to be halfway between the arterial and the venous values. Depending on the Hb content, cyanosis will occur at different levels of S_aO_2: for Hb 8 (anaemia), 14 (normal) and 20 $g \cdot dL^{-1}$ (polycythaemia), the respective S_aO_2 that is necessary for cyanosis is 65%, 78% and 85%. In the newborn, 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 (West, 2008). 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, and 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 P_aO_2 or, more readily, S_pO_2. Pulse oximetry is an invaluable clinical tool, considered by some as the fifth vital sign. Nevertheless, the possibility of abnormal Hb (*e.g.* carboxyhaemoglobin or methaemoglobin) should be taken into

Table 1. Differential diagnosis of cyanosis

Severe decrease of air entry	
Congenital malformations (may present as emergencies in the neonate)	Choanal atresia Supraglottic fusion of the larynx "Complete" laryngeal web Laryngeal cyst Cricoid ring dysplasia Vocal cord paralysis Vascular ring (usually presents later) Mediastinal cyst/mass Oesophageal atresia ± tracheo-oesophageal fistula Large bronchogenic cyst Congenital cyst adenomatoid malformation Congenital lobar emphysema Lung hypoplasia/agenesis Pneumothorax (due to rupture of cyst) Lymphangiectasia/chylothorax Congenital diaphragmatic hernia Severe thoracic dysplasia
Airway obstruction	Severe croup Foreign body Angio-oedema Retro-, parapharyngeal abscess Neck mass Asthma Bronchiolitis Chronic lung disease of prematurity CF Severe aspiration
Lung compression	Large pneumothorax (especial under tension) Pneumomediastinum Haemothorax Large space occupying lesion (congenital or acquired) Pleural effusion Prominent abdominal distention
Anatomical or functional abnormalities of the thoracic cage	Severe chest wall deformity Flail chest Diaphragmatic paralysis Neuromuscular disease (Guillain–Barré syndrome, botulism, poliomyelitis, diaphragmatic paralysis) Myopathy (muscular dystrophy, myasthenia gravis, Werding-Hoffman) Hypokalaemia Organophosphate poisoning

Table 1. Continued

Disorders of gas exchange (V'/Q' mismatch, dead space ventilation, alveolar-capillary block)	
Peripheral airway obstruction	Bronchitis Bronchiolitis Pneumonia Chronic lung disease of prematurity CF Exacerbation of severe bronchiectasis
ARDS	
Aspiration (from above or below)	Gastro-oesophageal reflux Swallowing dysfunction Congenital anomalies (laryngeal cleft, tracheo-oesophageal fistula) Meconium aspiration
Atelectasis	
Interstitial lung disease/pulmonary fibrosis	
Pulmonary oedema	CHF Smoke inhalation Chemical pneumonia High altitude
Idiopathic pulmonary haemosiderosis/ Heiner syndrome	
Pulmonary embolus	Rare in children (dyspnoea/respiratory distress and hypoxaemia are disproportionately severe to the auscultatory and chest radiography findings)
Cardiovascular disorders	
Cyanotic congenital heart disease	Transposition of the great arteries (variations) Tetralogy of Fallot Pulmonary atresia with ventricular septal defect Double-outlet right ventricle (variations) Total anomalous pulmonary venous return Tricuspid atresia Ebstein anomaly of the tricuspid valve Truncus arteriosus
CHF (cardiogenic shock)	Cardiovascular pump failure (myocarditis, arrhythmia, post-operative complication, metabolic disorder, drugs)
Right heart failure/pulmonary hypertension/ PPHN	
Restrictive pericarditis/myocarditis/ endocardial fibroelastosis/atrial myxoma	Pneumo- and haemopericardium (tamponade) are emergent situations
Inefficient tissue oxygenation	
Polycythaemia/HbF	Favour cyanosis

Table 1. Continued

Methaemoglobinaemia	Hereditary (HbM, Hb reductase deficiency) Acquired (aniline dyes, nitrites, nitrates, drugs: dapsone, nitroglycerine, benzocain, sulfonamides, *etc.*)
Shock	Haemorrhage Sepsis Cardiogenic Adrenal insufficiency
CNS irritation or depression	
Seizures	
Meningitis/encephalitis	
Cerebral oedema	
Haemorrhage	Intracerebral Subdural Subarachnoid
Drugs/toxins	Anaesthetics Narcotics Sedatives Spasmolytics
Peripheral cyanosis	
Vasoconstriction	Exposure to cold Drugs Autonomic nervous system disturbances (Raynaud phenomenon *etc.*)
Hypoperfusion	Clot Post-traumatic Vasculitis DIC Venous blood stasis
Skin colour	
Blue hues	
Blue-tinged skin lesions	Extended ectasia of the subcapillary venous bed Venous stasis Blood extravasation
Drugs	Amiodarone Silver toxicity
Other causes	
Breath hold	Infants and young children
Cry	
Hypoglycaemia	Infants
Familial dysautonomia	

V': ventilation; *Q'*: perfusion; ARDS: acute respiratory distress syndrome; PPHN: primary pulmonary hypertension of the newborn; CNS: central nervous system; DIC: diffuse intravascular coagulation.

account in the interpretation of the pulse oximetry reading (Fouzas *et al*., 2011). Table 1 presents the differential diagnosis of cyanosis/hypoxaemia.

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 (Pasterkamp, 2012):

- 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;
- the inversion of the phalangeal depth ratio, *i.e.* the ratio of the distal phalangeal diameter (measured most accurately by calliper at the level of the eruption of the nail) over the interphalangeal diameter (measured at the crease between the two distal phalanges) is >1 in clubbing instead of the normal <1 ratio;
- 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° as compared to the normal <180° value.

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

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Cough

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Cough is the most common symptom of airway lung disease. It is also a frequent reason for which medical advice is sought. Cough is an important physiological protective reflex that clears airways of secretions and inhaled or aspirated material. The importance of cough in maintaining respiratory health is evident in clinical situations where the cough is ineffective (*e.g.* generalised muscular weakness, tracheobronchomalacia and laryngeal disorders). When these conditions exist, atelectasis or collapse from retained secretions and recurrent pneumonia occur frequently. As a symptom, it is nonspecific and many of the potential causes in children are different from those in adults (Gibson *et al.*, 2010; Chang *et al.*, 2007).

Key points

- Cough has different major overlapping constructs based on duration, inflammation type, phenotype or clinical syndromes.
- It is not logical to try to suppress a cough that has a protective role.
- It is important to try to make a diagnosis and treat the underlying cause of cough. Potential causes in children are different from those in adults.
- There is little evidence that either nonspecific isolated cough or post-infectious coughing respond to any currently available treatment.
- There is good evidence that children with protracted (persistent) productive (moist or wet) cough benefit from treatment with antibiotics to cover the organisms associated with protracted bacterial bronchitis.

The cough reflex pathway involves cough receptors, mediators of sensory nerves and an afferent pathway, the vagus nerve, the cough centre, an efferent pathway, and the effectors. Cough has three defining features:

- an initial deep breath,
- a brief, powerful expiratory effort against a closed glottis, and
- opening of the glottis with closure of the nasopharynx and vigorous expiration through the mouth.

Within this definition, there are several variants. The act may be: a single deep inspiration followed by a single glottic closure interrupting an almost complete expiration near to residual volume; the same as this but with multiple glottic closures during the single expiration; or a ''bout'' of coughing, with each expiratory effort either completed or partial. Other acts, such as the ''huff'' of clearing the throat and the expiratory effort with glottis closure due to touching the vocal folds or trachea (the ''expiration reflex'') are, by definition, not cough but may be fragments of a cough (Widdicombe, 2003).

Cough can be initiated from the larynx, including its supraglottal part, from the trachea and from the larger bronchi. Irritation of the smaller bronchi, the bronchioles and the alveoli does not seem to cause effective cough because the luminal airflows and velocities would be too low to

have shear forces adequate to clear airway mucus and debris. Cough sound is due to vibration of larger airways and laryngeal structures during turbulent flow in expiration. Rheological properties of mucus and shearing of the secretions from the airways influence cough sound.

Causes

Cough has different major overlapping constructs based on:

- duration (acute, subacute or chronic),
- inflammation type (neutrophilic, eosinophilic, lymphocytic or neurogenic) or
- clinical syndromes (*e.g.* acute bronchitis, laryngotracheobronchitis, protracted bacterial bronchitis or aspiration bronchitis).

Although the inflammation classification may be useful in defining treatment (especially in eosinophilic bronchitis), phenotypic descriptions and clinical syndromes are usually used in the clinical arena. The characterisation of these clinical syndromes related to cough is dependent on many factors including the duration of cough (acute *versus* chronic), the setting (*e.g.* affluent *versus* less developed), selection criteria of the children studied (*e.g.* general practice *versus* specialist clinics), follow-up rate, depth of clinical history, examination and investigations performed (Chang, 2011). For example, bronchiectasis (a condition causing susceptibility to airway infection) is more common in places like Turkey than in Italy, and a child with bronchiectasis may be not correctly diagnosed unless followed up with a chest CT scan.

The common causes of acute and chronic cough in children are presented in tables 1 and 2. In addition to the many aetiologies of cough, there are also exacerbation factors, such as air pollution. The ascribed possible underlying aetiologies of chronic cough have a very wide spectrum that ranges from acute cough related to a viral infection, to chronic cough from nonspecific cough (that is more likely to resolve spontaneously), to serious causes such as foreign bodies in the airways and bronchiectasis. Not surprisingly, different centres report highly variable aetiologies (Chang, 2008) that are probably

Table 1. Common causes of acute cough (<2 weeks duration)

Associations or characteristic	Additional comments
Infection related	
Upper respiratory dominant	A large number of viruses can cause acute bronchitis May be associated with common cold, otitis media, sinusitis or pharyngitis
Croup	Stridor
Pertussis	Usually paroxysmal ± post-tussive vomiting In younger children, whoop may be present
Pneumonia	Tachypnoea ± dyspnoea and fever
Environmental	
Acute exposure to toxicants	For example, exposure to burning debris and other chemical pollutants
Others	
Foreign body inhalation	History of choking
Acute asthma	History and symptoms of asthma

This is not an exhaustive list. Any pathogen that infects the respiratory tract can cause bronchitis and this includes opportunistic pathogens, fungi and helminths. All the causes of chronic cough in table 2 can present as acute cough. Nonpulmonary conditions (*e.g.* acute leukaemia or cardiac failure) can also present with acute cough.

Table 2. Common causes of chronic cough (>4 weeks duration)

Associations or characteristic	Additional comments
Conditions where other symptoms and signs are mostly absent (nonspecific cough)	
Mycoplasma	
Pertussis	In the acute phase, cough is usually paroxysmal ± post-tussive vomiting In younger children, whoop may be present
Post-infectious cough	Cough that naturally resolves without treatment
Habitual tic (psychological)	
Early phase of specific cough	
Wet or productive cough	
Protracted bacterial bronchitis	Chest radiographs usually show only peribronchial thickening Tracheomalacia may co-exist especially if recurrent
Chronic suppurative lung disease or bronchiectasis	
Recurrent small volume aspiration	Many children have a neurodevelopmental problem as well but its absence does not indicate absence of recurrent aspiration
Other conditions where other symptoms and signs are mostly present (specific cough)	
Asthma	Dyspnoea with exertion Wheeze
Foreign body inhalation	History of choking

This is not an exhaustive list. Other less common conditions include the entire spectrum of lung disease, such as interstitial lung disease and plastic bronchitis, and other conditions external to the respiratory tract, such as cardiac disease, ear disease, gastro-oesophageal reflux and OSA; in the last two conditions, debates still exist as to cause and effect. Both the US (Chang *et al*., 2006b) and Australia/New Zealand (Chang *et al*., 2006a) guidelines classify chronic cough as duration >4 weeks but the British Thoracic Society (Shields *et al*. 2008) uses a duration of >8 weeks. The duration used in other European countries varies. For example, the Belgian guideline defines prolonged cough as a daily cough lasting for >3 weeks (Leconte *et al*., 2008).

(at least in part) related to inherent difficulties in studying chronic cough (Chang, 2011). Some of these are outlined here.

The most clinically important air pollutant in childhood bronchitis is tobacco smoke. Systematic reviews have described the link between cough and air pollution, both indoors and outdoors (Laumbach, 2010). It is increasingly appreciated, in human and animal studies, that environmental pollutants may have additive effects and influence the respiratory apparatus directly as well as indirectly, such as through the immune system and neural pathways. However, irrespective of exposure, cough should not be simply ascribed to pollutants such as environmental tobacco smoke (ETS) exposure. Cohort studies on children with chronic cough have shown that cough resolution was still achieved in children exposed to ETS (including a cohort with high exposure rates (56%)) (Asilsoy *et al*., 2008; Marchant *et al*., 2006b). This suggests that, while ETS is undoubtedly associated with increased coughing

illnesses and an important contributing factor, ETS alone is not the sole aetiology.

Defining causes and ascribing aetiologies In the interpretation of studies that describe cough aetiology, clinicians need to be cognisant of several key points. Firstly, clinicians should be aware of the "time-period" effect. The time-period effect, described Evald *et al.* (1989), refers to the spontaneous resolution of cough with time. Secondly, the placebo effect is as high as 80% in cough studies (Eccles, 2002). Hutton *et al.* (1991) described that "parents who wanted medicine at the initial visit reported more improvement at follow-up, regardless of whether the child received drug, placebo, or no treatment". Thus, in non-randomised controlled trial cough studies, the time factor and *a priori* definition of what constitutes an improvement in cough needs to be predetermined. Studies that do not predefine these have limited validity. Just by seeing a doctor who takes an interest in the child's cough, the cough score and quality of life improves before treatment (Marchant *et al.*, 2006a). Thirdly, studies that do not use validated outcome measures for cough research require scrutiny in light of the above. A small reduction in cough scores in association with a medication given does not mean that the treatment for the assumed aetiology is the true cause of the cough. The small change may be related to the variability of the test itself. Also, paediatric cough-related issues, like most other conditions, particularly in young children, share similarities but also have substantial important differences when compared to adults. Thus, publications on clinical issues of cough in adults may not be applicable in children (Chang, 2011).

Management

It is not logical to try to suppress a cough that has a protective role (see earlier). It is important to try to make a diagnosis and treat the underlying cause (*e.g.* asthma, CF and non-CF bronchiectasis).

Acute cough In upper respiratory tract infection with bronchitis, cough usually lasts more than 2–3 weeks in 10% of normal children. Provided the child is otherwise well with no pyrexia, tachypnoea or crackles, it is likely best to wait for resolution as aetiology is most often viral. There is limited evidence that any therapy is beneficial.

- Erythromycin is useful for early pertussis cases.
- Honey medications and vapour rub may reduce the severity of acute cough.
- Antibiotics may be beneficial for acute bacterial bronchitis but most bacterial cases resolve naturally anyway.

An inhaled foreign body is a possibility when there is a sudden onset of cough with no upper respiratory tract infection or after a choking episode; bronchoscopy is needed to remove the foreign body. In allergic rhinitis and post-nasal drip syndrome (throat-clearing type cough), intranasal steroids and/or antihistamines may be beneficial.

10% of normal children with acute cough due to upper respiratory tract infections are still coughing 3–4 weeks later. Some children with a "post-infectious cough" (prolonged acute coughing after an obvious upper respiratory infection) cough for much longer and this is especially true for those with pertussis (Hay *et al.*, 2005). Providing the child is otherwise well, waiting for a period of time allows natural resolution of post-infectious coughing and pertussis to occur.

Do not use a wait-and-see approach if there is:

- weight loss,
- night sweats,
- haemoptysis,
- sudden-onset cough or cough after a choking episode,
- coughing is relentlessly progressive (*e.g.* TB, expanding intrathoracic mass, retained foreign body, collapsed lobe or pertussis), or
- the child has a clinical history of symptoms or signs (or are at risk) of underlying chronic lung disease (*e.g.* finger clubbing, barrel-shaped chest, Harrison's sulci, recurrent pneumonia and immunodeficiency).

Chronic cough The underlying principle for the management of chronic cough is to make the correct diagnosis and manage the underlying condition. Remove child from ETS or other pollutant exposure. Children started on ACE inhibitors may have a dry cough, which stops with medication withdrawal.

Chronic cough is very common and often there are no pointers to a specific diagnosis (*e.g.* normal chest radiograph, normal lung function and dry isolated cough in otherwise well child). In such cases often a "trial of treatment" is used to confirm a diagnosis as it is neither feasible nor desirable to extensively investigate all such children. However, it is important to realise that natural resolution typically occurs with the passage of time and, therefore, a response to treatment must not be taken as confirming a diagnosis. Children responding to a trial of therapy should have the treatment stopped and only a second clear-cut response should be used to suggest a diagnosis.

There is little evidence that either nonspecific isolated cough or post-infectious coughing responds to any currently available treatment (inhaled corticosteroids (ICS), β_2-agonists, leukotriene antagonists, anti-gastro-oesophageal reflux therapy, cromones and environmental modification). Most of these coughs resolve naturally but over a considerable period of time. Ultra-high-dose ICS may have a small benefit but the side-effects seem to outweigh the benefits.

There is good evidence that children with protracted or persistent productive (moist or wet) cough benefit from treatment with antibiotics to cover the organisms associated with protracted bacterial bronchitis (*e.g. Haemophilus influenzae*, *Pneumococcus* and *Moraxella*), such as co-amoxiclav (Chang *et al.*, 2008). It is important that a full 14-day course is given and, sometimes, a prolonged course is needed for 4–6 weeks along with intensive physiotherapy before the persistent endobronchial infection is eradicated. A positive response to a full course of an appropriate antibiotic and the child returning to completely good health confirms the diagnosis. Failure to respond or other features of chronic disease should trigger further investigations as to an underlying cause, such as:

- persistent bacterial bronchitis,
- CF,
- immune deficiencies,
- primary ciliary disorders,
- recurrent pulmonary aspiration, or
- retained inhaled foreign body.

Care needs to be taken, especially in children with neurological or neuromuscular disabilities, to ensure dysfunction of swallowing and gastro-oesophageal reflux is treated to prevent recurrent pulmonary aspiration.

Psychogenic or habit coughing can be difficult to treat if there is some secondary gain associated with an underlying stressor and psychotherapy may be needed. More often behavioural therapies can be employed to empower the child to be able to resist the urge to cough on his/her own (*e.g.* the child takes a sip of hot lemon drink with each urge to cough)

Conclusion

The approach to a child with problem coughing involves firstly trying to arrive at a specific diagnosis (after taking history, examination and performing relevant tests) and using targeted treatments. Nonspecific isolated coughing in an otherwise well child may not need treating if natural resolution is occurring. In some, a trial of antiasthma therapy may help diagnose cough-predominant asthma but it is important to keep at the back of one's mind that the response to a trial of treatment may simply be natural resolution. Chronic wet cough suggests excessive mucus in the airways and may indicate potentially a serious lung condition. Protracted bacterial bronchitis seems to be the most common cause, which responds by definition to a full course of antibiotics. Care needs to be taken because these children, if not adequately treated, may develop bronchiectasis.

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Tachypnoea, dyspnoea, respiratory distress and chest pain

Josef Riedler

Definition

Tachypnoea describes abnormally high breathing frequencies and often accompanies dyspnoea. The normal respiratory rate decreases with age and can be quite variable, particularly in newborns and young infants. The mean values range from 25 to 35 breaths·min^{-1} in the first years of life and decrease to 15 to 20 breaths·min^{-1} in the adolescent. Tachypnoea without dyspnoea is seen in young infants with a compliant rib cage and in children with fever, anaemia and intoxication, and as a result of psychogenic causes.

The term dyspnoea refers to an abnormal breathing pattern usually with increased respiratory effort. Dyspnoea can be caused by different objective factors and is a very subjective feeling of difficult or painful breathing and often "air hunger". Objective signs of respiratory distress are suprasternal, intercostal or subcostal chest wall retractions, flaring of the alae nasi, use of accessory muscles such as the sternocleidomastoid muscle, head bobbing and a seesaw type of thoracoabdominal movements. Various diseases of the airways, lung parenchyma, rib cage and diaphragm, as well other organs, can cause dyspnoea and respiratory distress (table 1).

Key points

- Dyspnoea can be caused by respiratory, cardiac, metabolic, neuromuscular or psychogenic conditions.
- History taking and physical examination are cornerstones of a proper assessment of a child with dyspnoea, tachypnoea or respiratory distress.
- A clear diagnosis is mandatory for correct treatment.

The following are abnormal patterns of breathing with changes in breathing frequency, rhythm or respiratory effort.

- Apnoea: no breathing (central apnoea or obstructive apnoea).
- Hypopnoea: shallow breathing without the production of hypercarbia.
- Hyperpnoea: deep breathing without the production of hypocarbia.
- Bradypnoea: slow respiratory rate (metabolic alkalosis, increased brain pressure and respiratory muscle fatigue).
- Tachypnoea: high respiratory rate.
- Hypoventilation: decreased alveolar ventilation, which usually leads to hypercarbia.
- Hyperventilation: increased alveolar ventilation, which usually leads to hypocarbia.
- Biot breathing**:** irregular respiration at variable tidal volumes interrupted by apnoea (sign of brain damage).
- Cheyne–Stokes breathing**:** cycles of increasing and decreasing tidal volumes interrupted by apnoea (sign of brain damage).
- Kussmaul breathing: deep respiration (metabolic acidosis).

Chest pain is rather common in children. Whereas the most likely cause is musculoskeletal, functional or psychogenic, benign and self-limited in older children, serious conditions have to be excluded,

Table 1. Causes of dyspnoea

Respiratory
Extrathoracic obstruction (croup, epiglottitis, laryngospasm and foreign body)
Intrathoracic obstruction (asthma, obstructive bronchitis, bronchiolitis, foreign body aspiration and tracheomalacia)
Pneumonia, atelectasis, pneumothorax, pleural effusion, trauma, pulmonary embolus, pulmonary hypertension
Cardiac
Myocarditis, acute myocardial infarction, CHF, acute pulmonary oedema
Cardiac arrhythmias
Metabolic
Metabolic acidosis (diabetes mellitus, inborn error of metabolism)
Metabolic alkalosis (CF, hypertrophic stenosis of pylorus)
Neuromuscular and central
Defects or dysfunction of diaphragm
Myopathy and neuropathy
Poisoning, drugs, trauma and anaemia
Psychogenic
Hyperventilation
Anxiety and trauma
Vocal cord dysfunction

particularly in younger children (table 2). A thorough history often helps to find the cause and avoids unnecessary diagnostic steps. The following aspects of pain should be assessed:

- intermittent *versus* persistent pain,
- short lasting (hours or days) *versus* longer lasting (months),
- localised, sharp, superficial *versus* diffuse, deep, visceral,
- occurrence of cough, dyspnoea or fever,
- prevalent during sleep,
- related to swallowing or heart burn,
- association with posture, motion and exercise.

In most situations a multidisciplinary approach including a paediatric pulmonologist, cardiologist, orthopaedics and psychologist should be attempted.

Pathophysiology

In case 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 obstructive 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 by reducing the negative pharyngeal pressure. Flaring of the alae can also help reduce the inhalation time and respiratory muscle activities in situations of chest or abdominal pain.

In normal inspiration, the diaphragm contracts and moves downwards leading to outward motion of the thorax and the abdomen. Paradoxical breathing refers to

Table 2. Causes of chest pain

Musculoskeletal disorders (myositis, myalgia, costochondritis, Tietze syndrome and deformities of vertebral column)
Trauma
Herpes zoster
Mastitis and gynaecomastia
Pulmonary infarction
Sickle cell anaemia
Pneumothorax, pleuritis, atelectasis and foreign body aspiration
Mediastinitis
Chemical pneumonitis
Gastro-oesophageal reflux, hiatus hernia and diaphragmatic irritation
Pericarditis, myocarditits, coronary disease, idiopathic hypertrophic subaortic stenosis and arrhythmia
Pancreatitis and cholecystitis
Psychogenic

inward movement of the chest wall during inspiration, mostly due to paralysis of the intercostal muscles or the diaphragm. This breathing pattern with seesaw type of thoracoabdominal motion can also be seen in preterm babies and newborns with a very compliant thorax. In older children, however, the most likely cause 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 carbon dioxide and oxygen tension (P_{CO_2} and P_{O_2}, respectively) and in blood pH, as well as irritation of pain and thermo receptors and direct damage of neuronal receptors of breathing.

Assessment of the patient and differential diagnosis

History In a patient with severe respiratory distress, history taking will be limited. In any case, the time course of the symptoms, *i.e.* sudden onset or longer lasting, is essential. A past history of asthma or recurrent obstructive bronchitis helps in determining the cause of acute intrathoracic airway obstruction. Possible foreign body inhalation needs to be excluded in a young child with unilateral wheezing or diminished breath sounds on one side of the thorax. Risk factors such as known allergies, a positive family history, underlying cardiovascular conditions, psychological disorders, drugs or recent infections should be assessed. In patients with long lasting or recurrent episodes of dyspnoea, normal growth and normal physical fitness point towards a more benign course. Dyspnoea due to functional or psychological conditions usually disappear during sleep (fig. 1).

Inspection Correct observation is one of the most important parts of the physical examination in a child with dyspnoea. Tachypnoea at rest, particularly during sleep, is suggestive of increased effort in breathing. In a child with pneumonia, respiratory rate increases to improve oxygenation. Thus, visible tachypnoea is one of the most sensitive signs of restrictive lung disease, such as pneumonia, atelectasis,

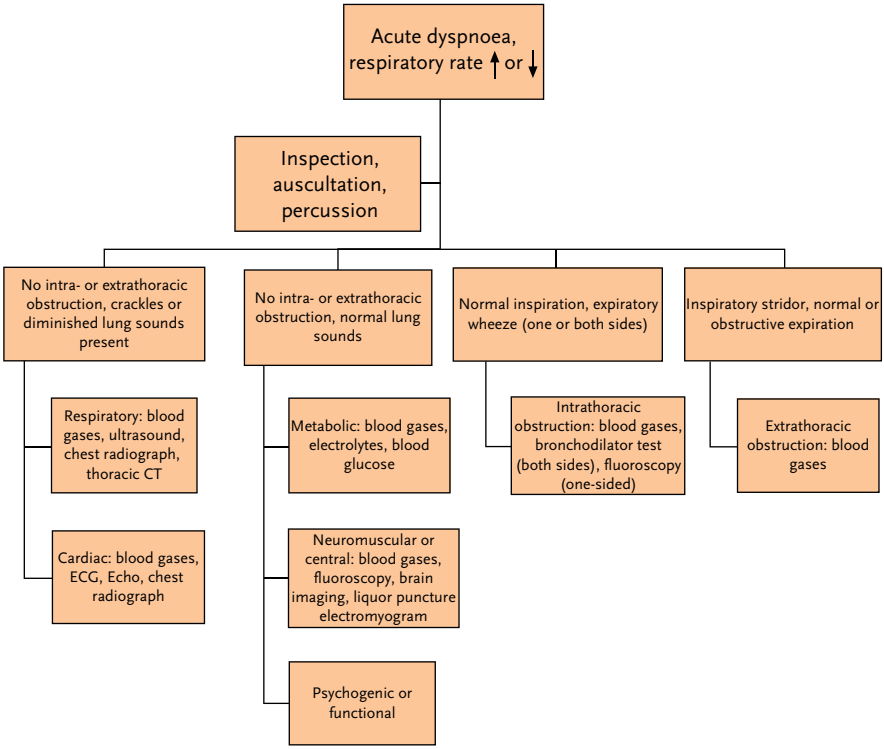

Figure 1. Assessment of acute dyspnoea.

alveolitis, or pleural effusion and pneumothorax. In airway obstruction of the younger child, indrawing of the suprasternal fossa or subcostal and intercostal tissue and nasal flaring is usually present. In unilateral diseases of the lungs, the rib cage or diaphragm are seen as asymmetric breathing motion. Chronic airway obstruction may result in a barrel-shaped chest with increased anteroposterior diameter. A bilateral skin fold below and a bluish coloration of the lower eyelid may be seen in atopy. Digital clubbing may accompany long lasting respiratory disease like CF, and can be found rarely in lung abscess and empyema. Peripheral or central cyanosis occurs when the absolute concentration of reduced haemoglobin in the arterial blood exceeds 3 g per100 mL.

Auscultation and percussion Inspiratory stridor indicating narrowing of the larynx or trachea usually can be heard without a stethoscope. The noise either comes from vibrations of the aryepiglottic folds or vocal cords (vocal cord dysfunction) or from dynamic compression of the extrathoracic part of the trachea just below the obstruction of the subglottic or proximal trachea (subglottic stenosis or croup). The sound may vary in pitch and intensity due to the site of obstruction. A more coarse character indicates pharygolaryngeal site (epiglottitis), whereas a sharp high-pitched tone may come from the subglottic region (croup). An additional expiratory stridor suggests involvement of the intrathoracic part of the trachea. Stridor of a baby that diminishes or even disappears in the prone position is very suggestive of a benign infantile floppy larynx.

Wheeze due to intrathoracic airway obstruction refers to polyphonic continuous

musical lung sounds, in some languages called "asthma concert" and is present in expiration and sometimes inspiration. Narrowing of a single central bronchus results in a unilateral monophonic wheeze often heard in a foreign body aspiration into a main bronchus. Crackles are non-musical, discontinuous sounds indicating air movements through secretions (bronchitis) or sudden opening or closing of airways or alveoli (pneumonia). They are coarse when they come from the bronchi and fine from bronchioli or alveoli. A dyspnoeic child with unilateral fine crackles most probably suffers from pneumonia, whereas bilateral fine crackles might be indicative of alveolitis, bronchiolitis or lung oedema. In pneumonia, the normally present bronchovesicular breath sounds are replaced by bronchial sounds because the bronchioli and alveoli component is lacking due to congestion and secretions. Unilaterally diminished lung sounds with dull percussion notes suggests atelectasis, tumour or pleural effusion. Less breath sounds and hypersonic/tympanic percussion on one side of the thorax might be a sign of pneumothorax.

Pulse oximetry and blood gases Pulse oximetry is a noninvasive means for measuring the body's S_{aO_2}. A slight decrease in oxygen saturation cannot readily be detected by simple inspection of the skin or the mucous membranes. Pulse oximetry is an essential tool in any child with dyspnoea or respiratory distress. Causes for desaturation are similar to those for cyanosis. By far the most likely cause is ventilation/perfusion mismatch (V'/Q') due to viral or bacterial infections of the lung. Sepsis, inhalation of toxic fumes, acute respiratory distress syndrome (ARDS) or pulmonary oedema may lead to oxygen diffusion impairment. In preterm babies, respiratory distress syndrome is caused by insufficient production of surfactant. Target values for oxygen saturation in these babies are in the range of 84–88% to avoid detrimental effects of oxygen on the eyes. Later in life, 92% is the lower limit of normal. In severe dyspnoeic children with signs of cardiorespiratory failure or in children with hypothermia and peripheral vasoconstriction, pulse oximetry cannot be relied on. In these situations arterial blood gas tests are mandatory. Besides this indication, assessing blood gases is crucial for information on P_{CO_2} and acid/base constellation. In a dyspnoeic child the rapid increase in P_{CO_2} (>5 mmHg per hour) is of great concern because this can be the first sign of impending respiratory failure and the need for ventilation. Hypocarbia and respiratory alkalosis is indicative of hyperventilation seen in psychogenic disorders or hyperventilation tetany. Hypocarbia and respiratory alkalosis also occur as compensation for metabolic acidosis. In ventilated children P_{CO_2} values are assessed and are necessary for monitoring ventilation parameters. P_{CO_2} measurement is essential for evaluating chronic lung disease (CF, chronic neonatal lung disease or severe restrictive lung disease) and assessment of possible long-term oxygen supplementation.

Respiratory imaging A very thorough and skilled physical examination with proper auscultation and percussion often leads to a definitive diagnosis without the need for further imaging in a child with dyspnoea. This is the case in most patients with obstruction due to asthma or typical viral bronchiolitis. A chest radiograph helps to rule out pneumonia, atelectasis or pneumothorax. Children with lung TB are rarely dyspnoeic or in respiratory distress, only in the case of miliary TB.

Usually, a radiograph sufficiently detects lung bleeding in haemosiderosis or chest trauma. However, in the work-up of lung, mediastinal or rib cage tumours, CT or MRI will be necessary. CT is diagnostic in bronchiectasis and mandatory in suspected interstitial lung disease. Chest radiographs are hardly ever useful in the assessment of dyspnoea due to upper respiratory tract pathology. In preterm babies a chest radiograph confirms clinical respiratory distress syndrome due to surfactant deficiency or suggests different pathology, such as lobar emphysema, cysts or other causes of congenital airway malformation.

In these cases CT or MRI will follow. In a dyspnoeic child with pleural effusion, sonography can be used to monitor the amount and consistency of the fluid and to guide tapping. Many centres now use interventional radiologists to insert chest drains under ultrasonic guidance.

Lung function measurement In most patients with acute dyspnoea, history taking, physical examinations, lab tests and imaging lead to diagnosis and lung function measurements are not necessary. Response to an anti-obstructive treatment of lower or upper airways is assessed clinically. However, in case of reported episodes of dyspnoea or limitations in physical activities and uneventful actual physical examination, lung function measurements may confirm or rule out obstructive or restrictive airway disease. In the diagnosis of obstruction, spirometry and flow–volume loop are essential whereas in suspected restriction vital capacity and TLC need to be assessed. Carbon monoxide diffusion is measured when an impairment of the alveolar–capillary diffusion capacity is suspected as a cause for dyspnoea. Impairment of diffusion can also be investigated by the means of pulse oximetry under physical stress. Standardised protocols for treadmill tests and bicycle ergometry are available. A drop in FEV_1 of >10% after standardised physical activity suggests exercise-induced bronchoconstriction. 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. In vocal cord dysfunction, the inspiratory and expiratory part of the flow–volume loop often shows saw-tooth like changes. In patients with neuromuscular or skeletal problems, lung function measurement is helpful in predicting potential limitations for surgery and anaesthesia.

Bronchoscopy and bronchoalveolar lavage In an acutely dyspnoeic child with unilateral diminished lung sounds and a possible history of foreign body aspiration, rigid bronchoscopy should be performed. Apart from removal of a foreign body there is virtually no indication for rigid bronchoscopy. However, the use of flexible bronchoscopy has substantially increased in the last 20 years and one of the most prevalent indications is dyspnoea with inspiratory stridor. Infantile larynx, congenital or acquired subglottic stenosis, subglottic haemangioma, or a vascular ring can be found. Bronchoalveolar lavage is warranted in a child in whom lung bleeding, gastric content aspiration, surfactant deficiency or certain infections (*Pneumocystis jirovecii*, *Aspergillus*, Cytomegalovirus), particularly in immunosuppression, are thought to cause dyspnoea. The role of transbronchial or open lung biopsies is particularly in severely sick patients with longer lasting or chronic dyspnoea in whom no diagnosis could have been made by investigations so far.

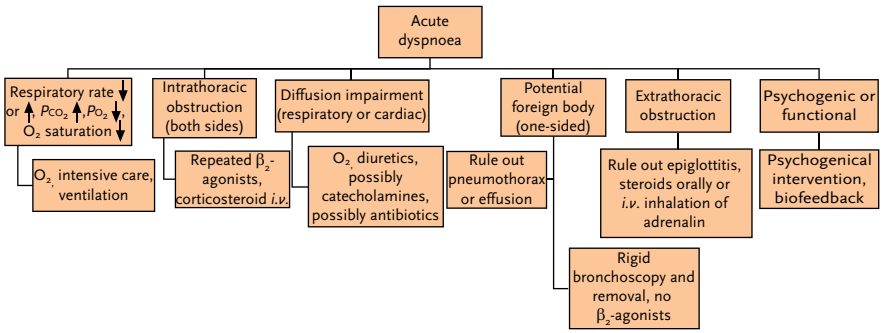

Figure 2. Management of acute dyspnoea. P_{CO_2}*: carbon dioxide tension;* P_{O_2}*: oxygen tension.*

Evaluation of non-respiratory causes of dyspnoea As seen in table 1, conditions other than respiratory ones also need to be considered in a child with dyspnoea. If a respiratory cause is unlikely, a cardiac assessment including electrocardiogram and echocardiography should be performed. Abnormalities in blood gases, blood glucose, lactate, pyruvate or ammonia suggest defects in metabolism. In some cases a detailed neurologic or psychological evaluation will be necessary.

General management

A clear diagnosis is essential before management can start in a dyspnoeic patient. Figure 2 depicts the different diagnostic paths and corresponding treatment modalities. However, some general management steps apply for most situations. Cardiopulmonary resuscitation is obligatory in any unconscious child with cardiac or respiratory arrest. As a general rule, children in respiratory distress should not be investigated or transported in a lying position but with upper body elevated. To find out whether oxygen needs to be supplemented, pulse oximetry has to be performed. Repeated checks of blood gases help to detect increases in PCO_2 and potential impending respiratory failure with the need of invasive or noninvasive ventilation. Nasogastric tubes should be avoided, particularly in infants with respiratory distress, because they substantially increase airway resistance and respiratory work load. Usually, enteral feeding is reduced to ~50% in these infants to avoid compression of lungs by abdominal distension. The necessary fluids are administered intravenously. Inadequate release of antidiuretic hormone often accompanies severe respiratory distress and warrants reduction in fluid administration.

In a toxic dyspnoeic child with typical symptoms of epiglottitis, rapid intubation and administration of antibiotics is 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. 400–1000 µg of salbutamol is inhaled in airway obstruction due to asthma or obstructive bronchitis. In these diseases the obstruction is reversible and wheezing and respiratory distress will diminish after application. If this is not the case, irreversible airway obstruction due to a foreign body or mechanical narrowing must be suspected. The later situation warrants bronchoscopy and further evaluation or treatment.

Further reading

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Snoring, hoarseness, stridor and wheezing

Kostas N. Priftis, Kostas Douros and Michael B. Anthracopoulos

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 oscillation of large 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, and it is caused by narrowed large, extrathoracic airways; its presence suggests significant obstruction of airflow in the larynx and proximal trachea.
- Snoring is produced during sleep and is due to obstructed air movement in the naso- and oropharynx; children who snore tend to have more collapsible airways and/or increased size of adenotonsillar tissue.
- Rattle is created by the movement of excessive secretions during normal airflow in the central and extrathoracic airways; it has a "rattling", noncontinuous quality, but quite commonly is mislabelled by parents as wheezing.
- 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.

Wheezing, stridor and snoring are common causes of noisy breathing, particularly in infants and young children, and their presence indicates a degree of airway obstruction. The term "noisy breathing" is used to describe respiratory sounds that are audible to the "naked ear" without the use of a stethoscope. Although the evaluation of noisy breathing is not always straightforward, the proper identification of these noises is of major clinical importance, as it can assist in localising the site of an obstruction and, thus, in the differential diagnosis of the potential underlying causes (table 1).

The cause is often obvious from the history and 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.

The difficulty in correctly recognising these 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. Parent's descriptions are often inaccurate, and their use of terms to describe a noise can be quite misleading; this can also be the case among physicians, as there is still ambiguity in the terminology used for respiratory noises in the medical literature, highlighting the need for a common nomenclature in each language. Nevertheless, a detailed history by the

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

Noise	Site of origin	Common causes
Wheezing (wheeze)	Intrathoracic airways (primarily expiratory)	Asthma Viral wheeze Bronchiolitis Foreign body Protracted bacterial bronchitis Tracheo/bronchomalacia
Stridor	Extrathoracic airways (primarily inspiratory)	Croup Epiglottitis Laryngomalacia Tracheomalacia Vocal cord paralysis VCD
Snoring	Oro/nasopharyngeal airway	Collapsible airways with increased size of adenotonsillar tissue Obesity Craniofacial disorders
Rattle	Intra- and extrathoracic airways	Acute viral bronchitis Protracted bacterial bronchitis Neurologic disorders with swallowing dysfunction and/or chronic aspiration
Grunting	Glottis	Respiratory distress syndrome (neonates) Pneumonia Bacterial infection
Snuffles	Blocked nasal passages	Upper respiratory tract infections Allergic rhinitis

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.

Computerised acoustic analysis technology has been used to evaluate the 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 section, wheezing, stridor and snoring will be discussed, and there will be a brief reference to some other quite common types of noisy breathing, namely rattle, grunting and snuffle. 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 originates from turbulent airflow, caused by partially blocked intrathoracic airways, that oscillates the airway wall and gives rise to the sound.

Although, in theory, wheezing can arise from throughout the conducting airways, it requires sufficient airflow that, practically, it is restricted to the large and medium-sized airways. Still, it is common experience that wheezing is audible in cases of extensive small airway narrowing, as is the case with asthma and with bronchiolitis. This could be due to air trapping in the lung periphery and the higher pleural pressures required to overcome the narrowing. Thus, the wheeze is thought to be produced by the resultant external compression of the larger airways, especially during infancy when the walls of the more central bronchi are more collapsible. Since the noise is produced by a multitude of airways throughout the lungs the wheeze consists of a multitude of distinct harmonics (differing acoustic characteristics) and is therefore "polyphonic". Conversely, when the sound is generated by one (*e.g.* stenosis, foreign body) or few, at the most, large airways, it consists of a much more limited number of harmonics and is termed "monophonic" (perhaps more precisely, "oligophonic"). The "focal" nature of the generation of the monophonic wheeze may explain the decrease of its loudness with the increase in the distance of the site of auscultation from the sound source (obstruction).

Assessment The most common cause of intermittent episodes of polyphonic wheeze in children is asthma. A prompt response of wheeze to a trial of bronchodilator is of great importance, as 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, bronchiolitis is the most likely diagnosis, although asthma cannot be excluded. The response to bronchodilators, the presence and/or a family history of atopy may all help to differentiate bronchiolitis or viral wheeze from asthma. Although simple noninterventional studies like chest radiography, allergy testing and spirometry may be useful in older children, more elaborate studies are usually not necessary.

Acute onset of monophonic wheeze raises the possibility of foreign body aspiration. The absence of a choking event is not reassuring, as ~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 or adenoma) or extraluminal compression of central airways by a growing 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. If foreign body aspiration is a strong possibility, urgent rigid bronchoscopy should be carried out, while mere suspicion should prompt investigation of the airways with a flexible bronchoscope.

Stridor

Stridor is a musical, monophonic, high-pitched sound, albeit much more harsh (oligophonic) 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 extrathoracic trachea. The generation of stridor can be explained by the dynamics of inspiration–expiration (particularly when forced) and Bernoulli's 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 (relative to that of the atmosphere) intrapleural pressure, which, in turn, is applied to the trachea. In normal individuals, this results in minimal collapse, which is not clinically relevant. 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 Bernoulli's 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 probably primarily responsible for the vibrations of the airway wall that are responsible for the creation of stridor. 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 (fig. 1).

Assessment The history and physical examination provides information on the persistence of stridor (chronic *versus* acute), acuity of onset (abrupt *versus* gradual), timing during the respiratory cycle (inspiratory, expiratory or biphasic), accompanying symptoms (fever or 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 is quite common and 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 whenever the beginning of stridor is abrupt and accompanied by severe respiratory distress. Rigid bronchoscopy constitutes the definitive procedure in this case, as it not only allows for the visualisation of the airways but also for the removal of the 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 depending on the respiratory effort and varies with the position of the patient. The obstruction is due to 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

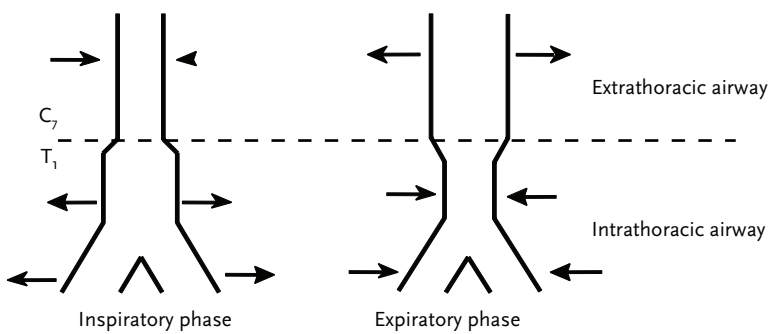

Figure 1. During inhalation, a negative (relative to that of the atmosphere) intrapleural pressure in extrathoracic airways is generated, which in turn is applied to the trachea. This results in minimal collapse, which, in normal individuals, is not clinically relevant. Exhalation induces a positive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

stridor, an alternative diagnosis needs to be sought.

Intermittent, sudden-onset, daytime episodes of stridor in school-aged children or adolescents may indicate vocal cord dysfunction (VCD). 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, and children $<$6 months of age require endoscopic evaluation.

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 the above characteristics are present, a more thorough investigation is in order. If an endoscopic evaluation is decided upon, it is preferable to perform both rigid laryngotracheoscopy and flexible bronchoscopy. Rigid instruments allow a much better view of the posterior aspect of the larynx and upper trachea, whereas flexible bronchoscopy is superior in evaluating airway dynamics. The entire airway should always be examined, despite the finding of a lesion in the larynx that can explain the stridor, since in ~15% of patients, an additional lesion will coexist in the lower airways.

If VCD is suspected, spirometry may show "truncated" inspiratory and expiratory flow–volume loops. However, 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 naso- and oropharynx. Children who snore tend to have more collapsible airways and increased size of adenotonsillar tissue. During rapid eye movement (REM) sleep, the tone in pharyngeal muscles is reduced, resulting in an increase in 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 (SDB).

Assessment 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, nor is the absence of snoring is sufficient to exclude OSAS, as 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

(including attention deficit hyperactivity disorder) are not unusual. 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, history and clinical examination are not sufficient to reliably identify OSAS and the definitive diagnosis has to rely on polysomnography (PSG), which is considered the gold standard for evaluating children for SDB. Still, 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 a number of other devices that monitor pulse oximetry with a combination of one or more parameters, like 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 a 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 resolution of symptoms is not achieved following surgery, nasal CPAP is usually effective.

Rattle

Parents tend to use ''wheeze'' as a generic term to describe a variety of abnormal respiratory sounds. One of the commonest errors is the misuse of the word ''wheeze'' to describe a coarse respiratory sound known as rattle. Rattle is characterised by a much lower pitch than wheeze, it has a ''rattling'', noncontinuous quality, is usually accompanied by chest wall vibrations that are easily detectable by parents, and it can be heard during both inspiration and expiration. It is found quite often in infants and toddlers and, although there is a paucity of data in the literature regarding the underlying mechanism, it is believed to be created by excessive secretions which are moving during normal airflow in the central and extrathoracic airways. The mislabelling of a rattle as wheeze may result in overdiagnosis (and overtreatment) of asthma in children.

The most common cause of rattle is acute viral bronchitis and, in preschoolers, upper airway viral infections. A rattle can be heard for a few days or weeks and subsides after the removal of secretions from cough and mucociliary clearance. 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. This mechanism may be considered as a self-administered form of peak end-expiratory pressure, since the slowing of expiratory flow increases the functional residual capacity 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, whereas in children with underlying chronic disease, it is considered as a sign of serious bacterial infection.

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, primary ciliary dyskinesia and 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 a 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 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 *versus* chronic, or intermittent *versus* continuous progressive, is of pivotal importance. Acute hoarseness is usually due to injury of the mucosa overlying the vocal chords 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 gastro-oesophageal reflux 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 area, or a mass lesion affecting both swallowing and vocalisation. It is imperative to ask whether 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. It can be bilateral or unilateral. The former is mostly caused by central nervous system anomalies like Arnold–Chiari malformation, 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 stridor, it may be absent and the lesion may manifest as a husky, weak cry. Bilateral vocal cord paralysis is a predisposing cause of chronic or recurrent aspiration pneumonitis. About half of these palsies recover spontaneously, largely irrespective of their cause.

In general, history and physical examination may help to distinguish between many of the pathological conditions causing hoarseness. However, direct inspection of the larynx by 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.

Conclusion

Distinguishing the various respiratory noises can, at times, be 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 parents' description and interpret their terms for the breathing noise that they are referring to. Acoustic analysis of respiratory sounds may improve communication among clinicians and audio–video recordings demonstrating the various sounds may prove quite useful in order to improve the accuracy of the information that is obtained.

The clinical usefulness of respiratory noises could be improved by technology, such as video recording and sound analysis, but although these techniques would clearly improve 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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Further listening

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Exercise intolerance

Kai-Håkon Carlsen

Exercise intolerance or the lack of ability to participate in physical activity and exercise together with peers may have many causes. Some of the most common causes of exercise intolerance are of respiratory origin and will be briefly dealt with here (table 1).

Participating in physical activity is important for children, for their growth, their long-term development and future health. In asthmatic children, physical fitness has been associated with psychological functioning.

One of the most common respiratory causes of exercise intolerance is exercise-induced asthma (EIA), a frequent manifestation of childhood and adolescent asthma. In the Oslo birth cohort, the Environment and Childhood Asthma study, exercise-induced bronchoconstriction (EIB) was found in 8.6% of all 10-year-old children and in 36.7% of children with current asthma, whereas in a Danish population-based study of 494 children aged 7–16 years, EIB with a $\geqslant$10% reduction in FEV_1 after exercise was found in 16% of the subjects.

When participating in systematic physical training, the fitness and quality of life of an asthmatic adolescent or child improves, as confirmed by a Cochrane-based meta-analysis of eight training studies including 226 asthmatics aged $\geqslant$6 years of age. Similar results were also reported when later studies were also included. Counil *et al.* (2003) confirmed improvement in aerobic and anaerobic fitness in asthmatic adolescents (mean age 13 years), but no improvement in lung function after 6 weeks of training with high-intensive bouts. Moreira *et al.* (2008) found no changes in asthma control after a 3-month training programme in children and adolescents (mean age 13.4 years), but they found a reduction in total IgE and specific IgE to house dust mite in the actively training group. Fanelli *et al.* (2007) conducted a 16-week training programme of 90 min twice a week in two groups (index and control) of children with moderate-to-severe persistent asthma. In the training group they found improved fitness (peak oxygen uptake ($V'O_2peak$), work rate and oxygen pulse during submaximal and maximal work), improved quality of life, reduction in exercise bronchoconstriction and reduced dose of inhaled steroids in 11 out of 21 subjects in the training group compared to four out of 17

Key points

- Participating in and mastering physical exercise is extremely important in children and adolescents.
- Participation in physical activity improves quality of life, fitness and life expectancy in many respiratory disorders.
- Treatment of childhood asthma should aim at mastering physical activity and exercise-induced asthma.
- Several chronic respiratory disorders of childhood may influence the ability to participate in physical activity. Assessment of the ability to participate in physical activity and setting up therapeutic procedures to counteract exercise intolerance should be part of the diagnostic assessment of children with respiratory disease.

Table 1. Causes of exercise intolerance in children and adolescents

Cause of exercise intolerance	Clinical characteristics	Diagnostic procedure
EIA	Expiratory dyspnoea occurring shortly after end maximal or sub-maximal exercise Clinical airways obstruction	Exercise test for exercise-induced bronchoconstriction
EIVCD	Inspiratory stridor occurring during maximal exercise	Continuous laryngoscopic exercise test
Exercise-induced anaphylaxis	Anaphylaxis occurring during or immediately after exercise, most often with food intake (allergenic) within the last 2 h prior to exercise	Food allergy evaluation Simultaneous food provocation and exercise test under safe emergency precautions
Other chronic respiratory disorders with reduced baseline lung function	Chronic respiratory disorder, which can be of different kind (CF, primary ciliary dyskinesia and bronchiectasis) Reduced baseline lung function	CPET with recording of breath to breath $V'O_2max$ and simultaneous tidal flow–volume loops every minute Detection of flow limitation and measure EELV
Dysfunctional breathing in asthma	Chronic or recurrent changes in breathing patterns causing respiratory (and non-respiratory) complaints Symptoms include dyspnoea with normal lung function, deep sighing, chest pain, chest tightness, frequent yawning, hyperventilation and breathlessness during exercise	Nijmegen questionnaire
Poor physical fitness	Breathlessness during exercise before ordinarily anticipated Muscle stiffness	CPET (maximum work capacity and/or $V'O_2max$)
Obesity		As for poor physical fitness
Other chronic disabling disorders	Varying clinical picture	Clinical assessment

CPET: cardiopulmonary exercise test; EELV; end-expiratory lung volume; $V'O_2max$: maximal oxygen uptake.

in the control group. Thus, the training subjects improved their exercise tolerance through physical training.

Subjects with higher physical activity levels were found in a review of longitudinal studies to have a lower incidence of asthma (OR 0.87, 95% CI 0.77–0.99), thus indicating a potential for protection of developing asthma by being physically active.

Some studies demonstrate that asthmatic children are as physically fit and as physically active as healthy children, whereas other studies have demonstrated that physical activity and fitness are related to asthma control and improve with optimal treatment and asthma control. Therefore, to master EIA is considered one of the main objectives of treating childhood asthma.

Exercise-induced vocal cord dysfunction

Exercise-induced vocal cord dysfunction (EIVCD) is caused by airways obstruction during exercise due to airflow limitation in

the laryngeal area. This was first described in 1983. This condition occurs frequently during adolescence, and is almost as frequent as EIB, especially among girls active in sport with high fitness levels. The symptoms consist of inspiratory stridor as the exercise load increases. When reaching a submaximal or maximal level, stridor usually appears. The laryngeal area represents the smallest orifice for the air to pass through during inspiration, and in well-trained youths, especially girls, the orifice becomes too small to allow entry of the required amount of air without the appearance of stridor and reduction of $V'O_2$peak. Several laryngeal structures can participate in the airflow limitation, and the treatment may vary depending on this. Treatment may be surgical or conservative. Lung function during exercise will, in many cases, be characterised by reduced inspiratory flow. This condition has often been misinterpreted as EIA, but with no effect of asthma treatment. Inspiratory stridor during maximal exercise may be observed during testing for EIB, but an exact diagnosis requires a continuous laryngoscopic exercise test.

Exercise-induced anaphylaxis

Exercise-induced anaphylaxis is a condition with anaphylaxis provoked by physical exercise. This is a rare, but dramatic disorder in which the anaphylaxis occurs during or immediately after exercise. It may be life threatening and is most often food dependent (food-dependent exercise-induced anaphylaxis (FDEIA)), but may also be due to exercise alone. Usually there is an associated food allergy, but this may be unknown to the patient as food allergy symptoms may not occur without simultaneous exercise. Most often both exercise and the specific food are independently tolerated in FDEIA, simultaneous exposure to both are usually required for the symptoms of anaphylaxis to occur. Wheat proteins have often been found to be the causative food in FDEIA, most often due to the major component allergen, tri Ω-gliadin. One should be aware that, in some cases, negative specific IgE may be found to wheat even with increased specific IgE to tri Ω-gliadin. Other food allergens may also be responsible. Usually, it is sufficient to secure removal of the causative food allergen from the food, with the patient then tolerating exercise. However, as a precaution the patient should still carry an Epi-pen. Diagnosis may be secured by simultaneous administration of the suspected food allergen and an exercise test with safe emergency precautions being taken.

Chronic lung diseases other than asthma

These may also cause exercise intolerance, but through other mechanisms. Whereas baseline lung function is usually normal or close to normal in asthma, exercise causes bronchoconstriction, which limits the ability of participating in physical exercise. In other chronic lung disorders, exercise usually does not cause bronchoconstriction, but reduced baseline lung function may represent a pulmonary limitation for participating in physical exercise similar to other children. This includes CF, primary ciliary dyskinesia, other causes of bronchiectasis, secondary lung disease to immunodeficiency and other chronic lung diseases with reduced baseline lung function. The reduced lung function will represent a flow limitation during exercise, which limits the possibility of increasing oxygen uptake with the increasing demands for oxygen during exercise, thus giving rise to an anaerobic metabolism. The resulting dyspnoea is due to reaching the limits of airflow and not due to obstruction of the airways due to the exercise, as in asthma. The patient will have an anaerobic metabolism during exercise at a much earlier time-point (fig. 1).

Some other causes of exercise intolerance are specific for athletes, such as exercise-induced arterial hypoxaemia and swimming-induced pulmonary oedema; therefore, these are only mentioned for completeness.

One condition that has received little focus in children is dysfunctional breathing. This condition is defined by chronic or recurrent changes in breathing patterns. Symptoms include dyspnoea with normal lung function, deep sighing, chest pain, chest tightness,

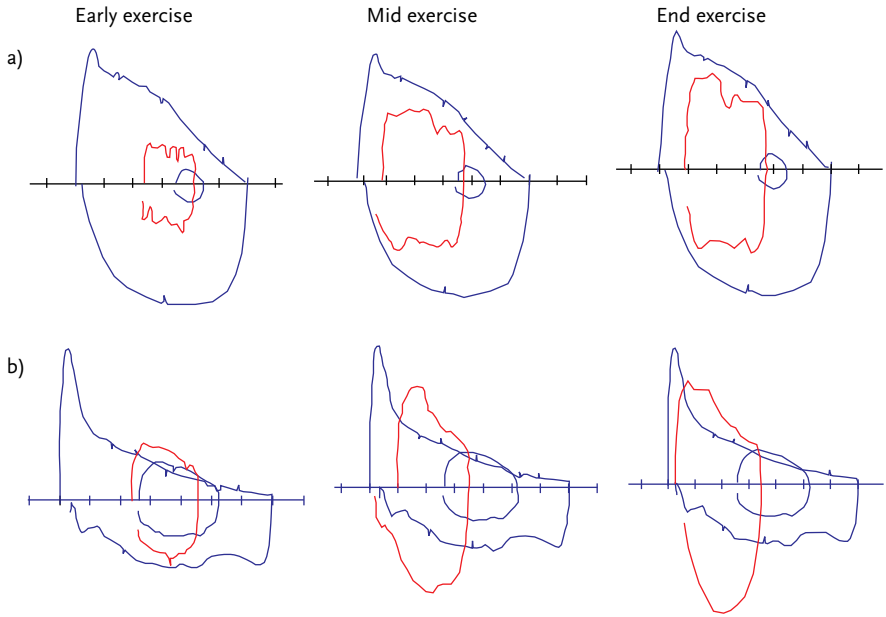

Figure 1. Tidal breathing during exercise in a) a patient with asthma and b) a patient with chronic lung disease (bronchiectasis). The patient with asthma demonstrated normal baseline lung function at early, mid and end exercise. The patient with chronic lung disease had reduced baseline lung function during early, mid and end exercise, demonstrating flow limitation and increased end-expiratory lung volume. There was no flow limitation in the patient with asthma.

frequent yawning, hyperventilation and breathlessness during exercise. A diagnosis is based on the Nijmegen questionnaire. A recent study demonstrated that this condition occurred in 5.7% of asthmatic children followed at a hospital outpatient clinic.

There are other non-respiratory causes of exercise intolerance that are not included in the above review. These often appear with breathlessness and muscular weakness as the most prominent symptoms. These include general physical illnesses such as cardiac disease and other general disabling diseases. Other causes are poor physical fitness, when the physical activity level does not meet expectations in the absence of any illness, and obesity with its limitations to physical activity (table 1).

To focus on exercise intolerance may represent a negative point of view. Rather, the opposite, to focus on mastering of physical activity and training, would represent a positive starting point. The patients presenting with exercise intolerance should be encouraged to participate in exercise to improve physical fitness and muscular strength. Physical training has been shown to prolong life expectancy in patients with CF, and systematic training in children with and without pulmonary disorders will improve fitness, quality of life and life expectancy. In children with chronic lung disease focus should be on optimal treatment of their respiratory disease in combination with a systematic training programme focusing on upper girdle muscles and fitness in order to enable them to master physical activity and to participate on an equal level with their peers in sports and outdoor living.

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Static and dynamic lung volumes

Oliver Fuchs

This section begins with a short review on static and dynamic lung volumes. Then, physiological principles underlying forced expiration and especially flow limitation will be highlighted. Lastly, the reader will be introduced to the field of lung function, and relevant literature in relation to current guidelines for those measurements in children as well as normative data will be pointed out.

Static lung volumes

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

Key points

- Lung volumes that are not affected by air flow are termed static lung volumes and consist of volumes and capacities (sum of specific volumes).
- The total lung capacity and the functional residual capacity include a volume of gas that cannot be exhaled (residual volume) and which is important for maintaining continuous gas exchange during profound expiration.
- Lung volumes that are affected by air flow are termed dynamic lung volumes and are measured during forced expiration.

Using additional techniques such as body plethysmography and gas dilution techniques, it is also possible to measure the residual volume (RV), which is important for maintaining continuous gas exchange during profound expiration. It cannot be exhaled and has thus to be measured indirectly. With these measurements, it is also possible to calculate the TLC and the functional residual capacity (FRC). The FRC is the volume of air in the lung after a normal expiration during tidal breathing. It is dependent on standing height, age, posture, compliance and tone of the diaphragm and represents the volume at which the elastic recoil pressures of the lung and of the chest wall are in balance. Static lung volumes that can be measured either directly or indirectly as well as capacities are displayed in the table 1 and figure 1 together with their respective acronyms.

Dynamic lung volumes

Lung volumes that are affected by air flow, are termed dynamic lung volumes and they are measured during spirometry with a forced expiration. Dynamic lung volumes, as well as expiratory flows that can be

Table 1. Static lung volumes

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

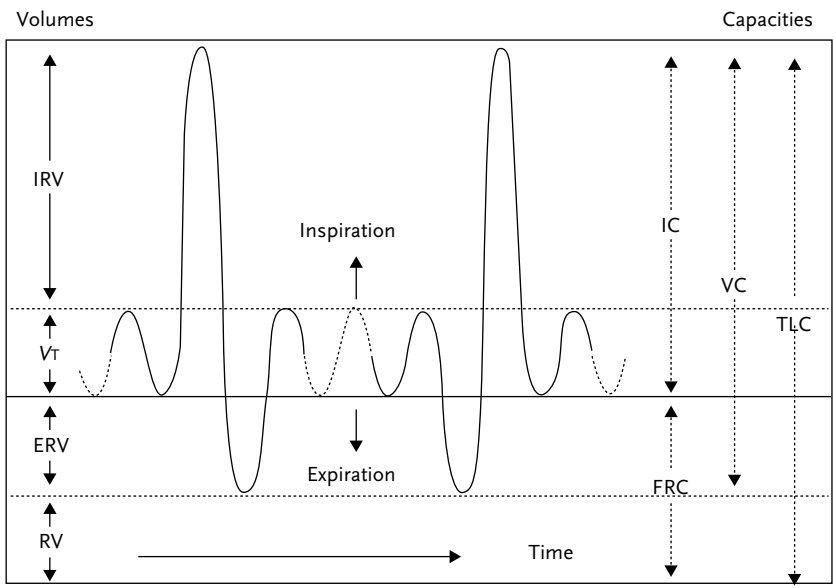

Figure 1. Spirogram with lung volumes (left) and capacities (right) and with expiratory (left) and inspiratory (right) vital capacity manoeuvres.

measured during spirometry, are displayed in table 2 and figures 2 and 3 together with their respective acronyms. Forced expiration rarely occurs under physiological conditions in everyday life, and it requires collaboration with inhalation to TLC and then exhalation down to the RV, both as long and as quickly as possible, thus provoking flow limitation without any further effort dependence. This measurement displays limitations in non-cooperative subjects, which is why a forced expiratory manoeuvre is usually possible only from late preschool age onward. In order to better understand the performance of such a manoeuvre, and its results, one needs to be familiar with the mechanics of the airways and also with respiratory mechanics, as well as the physiological principles underlying forced expiration in spirometry.

As described elsewhere in this *Handbook*, the airways are interconnected by surrounding lung tissue leading to pulmonary tethering. During inspiration, the lung expands and the airway calibres increase due to this tissue network. During expiration, the lung deflates and the airway diameter decreases concurrently, reflecting breathing-dependent changes in airway

Table 2. Dynamic lung volumes and expiratory flows that can be measured during spirometry

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

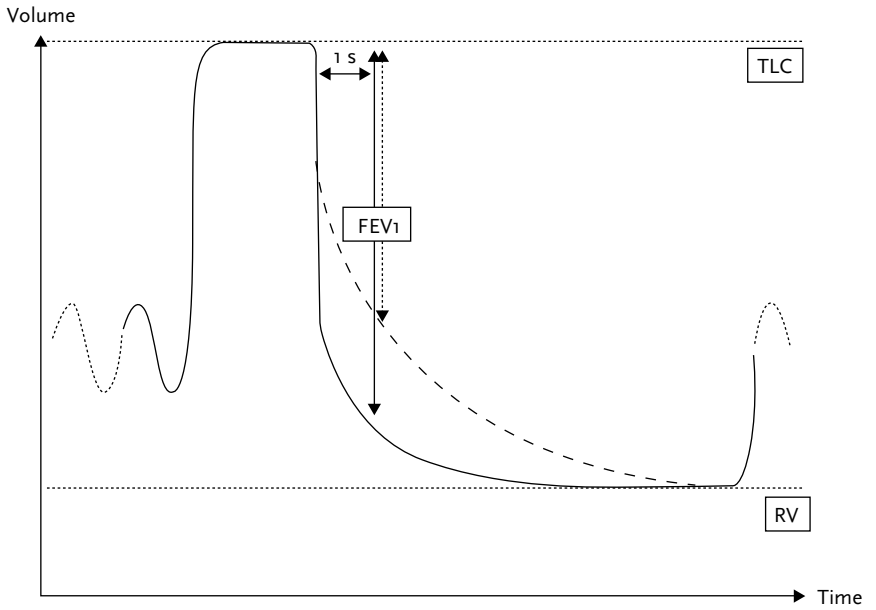

Figure 2. Volume–time relationship during forced expiration. The solid line represents measurement in a healthy subject; the broken line represents measurement in a subject with obstruction and a lower value of FEV1.

resistance. Thus, the airways do not resemble a system of rigid, but – still an oversimplification – of compliant and moreover also compressible tubes building up resistance to air flow. This air flow results from a pressure difference between the ends of the tube system, the airway opening (mouth), usually the barometric pressure (P_m) and the pressure in the alveoli (P_{alv}), with the latter being below P_m during inspiration and above P_m during expiration. While expiration during quiet tidal breathing usually happens passively, this is not the case during forced expiration which is additionally supported by active muscular contraction. Active expiration results in a reduced transversal and sagittal diameter of the thorax (due to activity of the internal intercostal muscles), elevation of the diaphragm and, as the main contributor of the expiratory driving force, increased intraabdominal pressure (activity of rectus abdominis, transversus abdominis and external as well as internal oblique muscles).

The consequent driving force of expiratory flow (the resulting pressure drop from the alveoli along the airways to the airway opening) the transairway pressure (P_{ta}) can be calculated as:

$$P_{ta} = P_{alv} - P_m \quad (1)$$

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

$$P_{alv} = P_{st} + P_{pl} \quad (2)$$

This results in expiratory flow (V') which can be calculated as:

$$V' = P_{ta} / R_{AW} = [(P_{st} + P_{pl}) - P_m] / R_{AW} \quad (3)$$

Hence, any change in V' is dependent on both resulting pressure P_{ta} and resulting resistance R_{AW}. By measuring flow during spirometry, one cannot know whether any change in flow is due to a change in pressure or in resistance. Under the

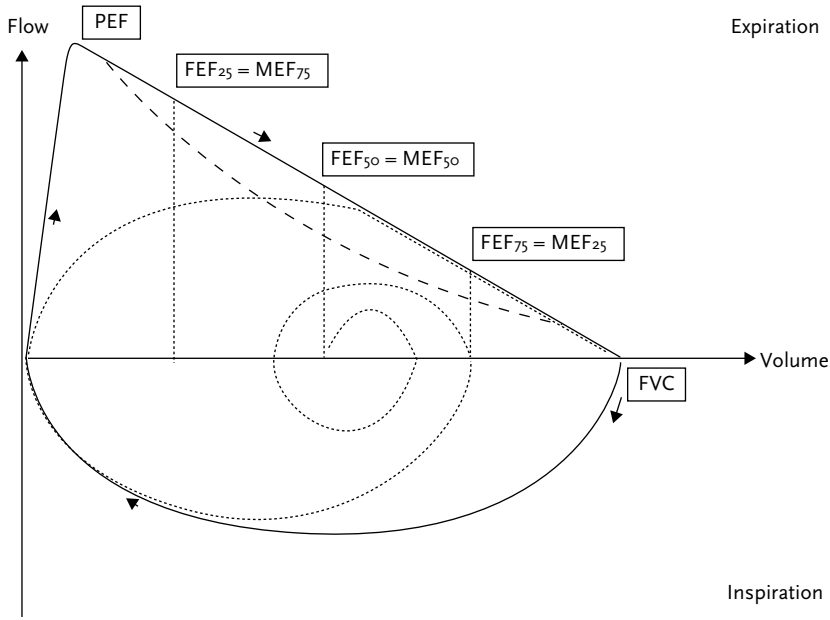

Figure 3. Flow–volume loops before and during forced expiration. Flow–volume loops during inspiration (below) and expiration (above) before (dotted line, light grey) and during forced expiration. The solid line represents measurement in a healthy subject and the broken line represents measurement in a subject with obstruction.

condition of flow limitation with maximal muscular activity, however, flow is independent of any further increase in driving force and thus representative of airway calibre. The following section depicts why this is the case during forced expiration.

Dynamic airway compression As highlighted above, inhaling deeply and then exhaling with maximum effort increases P_{pl} and P_{alv} well above P_m, thus creating the driving force for airflow in forced expiration. The positive P_{pl} results in pressure on the whole lung tissue and importantly, also on airways. Accordingly, not only P_{alv} but also pressure in the airway lumen ($P_{intrabronch}$) increase as a result of P_{st} and positive P_{pl}.

$$P_{intrabronch} = P_{st} + P_{pl} \quad (4)$$

$P_{intrabronch}$ slowly decreases from the alveoli ($=P_{alv}$) towards the airway opening ($=P_m$). Under the condition of maximum forced expiration and flow limitation, there will be a point in the airway tree where intrabronchial and extrabronchial pressures are equal, *i.e.* where $P_{intrabronch}=P_{pl}$. This point is termed the equal pressure point (EPP). According to equation (4), the pressure drop along the airway equals P_{st} at the site of EPP, with P_{st} – as highlighted above – being volume-dependent. This has an important implication. During expiration, lung volume decreases and consequently so does P_{st}. Hence, the EPP will be closer to the alveoli with small lung volumes (e.g. towards the end of expiration) as compared to the start of forced expiration, where it is located near the upper thoracic aperture. One can imagine the EPP entering the trachea during expiration and then splitting up into several EPPs in segmental, more compliant bronchi making up an EPP wave front.

The movement of the EPP during forced expiration is the reason why this airway compression is called dynamic. Upstream of the EPP, towards the alveoli, airways are not

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

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

Measurement of static and dynamic lung volumes

As highlighted above, the static lung volumes V_T, IRV, ERV, IC, and VC can be directly measured during spirometry, while others (RV, FRC and TLC) require body plethysmography or gas dilution techniques such as multiple-breath washouts (MBW). Importantly, body plethysmography and MBW do not measure exactly the same. In short, body plethysmography is a measure of compressibility of thoracic gas volume based on Boyle's law. The measured volume includes non- or poorly ventilated lung regions. This in contrast to the measurement of FRC by MBW (FRC-MBW), which reflects a volume that communicates with larger airways. FRC-MBW can be computed by either mass spectrometry or devices based on ultrasonic flow meters which are also able to measure molar mass of gas. Here, FRC-MBW is calculated on the basis of conservation of mass. This means that any amount of gas within the lung may be computed after measuring the concentration of this gas in expired air as well as the total volume of expired air if one washes this gas out of the lung, such as by inhaling pure oxygen to measure washout of nitrogen. With MBW it is also possible to calculate parameters that allow assessment of ventilation homogeneity, such as the lung clearance index (LCI), which is important in small airway diseases such as CF but also in asthma.

Detailing all the guidelines for lung function measurements in children would be clearly beyond the scope of this chapter. Measurements during quiet tidal breathing are possible even in infants, and if sedation is used also in toddlers. Due to lack of cooperation, early childhood may impose difficulties for any lung function measurements. From preschool age on, measurements during tidal breathing and especially those requiring either forced expiration or a VC manoeuvre are once again

feasible, especially in experienced paediatric centres. For guidelines and recommendations as well as peculiarities of paediatric lung function testing across age groups, the interested reader is referred to the respective chapters in this *Handbook* and to the relevant literature. For recent advances relating to normative data for spirometry covering large age ranges and also early childhood, the author would also like to refer to the relevant literature (Stanojevic *et al.*, 2007; Quanjer *et al.*, 2012) as well as to www.growinglungs.org.uk.

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Respiratory mechanics

Oliver Fuchs

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

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

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

Key points

- Respiratory mechanics are helpful in understanding the cyclic changes in airflow due to pressure differences during breathing and the influence of elastic (compliance) and dynamic properties of the respiratory system (resistance).
- Both compliance and resistance are volume dependent and display influence of age due to growth and development from infancy throughout childhood to adulthood.

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

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

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

Elastic properties of the respiratory system: compliance

Elastic properties of thorax and lungs act in opposite directions. While the thorax is predisposed to expand due to its structure, lungs tend to collapse because of their content of elastic fibres and surface tension at the alveolar gas–water interface. Adhesion forces in the pleural space, which make the lung tissue follow any change in thoracic diameter during inspiration and

expiration, prevent lung collapse. Pulmonary tethering transmits these forces throughout the lung tissue; pressure differences (P_A–P_{atm}) are built up and enable airflow towards alveoli.

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

$$P = 2T/r$$

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

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

$$C\ [\text{L}\cdot\text{kPa}^{-1} \text{ or } \text{cmH}_2\text{O}] = \Delta V/\Delta P = 1/E$$

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

$$1/C_{RS}\ [\text{kPa or } \text{cmH}_2\text{O/L}] = 1/C_{CW} + 1/C_L$$

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

Compliance is volume dependent There is a direct relationship between compliance and the ratio of volume over pressure gradients. Accordingly, compliance is volume dependent, visualised in a pressure–volume curve (fig. 1). The pressure–volume curve for C_{RS} has a characteristic S-shape with inflection points. The slope reflects C_{RS}, which is largest in the steep middle part of the curve. Thus, the physical work needed for inflation during inspiration is lowest in this range. Beyond inflection points physical work is increasing and respiration becomes less efficacious. The lower part of the curve results from closure of smaller airways and alveoli below a specific lung volume, the so-called closing volume. The upper part results from exhaustion of elastic properties in the lung structure due to distension of elastic fibres, thorax and alveolar septa. Thus, mechanical ventilation beyond the upper inflection point may carry the risk of volutrauma or barotrauma. As the compliance is volume dependent, its value is standardised by relating it to a certain lung volume, usually the functional residual capacity (FRC), resulting in the specific compliance. Interestingly, volume decreases less in relation to pressure during expiration than inspiration. The pressure–volume curves for inspiration and expiration are not identical, which is known as hysteresis. This is possibly due to reorganisation of surfactant molecules during expiration with complex folding processes, the creation of several surfactant layers and perhaps even partitioning into different surfactant sub-compartments.

Influence of age on C_L, C_{CW} and C_{RS} FRC reflects the intrapulmonary volume at which elastic properties of both C_{CW} and C_L equal each other. Here, tendencies towards expansion and collapse are in balance. Generally, this is the case for a higher FRC in

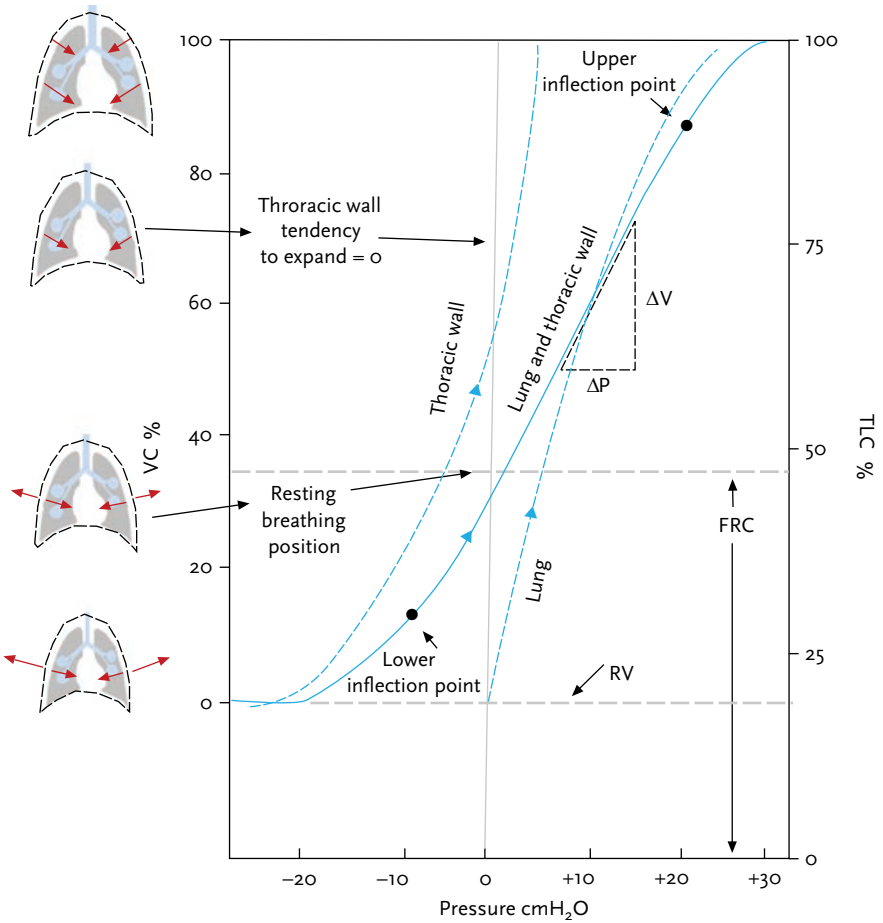

Figure 1. Inspiratory pressure–volume curves for C_{CW}, C_L *and* C_{RS}. *The dashed lines represent* C_{CW} *(thoracic wall) and* C_L *(lung). The solid line represents* C_{RS} *(whole respiratory system,* i.e. *lung and thoracic wall). The different states of the respiratory system and resulting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

older children and in adults than it is for newborns or toddlers. In addition to surfactant, elastic properties of the pulmonary system also depend on lung structure, especially elastic fibres. Owing to ageing, elastic retraction forces increase from birth through adolescence, but then decrease again. Thus, in both newborns and in older people, FRC can be below the closing volume. Accordingly, the newborn and the aged lung are very similar with regard to their tendency for airway collapse below the closing volume which is, therefore, itself age-dependent. This is also the reason for the higher amount of functional shunts early in life and the increasing incidence of shunts among older people. In order to circumvent airway collapse in dependent lung areas the newborn has several mechanisms available to dynamically upregulate FRC, leading to either a shorter duration of expiration or to a

decrease in expiratory flow (expiratory braking).

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

Dynamic upregulation of FRC lasts approximately until the end of the first year of life, when elastic retraction forces of the thoracic skeleton increase due to progressing ossification, *i.e.* when C_{CW} slowly decreases. At the end of the second year of life C_L equals C_{CW} in resting expiratory position without any necessary regulatory measures. C_{RS} changes predominantly due to increasing numbers of alveoli during childhood, further influenced by the development of upright walking.

Dynamic properties of the respiratory system: resistance

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

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

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

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

R_{AW} is influenced by both airway diameter and fluid flow behaviour of air. Depending on airway generation and pathological conditions, such as airway obstruction, airways may demonstrate different shares of laminar and turbulent flow. The Hagen–Poiseuille equation describes laminar flow. According to this equation, airway resistance is proportional to airway length (l) and dynamic gas viscosity (η) and inversely proportional to the fourth power of the airway radius (r) and π:

$$R\ [kPa \cdot L \cdot s^{-1}] = 8l\eta/r^4\pi$$

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

$$Re = V'L\rho/\eta$$

Above a critical value of Re (>1500) laminar flow passes on to turbulent flow. Pure laminar flow can be found for smaller Re of <1000, usually in small peripheral airways, while flow in larger airways is predominantly turbulent. Airway branching and bending, as well as abrupt changes in airway diameter, as in the case of airway obstruction, play a role. Hence, peripheral airways only account for ~10–20% of R_{RS} despite their total share in airway diameter, of ~95%. The biggest

portion of R_{RS} results from airway resistance secondary to turbulent flow in larger, more central airways.

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

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

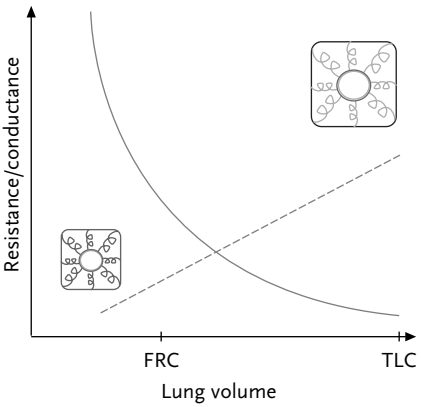

Figure 2. Volume dependency of resistance and conductance; pulmonary tethering. The boxes represent elastic fibres stabilising airway diameter in relation to lung volume (tethering). The solid line represents resistance, and the dashed line represents conductance in relation to lung volume.

Resistance of the upper airways

In infants, the nasopharyngeal space can account for up to 40% of R_{RS}, and in adults up to 60%. The larynx is the narrowest part of the upper airways; in infants and toddlers this is due to the anatomy of the cricoid, owing to growth it is the glottis in older children and in adults. Before it descends during growth, the larynx is initially located further forward and higher (C2–C3) in newborns and infants than in adults (C3–C6), favouring breathing through the nose and making simultaneous breathing and drinking possible. Accordingly, due to the laryngeal anatomy breathing through the mouth is rather disadvantageous early in life. This explains the significant nuisance of infants and, to the lesser extent, of toddlers in case of upper airway infections with nasal obstruction.

Resistance of the lower airways

In contrast to their small individual diameter, the total share of the small peripheral airways is high in relation to that of other airways. In older children and adults, the portion of R_{RS} formed by small airways is, nevertheless, 10–20%. Consequently, measuring resistance is not very sensitive with regards to quantifying obstruction of small airways in these subjects. In infants, however, small peripheral airways may account for up to 50% of R_{RS}. Thus, as with nasal obstructions, even minor peripheral airway obstructions may be associated with significant impairment in this age group. Furthermore, in dyspnoeic infants airways

are more prone to collapse due to their relatively high compliance during forced inspiration and due to increased transmural pressure in the case of crying. This is the reason why measures of calming down agitated infants or even the use of sedatives may help to reduce resistance and thus to improve the clinical status.

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Reversibility, bronchial provocation testing and exercise testing

Kai-Håkon Carlsen

Key points

- Bronchodilator reversibility demonstrates reversible bronchial obstruction and is a diagnostic marker of active asthma.
- Bronchial challenge with methacholine/histamine is a sensitive measure of asthma, but is not so specific.
- Indirect measures of bronchial responsiveness (exercise, inhaled adenosine monophosphate, hypertonic saline and mannitol, and EVH) are specific, but not sensitive, measures of asthma.
- Indirect measures of bronchial responsiveness (exercise, *etc.*) respond rapidly (over 1–3 weeks) to inhaled steroids.
- Direct measures of bronchial responsiveness (methacholine and histamine) respond slowly to inhaled steroids (over 3 months).
- Direct measures of bronchial responsiveness (methacholine and histamine) are presently the most exact monitoring tool for asthma and reflect airway remodelling.
- Indirect measures of bronchial responsiveness reflect airway inflammation.
- BHR in childhood may predict later asthma.

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

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

This variability in bronchial tone is assessed both in diagnosis and in monitoring of asthma.

Reversibility: bronchodilator responsiveness

The reversibility to bronchodilator drugs is usually measured in a standardised way by first measuring lung function, usually FEV_1, then inhaling a bronchodilator drug and then again measuring FEV_1 after a suitable time, enabling the bronchodilator drug to have an effect upon bronchial smooth muscle. In addition, other measures of lung function may be used. The procedure has been standardised by a joint Task Force of European Respiratory Society (ERS) and American Thoracic Society (ATS), and an increase in FEV_1 of 12% or $\geqslant$200 mL after inhaled bronchodilator has been selected as a significant increase in lung function and as a criterion for a positive reversibility test (Pellegrino *et al.*, 2005). Either salbutamol or another bronchodilator, such as ipratropium bromide, may be used. Inhaled

salbutamol at a dose of 100 µg given four times from a metered-dose inhaler through a suitable inhalation chamber with a mouthpiece is the recommended dose in adults and in children/adolescents from 12 years; in younger children, half the dose should be used. Alternatively, ipratropium bromide 160 mg (4 × 40 mg) may be used. If preferred, inhalation may be given by nebuliser or powder inhaler but it is important to know the delivery of drug from the device in order to ascertain that sufficient drug has reached the patient. Lung function is measured 15 min after salbutamol inhalation or 30 min after ipratropium bromide inhalation (Pellegrino *et al*., 2005). In order to assess the full reversibility, the patient should not be under the influence of any other bronchodilator. The following recommendations are given by the ERS/ATS Task Force (Miller *et al*., 2005). Short-acting inhaled drugs, such as the β_2-agonist salbutamol or the anticholinergic agent ipratropium bromide, should be withheld for $\geqslant$4 h; long-acting β_2-agonists (salmeterol and formoterol), and oral therapy with aminophylline and slow release β_2-agonists should be withheld for 12 h prior to the test. It is also recommended that smoking should be avoided for $\geqslant$1 h before the procedure.

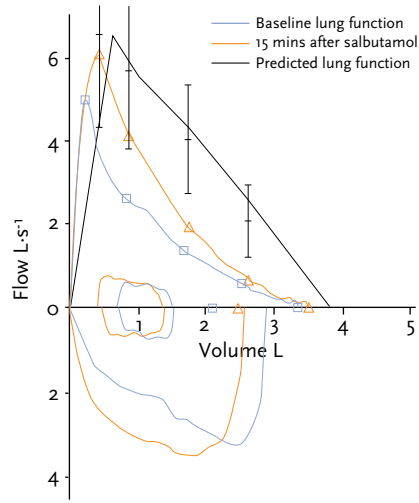

Figure 1. Lung function in a 13-year-old boy showing maximal flow–volume loops before and after inhalation of nebulised salbutamol (5 mg·mL^{-1}, 0.5 mL in 2 mL isotonic saline nebulised by a CR 60 nebuliser). Baseline FEV$_1$ was 2.09 L·s^{-1} (66% predicted); 15 min after inhalation of salbutamol, it had risen to 2.46 L·s^{-1} (78% predicted), presenting an increase of 18% and demonstrating a positive reversibility test. The baseline lung function test was performed without the influence of any bronchodilator.

Figure 1 shows lung function from a 13-year-old boy as maximal flow–volume curves before and 15 min after inhalation of salbutamol.

In the Childhood Asthma Management Program (CAMP) study, the consistent presence of a positive bronchodilator response over a 4-year period in asthmatic children was associated with persistently lower baseline FEV$_1$ values as well as a lack of use of inhaled steroids, thus demonstrating the usefulness of bronchodilator reversibility in the monitoring of childhood asthma (Sharma *et al*., 2008). In severe, steroid-resistant asthma, FEV$_1$ was persistently reduced together with a reduced bronchodilator response in spite of therapeutic trials with prednisolone. The combination of a lack of bronchodilator response in the presence of persistently reduced FEV$_1$ may possibly indicate the presence of airway remodelling (Goleva *et al*., 2007).

In addition, in preschool children, assessment of reversibility has been made by assessment of airway resistance by use of the interrupter technique (R_{int}), setting the limit for a positive response to a decrease in R_{int} at 32% of baseline or a decrease in Z-score of 1.25 (Mele *et al*., 2010), as well as using tidal breathing parameters (time taken to achieve peak tidal expiratory flow (t_{PTEF})/expiratory time (t_E) ratio), which was found to discriminate between children with asthma and healthy children. An increase in t_{PTEF}/t_E of at least two standard deviations of intrasubject variation was used as a criterion for a positive response to bronchodilator, and a highly significant correlation between reversibility and a

marker of eosinophil inflammation, serum eosinophil cationic protein, was reported (Lødrup Carlsen *et al*., 1995). Other lung function techniques have also been used to assess reversibility to bronchodilators in preschool children, such as the forced oscillation technique. A change of 32% (and z-score change of -1.85) from baseline values has been suggested as a significant relative bronchodilator response for the resistance of the respiratory system (R_{rs}) at 8 Hz (Calogero *et al*., 2013). None of these techniques require sedation of the child.

Classification of BHR

Bronchial responsiveness, which reflects the variability in bronchial tone in asthma, may be described as subjective, as demonstrated by the symptoms experienced by the asthmatic child and adolescent, or objective, as measured by procedures in the pulmonary physiological laboratory. BHR is defined as "an increase in the ease and degree of airflow limitations in response to bronchoconstrictor stimuli *in vivo*" (Sterk, 1996).

The specific bronchial responsiveness, the bronchial responsiveness to specific inhaled allergens, may be measured by the allergen bronchial provocation test (BPT) (Aas, 1970).

The non-specific BHR may be measured in several ways. According to the mechanisms of bringing about the bronchial response, the methods can be classified as direct and indirect (Pauwels *et al*., 1988). Direct bronchial responsiveness is measured by bronchial provocation with the transmitter methacholine (Hargreave *et al*., 1981) or the mediator histamine (Cockcroft *et al*., 1977a), acting directly upon the bronchial and vascular smooth muscle. Examples of indirect methods of measurement of the nonspecific BHR are by measuring exercise-induced bronchoconstriction (EIB) (Jones *et al*., 1963) or the reaction brought about by inhalation of dry cold air (Zach *et al*., 1987), hyperventilation caused by dry air (Rosenthal, 1984), or inhalation of other substances, such as adenosine monophosphate (AMP) or the hyperosmolar agent mannitol (Avital *et al*., 1995; Brannan *et al*., 2005). The reaction, measured as a reduction in lung function, is brought about indirectly through an effect of mediator release.

Methods of measuring bronchial responsiveness

Originally, direct bronchial responsiveness was measured qualitatively through a BPT by inhaling the test substance in 10-fold increasing concentrations (Aas, 1970), whereas during the last 25 years, quantitative assessment has been performed by doubling the concentration/dose of the test substance (Cockcroft *et al*., 1977a).

Figure 2 shows the dose–response curve obtained in a BPT, with a reduction in FEV_1 caused by inhaling doubling concentrations of methacholine and interpolation to determine provocative concentration causing a 20% fall in FEV_1 (PC_{20}) (Cockcroft *et al*., 1977a). Later, a simplification of the test was introduced, inhaling single doubling doses of methacholine, determining the provocative dose causing a 20% fall in FEV_1 (PD_{20}) (Yan *et al*., 1983).

The test is performed under standardised conditions (Hargreave *et al*., 1981; Cockcroft *et al*., 1977b), with specified nebulisation rates for the tidal breathing method (PC_{20}), inhaling the test agent for 2 min, then measuring FEV_1, and then inhaling the doubled concentration. The test is stopped when FEV_1 is reduced by $\geqslant$20% and the

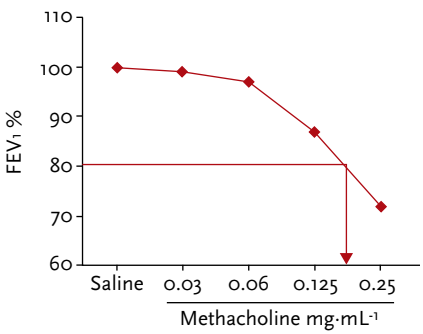

Figure 2. Determination of PC_{20} by interpolation on the logarithmic x-axis.

PC_{20} or PD_{20} is determined by interpolating on the semilogarithmic dose–response curve (fig. 2).

When determining bronchial responsiveness by measuring PD_{20}, the cumulated dose inhaled is determined. An inspiration-triggered nebuliser is most often used as the delivery device, such as the Spira nebuliser (Spira Respiratory Care Centre, Hämeenlinna, Finland) (Nieminen *et al.*, 1988) or the Aerosol Provocation System (Jaeger, Würzburg, Germany), enabling inhalation by controlled tidal ventilation. Alternatively, a handheld DeVilbiss (Mannheim, Germany) nebuliser has been used (Yan *et al.*, 1983).

Recommendations for the measurements of bronchial responsiveness were given by an ERS/ATS Task Force (Crapo *et al.*, 2000).

Determination of PC_{20} or PD_{20} are used both for BPT with methacholine, histamine and AMP, and may be used for allergen BPT. A mannitol BPT was recently developed and launched commercially; it is performed by inhaling cumulative doses of mannitol through a powder inhaler, with a 15% reduction in FEV_1 (PD_{15}) as the cut-off (Brannan *et al.*, 2005).

Eucapnic voluntary hyperpnoea (EVH) is another BPT. In this test, the subject inhales dry air with 4.9% carbon dioxide for 6 min at a preferred ventilation rate of 85% of their maximal voluntary ventilation (MVV), often calculated as $30 \times FEV_1$, but tolerating a ventilation rate down to 65% MVV ($22 \times FEV_1$) (Rosenthal, 1984). A reduction in $FEV_1 \geqslant 10\%$ is taken as a positive test. EVH tests have been shown to be particularly sensitive for asthmatic athletes, in particular endurance athletes (Rosenthal, 1984; Stadelmann *et al.*, 2011). Endurance athletes are particularly prone to developing BHR. This has been suggested to be due primarily to epithelial damage caused by the frequent high-ventilation periods during training and competition, leading to airway inflammation and BHR. Environmental factors (chlorine exposure in swimmers, cold air exposure in winter athletes, and environmental pollution in cyclists and marathon runners) are thought to contribute. Endurance training has specifically been demonstrated to increase parasympathetic tone. Thus, several factors probably contribute in the development of athletes' asthma (Carlsen, 2012).

Exercise testing

Most guidelines for treating childhood asthma have control of EIB as one of their main aims due to the appreciation of the importance for children of being able to participate in physical activity and play together with their peers.

Testing for EIB also represents a measure of bronchial responsiveness, and is an example of an indirect test (Pauwels *et al.*, 1988). Different types of exercise have been standardised for testing EIB: running is more provocative in children than cycling (Anderson *et al.*, 1971) and a duration of 6–8 min gives a greater decrease in post-exercise FEV_1 than shorter or longer exercise periods (Godfrey *et al.*, 1975). It is common to employ a treadmill incline of 5.5% (3°) with rapidly increasing speed until a steady heart rate of approximately 90–95% of the calculated maximum is reached within the first 2 min of running and then maintained for 4–6 min (Crapo *et al.*, 2000; Carlsen *et al.*, 2000). In children, heart rate should be followed electronically, whereas in adults it should be followed by ECG. The running test should preferably be performed at room temperature (20–22°C) and a relative humidity of ~40%. Lung function is measured before, immediately after, and 3, 6, 10, 15 and 20 min after running. FEV_1 is the most common lung function parameter employed, with a 10% fall in FEV_1 most frequently used for diagnosis of EIB.

Sensitivity of the test can be markedly increased while maintaining specificity by adding an extra stimulus to the exercise test, such as running on a treadmill with inhalation of cold (-20°C) or dry air (Carlsen *et al.*, 1998).

There are several differential diagnoses to exercise-induced asthma (EIA), including exercise-induced vocal cord dysfunction as the most frequent (Landwehr *et al.*, 1996;

Refsum *et al.*, 1983). The exercise test may help to discriminate between EIB and exercise-induced vocal cord dysfunction. With EIB, the dyspnoea is expiratory and occurs after exercise with a simultaneous decrease in FEV_1, whereas for vocal cord dysfunction, the dyspnoea is inspiratory, usually audible and occurs during maximum exercise intensity. Vocal cord dysfunction is best diagnosed by continuous laryngoscopy during exercise testing.

Safety precautions during bronchial challenges and patient preparations

Bronchial challenges with bronchoconstrictive agents as well as with indirect measures, like exercise and EVH testing, require that the laboratory has the necessary competence and equipment for treating severe bronchoconstriction, including the preparedness for treating anaphylaxis. A physician should be present during testing and equipment for cardiopulmonary resuscitation immediately available. Whereas progressive pharmacological challenge testing with interval spirometry gradually builds up a bronchoconstriction, an exercise or EVH test represents a maximal or near-to maximal stimulus for bronchoconstriction, requiring special awareness. Preferably, oxygen saturation should be monitored during exercise or EVH testing. FEV_1 should be at baseline or $\geqslant$75% pred before exercise and EVH testing.

The patient should be without the influence of bronchodilators during testing unless the exercise test is performed to assess protection by the bronchodilator. Inhaled corticosteroids should not be used on the day of the test (Thio *et al.*, 2001).

Vigorous exercise should be avoided for 6 h before testing, as exercise may cause a refractory period for eliciting EIB of up to 4 h (Edmunds *et al.*, 1978; Stearns *et al.*, 1981).

Effect of environmental conditions on BHR

Several environmental conditions influence BHR. Cockcroft and co-workers (1977, 1983) documented the link with atopy and allergen exposure by reporting that the late allergic response after allergen bronchial provocation increased direct BHR and that nonspecific BHR increased through exposure to seasonal allergens. Thus, a seasonal allergic sensitisation may contribute to a perennial asthma by increasing the nonspecific BHR through seasonal allergen exposure. Clough *et al.* (1991) reported that the presence of atopy had an impact both on lung function and BHR in asthmatic 7–8-year-old children.

Respiratory virus infections, particularly rhinovirus infections, are the main environmental factor provoking acute asthma during childhood (Carlsen *et al.*, 1984; Johnston *et al.*, 1995). Respiratory virus infections increase bronchial responsiveness to histamine in healthy subjects (Empey *et al.*, 1976), asthmatic and atopic individuals (Bardin *et al.*, 1995), and animals (Nakazawa *et al.*, 1994).

Air pollution has also been reported to increase BHR (Forastiere *et al.*, 1994a), including exposure to diesel exhaust (Nordenhall *et al.*, 2001), and living in an industrially polluted area during the first 2 years of life was found to be related to BHR to methacholine at school age (Soyseth *et al.*, 1995). Although not a consistent finding (Gehring *et al.*, 2010), assessment of BHR in relationship to traffic air pollution has shown that children with BHR is particularly sensitive to traffic-related air pollution (Janssen *et al.*, 2003).

Second-hand smoke is among the most important air pollutants, and an effect upon BHR in children has been reported, although the results are not unequivocal. Forastiere *et al.* (1994b) reported a dose–response relationship between the number of cigarettes smoked by mothers and BHR in daughters of school age.

Exercise and physical training have been reported to influence bronchial responsiveness. Short-term intensive exercise increases direct bronchial responsiveness both in asthmatic and healthy children (Carlsen *et al.*, 1989). Intensive physical endurance training and competition increase bronchial

responsiveness in actively training young skiers (Heir, 1994; Heir *et al*., 1995a), and a combination of respiratory virus infections and heavy training induce an increase in bronchial responsiveness for 4–6 weeks (Heir *et al*., 1995b). In addition, adolescent competitive swimmers have very frequent BHR measured both by methacholine bronchial challenge and EVH (Stadelmann *et al*., 2011). The environment is important in this regard, as chlorine products affect the swimming environment and cold air inhalation is an important part of daily exposure in winter athletes.

Thus, several environmental factors may increase BHR in susceptible subjects and individuals with BHR may be particularly sensitive to environmental exposures. Conversely, for asthmatic subjects, staying in the mountains, with low allergen exposure and low air pollution, improves both in respiratory symptoms and bronchial responsiveness as measured by methacholine provocation (Peroni *et al*., 1994). Measuring bronchial responsiveness, either by direct or indirect means, may thus assess the effect of environmental exposure upon respiratory health.

Relationship of BHR to respiratory symptoms and variation with age

Tiffeneau (1955) suggested that BHR was the most important characteristic of asthma. Later studies have shown that BHR is not obligatory for asthma and that different ways of measuring BHR may relate differently to asthma severity. Hargreave *et al.* (1981) found a distinct relationship with asthmatic symptoms and severity in asthmatic subjects, whereas Salome *et al.* (1987), in a population-based study, found that a number of asthmatic children did not have BHR and some children with BHR were not asthmatic. In addition, children with mild recurrent wheeze were found to include children both with and without BHR (Roizin *et al*., 1996).

Hopp *et al.* (1985) reported that bronchial responsiveness to methacholine varied markedly throughout the lifespan. Bronchial responsiveness to methacholine decreased significantly from 10 to 16 years of age in a population-based birth cohort (Riiser *et al*., 2012a), but in the same birth cohort, BHR to methacholine at 10 years of age in children without asthma was a significant though modest predictor of asthma at 16 years of age (Riiser *et al*., 2012b), suggesting that BHR may develop before active asthma symptoms appear.

Diagnostic significance of BHR

As BHR may be found both in children with and without asthma, and asthmatic children may not demonstrate BHR, measurement of BHR cannot be a conclusive tool for the diagnosis of asthma. In a study of 500 young university students, Cockcroft *et al*. (1992) reported a sensitivity of 100% for histamine $PC_{20} \leqslant 8\ mg \cdot mL^{-1}$ for current symptomatic asthma, a specificity of 93%, a negative predictive value of 100% and a positive predictive value of current asthmatic symptoms of only 29%. While a $PC_{20} > 8\ mg \cdot mL^{-1}$ ruled out current asthma, a PC_{20} of $1\ mg \cdot mL^{-1}$ was almost diagnostic for current asthma. Studies comparing direct and indirect measurements of BHR in asthmatic children and children with other chronic lung diseases show that direct measurements by histamine or methacholine challenge are sensitive tools to identify asthmatic children, but with a rather low specificity towards other chronic lung diseases. However, indirect measurements by exercise tests or by inhalation of cold, dry air have low sensitivity but high specificity (Godfrey *et al*., 1991). When combining exercise testing with inhalation of cold, dry air, the sensitivity of the test increases while maintaining a high sensitivity for comparing asthma and other chronic lung disorders (Carlsen *et al*., 1998). A positive diagnosis by an exercise test thus favours the diagnosis of asthma. Furthermore, by use of exercise tests in children, information about physical skill, fitness and motor development are obtained by an experienced observer.

Effect of therapy on BHR

Anti-inflammatory therapy by inhaled steroids improves BHR in asthma. This may be assessed by repeated measurements of

both direct and indirect BHR. However, it has been demonstrated that inhaled steroids improve direct and indirect BHR to a different degree and with different speed. No effect on BHR was found from a single dose of inhaled steroid (van Essen-Zandvliet *et al.*, 1993). However, after 1 week of inhaled steroids, protection against EIB has already occurred, further increasing over the next 4 weeks (Henriksen *et al.*, 1983). This was confirmed by Waalkens *et al.* (1993), who showed that the effect on EIB reached a plateau effect within 2 months. However, improvement of methacholine PC_{20} did not occur until after 2–3 months of treatment with inhaled budesonide, but then continued throughout a 22-month study by van Essen-Zandvliet *et al.* (1993). Thus, the direct and indirect tests of BHR may reflect different properties of nonspecific bronchial responsiveness in asthmatic children.

BPT measurements may thus be used to monitor treatment effects in asthma. By assessment of airway inflammation and airway remodelling (reticular layer of the epithelial basement membrane) in bronchial biopsies, it has been shown that methacholine BPT is superior to clinical assessment and lung function measurements in the follow-up of asthma patients (Sont *et al.*, 1999). Based upon the rapid response to inhaled steroids and the relationship of EIB with markers of airway inflammation, the slower response to treatment, and the relationship of methacholine BHR with basement membrane thickness, it has been stated that EIB reflects airway inflammation, whereas direct bronchial responsiveness to methacholine reflects airway remodelling.

Conclusion

Measurements of BHR are useful tools in assessing the severity of childhood asthma. However, the different methods of assessment differ to a certain extent in their ability to differentiate asthma from other chronic lung diseases, and they are influenced by therapy to a different degree. Measurements of BHR have given insight into the pathophysiological mechanisms of asthma and they are frequently employed in epidemiological studies as objective measures. Tests of BHR are valuable tools, particularly in assessing severe asthma, but they cannot replace careful clinical examination and assessment of children with asthma.

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Blood gas assessment and oximetry

Paola Papoff, Fabio Midulla and Corrado Moretti

In clinical practice, arterial blood gas (ABG) analysis is needed to assess patients with respiratory diseases and those with other disorders influencing pulmonary gas exchange and acid–base disturbances. ABG analysis is also needed to establish the diagnosis of respiratory failure.

ABG analysis helps to evaluate the following:

- acid–base equilibrium (pH)
- respiratory function ($PaCO_2$, PaO_2 and SaO_2)
- metabolic function (bicarbonate, base excess and anion gap).

The principles underlying traditional ABG measurement are based on the electrochemical interaction between respiratory gases and selected metals within electrodes (Clark, 1956). Whereas PaO_2, $PaCO_2$ and pH are measured directly, other variables, such as bicarbonates (actual and standard) and SaO_2, are calculated using well-defined equations.

A systematic approach to ABG interpretation is demonstrated in table 1.

Key points

- Acid–base disturbances can be classified using a three step systematic approach: pH, $PaCO_2$, bicarbonate.
- If pH is abnormal, determine if acidaemia or alkalaemia.
- If the measured pH and $PaCO_2$ are both abnormal, assess the direction of change; if they change in opposite directions the primary acid–base abnormality is respiratory, otherwise it is metabolic.
- When an acid–base imbalance is diagnosed look for compensation or mixed disorders.

Compensation for respiratory or metabolic disorders

Because the body attempts to maintain blood pH at 7.4, respiratory or metabolic disorders normally trigger an equal counterbalancing effect in the other systems. Table 2 summarises the formulas used for estimating the compensation level. Under these circumstances the respiratory and metabolic components are both abnormal, but pH is almost normal (table 1). The body never overcompensates, and may even fail to reach complete compensation (Carmody *et al.*, 2012). Failure to reach the predicted compensation level should lead the clinician to suspect a mixed disorder.

Mixed disorders

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

Table 1. Interpretation of acid–base disorders: examine the pH, determine the primary disorder and look for compensation

Normal pH 7.35–7.45

- Acidaemia: decreased pH <7.35
  - Respiratory acidosis: decreased pH, increased P_{aCO_2}
    - Renal compensation:
      - Kidneys reabsorb bicarbonate
      - pH ≈, increased bicarbonate
  - Metabolic acidosis: decreased pH, decreased bicarbonate
    - Pulmonary compensation:
      - Hyperventilation releases CO_2
      - pH ≈, decreased P_{aCO_2}
- Alkalaemia: increased pH >7.45
  - Respiratory alkalosis: increased pH, increased P_{aCO_2}
    - Renal compensation:
      - Kidneys excrete bicarbonate
      - pH ≈, decreased bicarbonate
  - Metabolic alkalosis: increased pH, increased bicarbonate
    - Pulmonary compensation:
      - Hypoventilation retaining CO_2
      - pH ≈, increased P_{aCO_2}

pH

pH is a scale for measuring acidity or alkalinity. Normally, blood is slightly alkaline (pH 7.4) with an acceptable range of 7.35–7.45. If the pH is <7.35 the patient is acidaemic, if it is >7.45 the patient is alkalaemic. Acidosis and alkalosis, the processes leading to these states, are either respiratory or metabolic (Carmody *et al.*, 2012). Significant deviations in pH from normal ranges rapidly become

Table 2. Compensatory response of a metabolic or respiratory disorder

Disorder	Expected compensation
Metabolic acidosis	P_{aCO_2} = 1.5 (bicarbonate) + 8±2 (Winter's formula)
Metabolic alkalosis	P_{aCO_2} = 0.7 (bicarbonate) + 20±1.5
Acute respiratory acidosis	Bicarbonate will increase by 1 mEq·L^{-1} for each 10 mmHg rise in P_{aCO_2} above 40 mmHg
Chronic respiratory acidosis	Bicarbonate will increase by 3–4 mEq·L^{-1} for each 10 mmHg rise in P_{aCO_2} above 40 mmHg
Acute respiratory alkalosis	Bicarbonate will decrease by 2 mEq·L^{-1} for each 10 mmHg decrease in P_{aCO_2} below 40 mmHg
Chronic respiratory alkalosis	Bicarbonate will decrease by 5 mEq·L^{-1} for each 10 mmHg decrease in P_{aCO_2} below 40 mmHg

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life-threatening; Marieb *et al.* (2007) suggested "absolute blood pH limits for life" are 7.0–7.8, although patients may survive if isolated samples exceed this range. Both carbon dioxide and bicarbonate affect pH. To better quantify the relationship between pH, carbon dioxide and bicarbonate, Henderson (1913) developed the following formula demonstrating that the ratio of bicarbonate and carbon dioxide, not the absolute values, determines pH:

$$pH = 6.1 + \log([HCO_3^-]/[0.03 \times PaCO_2])$$

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

Respiratory disorders

Measures that assess adequacy of ventilation
Air normally contains almost no carbon dioxide (0.04%); blood carbon dioxide is a normal metabolic waste product. Normal $PaCO_2$ ranges from 35 to 45 mmHg. Blood levels depend on clearance, which, in turn, depends on ventilation.

Small tidal volumes, low frequencies or obstructed airways lead to reduced carbon dioxide clearance and, therefore, high blood carbon dioxide (respiratory acidosis). For every increase in $PaCO_2$ of 20 mmHg above normal the pH falls by 0.1. For every decrease in $PaCO_2$ of 10 mmHg below normal the pH rises by 0.1. Any change in pH outside these ranges suggests a mixed disorder. $PaCO_2$ may also be elevated in compensated metabolic alkalosis (table 2).

Hyperventilation leads to increased carbon dioxide removal and then to a decreased $PaCO_2$ and an elevated pH (respiratory alkalosis). Low $PaCO_2$ levels can be also found in compensated metabolic acidosis (table 2).

Mechanisms for metabolic compensation in a respiratory disorder When respiratory acidosis persists beyond 6–12 h, the kidneys generate bicarbonate by excreting ammonium with chloride in the urine and, in this process, bicarbonate is added to the plasma leading to the hypochloraemic alkalosis typically seen in chronic respiratory acidosis. Metabolic compensation of respiratory acidosis takes time to reverse. Rapidly correcting chronic respiratory acidosis will, therefore, result in a self-resolving metabolic alkalosis.

Measures/indices that assess adequacy of oxygenation
PaO_2: blood oxygen measurement serves as a surrogate for tissue oxygen measurement. Tissue oxygen is far lower than blood oxygen. Oxygen in the arterial blood is present as PaO_2 (dissolved oxygen) and SaO_2 (oxygen bound to haemoglobin). As long as the PaO_2 is >60 mmHg, SaO_2 remains above 90%. If PaO_2 is <60 mmHg, this may lead to a significant reduction in SaO_2 and impaired oxygen delivery to tissues (fig. 1).

PaO_2*/inspiratory oxygen fraction* (FiO_2): this ratio can be used to compare arterial oxygenation in patients breathing different FIO_2 values. A patient who has a normal PaO_2 of ~100 mmHg while breathing room air should have a PaO_2/FiO_2 ratio of 100/0.21=500. The normal range for the PaO_2/FiO_2 ratio is 300–500. Values of less than 250 imply a significant problem in the lung gas exchange mechanisms. For this calculation the percentage of oxygen being administered must be entered in the blood gas analyser.

Alveolar–arterial oxygen tension difference ($PA–aO_2$): is the difference between the alveolar oxygen pressure (PAO_2) and PaO_2. PaO_2 is derived from the ABG analysis, whereas PAO_2 may be calculated from the simplified alveolar gas equation:

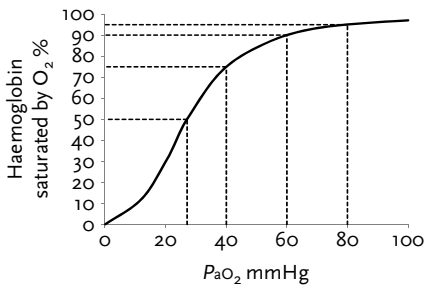

Figure 1. The oxyhaemoglobin dissociation curve.

$P_{AO_2} = (P_{atm} - 47\ mmHg) \times F_{IO_2} - P_{aCO_2}/0.8$

47 mmHg is the water vapour added by the airways and 0.8 is the respiratory quotient.

In normal lungs, the P_{A-aO_2} is <12–15 mmHg in room air and <70 mmHg in 100% oxygen. A high P_{A-aO_2} gradient implies a defect in oxygen diffusion across the alveolar–capillary membrane or a defect in ventilation/perfusion ratio or right-to-left shunting. Conversely, if the P_{A-aO_2} gradient is not increased, lack of oxygenation is due to low respiratory effort. For example, a healthy person who hypoventilates would have hypoxia, but a normal P_{A-aO_2} gradient (Carmody *et al.*, 2012).

P_{aO_2}/P_{AO_2} ratio: this offers better accuracy over a broader F_{IO_2} range than the P_{aO_2}/F_{IO_2} ratio. It is considered a somewhat better index of oxygenation. When the P_{aO_2}/P_{AO_2} ratio is very low, high F_{IO_2} values obviously do not translate into improved blood oxygenation: in such situations, a high shunt fraction can be expected.

Metabolic disorders

Metabolic disorders will initially cause alterations in the serum bicarbonate concentrations and, thus, pH. The base excess/deficit is a calculation that estimates the metabolic component in the acid–base. Whereas a positive base excess may indicate metabolic alkalosis, a negative base excess usually suggests metabolic acidosis. Blood with a pH 7.4 and P_{aCO_2} 40 mmHg at 100% oxygen saturation has a base excess of zero. Most blood gas analysers offer the option of calculating either the base excess of the blood sample, also called standard base excess, or the base excess of the extracellular fluid, also called actual base excess. The blood base excess does not truly indicate the base excess of all extracellular fluids, as buffering capacities (*i.e.* haemoglobin concentration) differ between the intravascular and the extravascular compartments. Therefore, to be representative of the whole extracellular compartment (intravascular and extravascular), the blood base excess value is calculated on a haemoglobin level of 5 $g \cdot dL^{-1}$ (*i.e.* blood that is approximately one-third of the extracellular fluid).

Metabolic acidosis

Metabolic acidosis is defined as a serum bicarbonate <22 $mEq \cdot L^{-1}$ and a pH <7.35. Metabolic acidosis may be caused either by adding acid or removing buffer. Help in distinguishing these two conditions comes from calculating the anion gap. With the onset of metabolic acidosis a certain amount of respiratory compensation takes place in the form of hyperventilation (table 2). When the carbon dioxide tension (P_{CO_2}) is outside the expected range for a given bicarbonate concentration, a superimposed respiratory acid–base disturbance is present.

Anion gap

Organisms exist in a state of electro-neutrality with major and minor cations balanced by similar anions (fig. 1). The major extracellular cation is sodium, while the other minor cations (potassium, calcium, magnesium, *etc.*) are grouped as unmeasured cations. Similarly, the major commonly measured anions are chloride and bicarbonate, whereas other anions (*e.g.* albumin, phosphates and sulfates) are grouped as unmeasured anions (Carmody *et al.*, 2012). In normal conditions, a small unmeasured anion excess represents the anion gap (fig. 2).

$$\text{Anion gap} = \text{unmeasured anion} - \text{unmeasured cations} = 10–14\ mEq \cdot L^{-1}$$

or indirectly

$$\text{Anion gap} = Na^+ - (Cl^- + HCO_3^-) = 10–14\ mEq \cdot L^{-1}$$

In low albumin states, 2.5 $mEq \cdot L^{-1}$ should be added to the calculated anion gap for every 1 $g \cdot dL^{-1}$ of albumin below the usual normal value (Oh, 2010). Metabolic acidosis with a normal anion gap occurs when the bicarbonate concentration falls and the chloride concentration increases proportionately to maintain electrical neutrality. This happens when bicarbonate is lost either in the gastrointestinal tract, as in diarrhoea, or in urine (renal tubular acidosis).

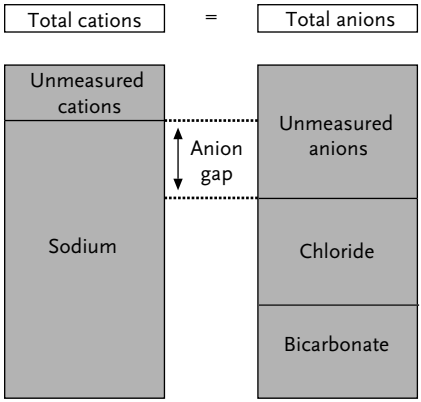

Figure 2. Schematic representation of the concentration of plasma cations, mainly represented by sodium, plasma anions (bicarbonate and chloride), and the anion gap.

An abnormally large anion gap indicates that the metabolic acidosis depends on accumulation of acids not normally found in significant quantities in the body (*e.g.* ketoacids, lactic acid and salicylic acid).

Metabolic alkalosis

Metabolic alkalosis is defined as a serum bicarbonate >26 mEq·L^{-1} and a pH >7.45. Compensatory hypoventilation may cause a slight rise in $P_{a}CO_2$ (table 2), but this is typically minor. The development of alkalosis is usually due to excessive loss of hydrogen ions either from the stomach (vomiting) or the kidney (when excess aldosterone increases the activity of a sodium–hydrogen exchange), which results in regeneration of the titrated plasma bicarbonate. Important to the pathogenesis of the alkalosis is chloride and potassium depletion, which also leads to bicarbonate reabsorption. This leads to further reabsorption of bicarbonate. Chloride and potassium depletion can be induced in a number of ways by:

- corticosteroid medication,
- diuretic therapy,
- gastric suction.

Metabolic alkalosis is classically delineated into two types: chloride responsive and chloride unresponsive. A helpful way to differentiate between the two is to evaluate urine chloride. Patients with a low urine chloride (<10 mEq·L^{-1}) are those who have chloride responsive alkalosis (*e.g.* loss of acids from the gastrointestinal tract and diuretics), whereas patients who have a normal or high urine chloride (>10 mEq·L^{-1}) have chloride unresponsive alkalosis. In most patients with chloride unresponsive alkalosis, urine potassium will also be elevated (>30 mEq·L^{-1}), indicating significant renal losses of potassium. The pathophysiology of chloride unresponsive metabolic alkalosis involves potassium depletion along with excessive mineralocorticoid activity (*e.g.* hyperaldosteronism, Cushing's disease or Bartter's syndrome) (Carmody *et al.*, 2012; Ayers *et al.*, 2012).

Specific issues

Type of blood sample for blood gas Although blood gas has historically been analysed in arterial blood, obtaining arterial samples may be difficult and lead to complications. Capillary blood is routinely used in neonates or other patients when an arterial sample is not easy to collect. Capillary blood is a mix of arteriolar, capillary and venous blood with a small contribution of interstitial and intracellular fluid. Although the relative higher pressure on the arterial side of the circulation increases the proportion of arterial blood in the capillary sample, only pH and P_{CO_2} are acceptable because of their low arterio–venous gradient; on the contrary, P_{O_2}, which exhibits a relatively high arterio–venous difference, is less likely to show good agreement between capillary and arterial blood (Sauty *et al.*, 1996). Increasing local blood flow by the so-called "arterialisation" of capillary blood (warming) does not show significant difference of pH and blood gas compared to the non-warmed capillary blood. Another acceptable alternative for the initial assessment of a patient with mild respiratory problems is peripheral venous sampling (table 3). Arterial and venous pH,

Table 3. Arterial and venous blood gas reference values

	Arterial blood	Venous blood	Capillary blood
pH	7.40 (7.35–7.45)	7.36 (7.31–7.41)	7.35–7.45
P_aCO_2 mmHg	40 (35–45)	42–55	36–45
P_aO_2 mmHg	95 (80–100)	30–50	50–80
Bicarbonate mEq·L^{-1}	24 (22–30)	24–28	22–27
Base excess mEq·L^{-1}	-3–3	-3–3	-3–3
O_2 saturation %	>90	60–85	

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

bicarbonate and base excess yield acceptable agreement in patients with normal peripheral circulation. The mean arterio–venous difference in pH is ~0.035 pH units, for PCO_2 is 5.7 mmHg, and for bicarbonate is -1.41 mmol·L^{-1} (Kelly, 2010). Owing to the wide variations in venous PCO_2, a venous sample can be used only to screen for arterial hypercarbia or to monitor trends in PCO_2 for selected patients, but not to establish the diagnosis of respiratory failure.

Pitfalls in ABG interpretation ABG samples must be collected, handled and analysed properly for accurate results. Every sample must be obtained anaerobically and be anticoagulated. After collection, the sample should be immediately analysed or properly chilled and analysed within 30 min. Supplemental oxygen should be entered in the blood gas machine to obtain oxygenation indices. Factors influencing the results of ABG analysis include:

- the type of syringe used for collection (unless the sample is analysed within 15 min),
- the presence of air bubbles (causing an artificially high P_aO_2 and underestimating the true P_aCO_2),
- using too much heparin as an anticoagulant (decreased P_aCO_2).

Blood gas analysis values during systemic hypothermia Physical laws determine that gas solubility within a liquid decreases when the temperature diminishes. During therapeutic hypothermia, arterial P_aCO_2 therefore decreases and pH increases. Each degree above or below 37°C will result in a 5 mmHg change in P_aO_2 and a 2 mmHg change in P_aCO_2. All blood gas machines have the option of analysing the blood at an ''actual'' temperature but this is rarely carried out. When blood gases are measured at 37°C, P_aO_2 and P_aCO_2 increase; therefore, the normal range for blood gases should be increased (Thoresen, 2008).

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Exhaled nitric oxide, induced sputum and exhaled breath analysis

Johan C. de Jongste

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

Key points

- At present, *F*eNO is the only biomarker in exhaled air that has been standardised, developed and validated for clinical application.
- Increased *F*eNO is suggestive of eosinophilic airway inflammation and *F*eNO has a role in the diagnosis and management of asthma after preschool age. Low *F*eNO is seen in suppurative airways disease, including CF, and low nasal nitric oxide is typical for primary ciliary dyskinesia or sinusitis.
- Dose titration of inhaled steroids on the basis of induced sputum eosinophilia has been shown to reduce exacerbations in adult asthmatics, but studies in children are few and inconclusive. The methodology of sputum induction in children is demanding and unlikely to become useful in clinical routine.
- A large number of other potential biomarkers in exhaled air, or in EBC, await further standardisation. Careful evaluation is needed before these can be applied in clinical practice.

Exhaled nitric oxide fraction

Exhaled nitric oxide fraction (*F*eNO) is the best studied and validated noninvasive marker of airway inflammation, and is the only inflammation marker that has widely gained acceptance in routine patient care. Nitric oxide is a free radical gas that is produced from L-arginine, involving constitutively expressed nitric oxide synthases (NOS). One of the isoforms of NOS, inducible NOS, also called type 2 NOS or iNOS, is present on airway epithelial cells, where it is upregulated by proinflammatory cytokines and then produces relatively high amounts of nitric oxide into the airway lumen. This nitric oxide can be measured at the mouth during exhalation, and with appropriately standardised methodology the *F*eNO is highly reproducible. Exhaled nitric oxide levels are measured in parts per billion (ppb), and hence extremely sensitive analysers are needed. *F*eNO analysers for clinical purposes are commercially available, and have evolved from bulky, expensive, delicate chemoluminescence analysers into hand-held, user-friendly devices using a more robust electrochemical cell-based technology (fig. 1). Unfortunately, the different devices do not necessarily produce the same results, and the smaller hand-held analysers cannot be adjusted. Hence, different equipment cannot be used interchangeably unless formal comparisons have shown equivalence.

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

Methodology of FeNO The recommended technique to assess *F*eNO is an on-line measurement during a constant expiratory flow of 50 $mL \cdot s^{-1}$, for at least 10 s (children with vital capacity <3 L: 6 s), through a mouthpiece. Contamination with air from the nose should be avoided, as the nose and paranasal sinuses produce nitric oxide in much higher amounts than the lower airways. This is accomplished by exhaling against a positive pressure that ensures closing of the soft palate, thus closing the nose off from the lower airways.

Ideally, the equipment provides one or more biofeedback signals to help the patient to standardise the expiration flow and duration, and accepts only attempts that fulfil quality criteria. The recommended procedure is feasible in children from the age of 6–7 years; in younger children the success rate falls rapidly. For preschool children, a number of offline methods have been described, which make use of collection devices where exhaled air is stored and analysed, with or without tidal flow control. In infants, *F*eNO measurements have been performed by collecting mixed nasal-oral exhaled air samples in a nitric oxide inert collection bag, or online using various, often complicated approaches, that require an academic setting and dedication. Such methods have not been well standardised and are not suitable for clinical practice.

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

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

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

Clinical applications of FeNO in children Normative values of *F*eNO in children have been published, and show an age-dependent increase during childhood (fig. 2). The upper level of normal ranges from 15 ppb in early childhood to 25 ppb in adolescence, and is slightly higher in males than in females. Higher normal levels are also seen in atopic individuals and in certain non-Caucasian ethnic groups. In asthma, *F*eNO shows daily fluctuations and the minimal change that may be clinically relevant has been proposed as 10 ppb if *F*eNO is <50 ppb or 20% with higher values.

High *F*eNO, especially above 40–50 ppb, is strongly associated with eosinophilic airway inflammation. An abnormally low *F*eNO may be seen during suppurative airway infection, *e.g.* in CF, and is of some diagnostic value in primary ciliary dyskinesia. For the latter

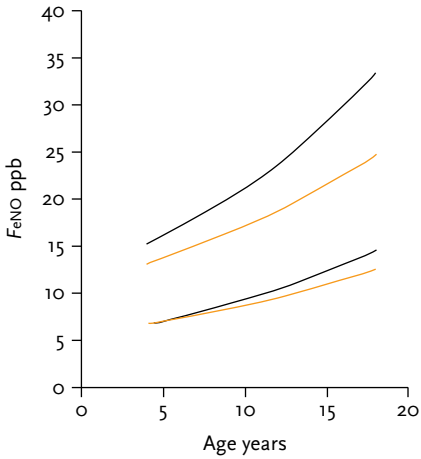

Figure 2. Normative values of FeNO in children. Black lines show mean and upper 95% FeNO (n=405). Orange lines show mean and upper 95% FeNO excluding outliers and atopics (n=332). Reproduced with modification from Buchvald et al. *(2005) with permission from the publisher.*

purpose, nasal nitric oxide measurements have better specificity and sensitivity.

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

FeNO can be of help in the diagnosis of atopic asthma, especially if symptoms are indeterminate. Most published studies on the diagnostic value of *FeNO* in asthma compared clear asthma cases with normal patients, thus providing a strong contrast that is often lacking in daily practice. Hence, the diagnostic value will be lower in less clearly defined populations of children. In contrast to spirometry, which is often normal in children with asthma, elevated *FeNO* commonly persists in asymptomatic episodes and, as a diagnostic test, *FeNO* performs better than FEV_1 or other tests of airway patency. A limitation of *FeNO* is that it reflects eosinophilic inflammation, but not other types of inflammation. *FeNO* may be low in neutrophilic inflammation, which occurs in a considerable proportion of asthmatic children, and this may alternate with eosinophilic patterns.

Inhaled corticosteroids (ICS) reduce *FeNO*, an effect that occurs within a few days of daily treatment. The diagnostic value of *FeNO* is, therefore, limited in subjects who are already on ICS treatment. The effect of ICS on *FeNO* may be used to alert for nonadherence if a child with a documented *FeNO* response on ICS exhibits high *FeNO* levels. Elevated *FeNO* is predictive of successful treatment with ICS, and an increase in *FeNO* has been shown to precede loss of control in children who stop or taper their ICS dose while in clinical remission. *FeNO* above 40–50 ppb is associated with an increased risk of exacerbation and loss of control. In an individual, the predictive value is, however, limited and the benefits of regular *FeNO* assessment to prevent loss of control remain to be shown.

Studies in adults with difficult-to-treat asthma indicated that *FeNO* monitoring may be helpful to identify patients who have an accelerated decline in lung function, and to identify subjects who might benefit from higher doses of ICS. Similar studies in children are lacking.

Several studies in children and adults have tried to improve asthma management by titrating the dose of ICS in *FeNO*. Although most of these studies report some significant benefit of *FeNO* monitoring on secondary end-points, only a few found an effect on the primary end-point that differed between studies. These studies had important methodological flaws, and differed in many other aspects as well, in particular how often and to what degree *FeNO* could indeed influence treatment decisions. The dosing algorithm is entirely responsible for this, and had to be defined on arbitrary grounds. Unfortunately, the heterogeneity of dose titration studies impairs meta-analysis and, therefore, the issue of whether tailoring the ICS treatment in asthma on *FeNO* is beneficial is still

unresolved, and the use of *F*eNO for ICS dose titration can not, at present, be recommended for clinical routine.

An important observation was that among adult asthma patients, there are subjects in whom *F*eNO and symptoms are concordant while in others there is discordancy, with high symptom scores and normal *F*eNO, or *vice versa*. Clearly, any added benefit of *F*eNO monitoring compared to classical symptom monitoring cannot be expected if there is a perfect concordance of *F*eNO and symptoms, and none of the paediatric ICS dose titration studies has taken this aspect into account.

The potential benefit of *F*eNO as a monitoring tool in asthma treatment still requires more study, focussing on well-defined subgroups and exploring the effects of different algorithms.

Induced sputum

Several studies in adults with asthma have examined the potential of incorporating sputum eosinophilia as a marker of airway inflammation in asthma management. The first proof-of-concept study in adults showed benefits of a treatment strategy that was aimed at reducing sputum eosinophilia. These included a substantial reduction of the number of exacerbations and hospital admissions, with no concomitant need for higher doses of anti-inflammatory medication.

Methodology of sputum induction Most children with asthma will not spontaneously expectorate sputum. This makes it difficult to use sputum for regular assessment of airway inflammation. The procedures to induce sputum have been standardised by a European Respiratory Society Task Force and are suitable for use from the age of 8 years. Commonly, sputum is induced by inhaling hypertonic saline, and whole expectorated samples, or selected sputum plugs, are pre-treated with a mucolytic before examination. Reported characteristics include total differential cell counts and contamination with epithelial squamous cells in cytospin preparations, soluble components in the supernatant, and cytokines and mediators of inflammation.

Induced sputum may be valuable for the diagnosis of airway infections in children who do not expectorate, and has been used as a diagnostic, *e.g.* in CF and for the diagnosis of pulmonary TB.

Inhalation of hypertonic saline may cause bronchoconstriction, especially in asthmatics, and pre-treatment with an inhaled β-agonist is therefore needed. There is some risk of microbial contamination of laboratory personnel due to the induced coughing, and appropriate protective measures need to be taken.

In experienced hands, sputum induction in school-age children has been reported with success rates of 60–85%, occasionally even higher, while much lower proportions have been reported for younger children, in whom voluntary expectoration is often problematic and specimens may be only obtained by using a suction cannula. The success rate will depend on subject selection and on the experience and skills of the laboratory technician. The success of repeated procedures is lower, and this is a significant problem if sputum is to be used for regular monitoring purposes. Paediatric normal values of differential cell counts in sputum have been published previously.

Clinical application of sputum induction in children The only paediatric study to date that incorporated sputum eosinophils in the management of asthma showed no benefits in terms of improved asthma control or overall exacerbation rates. This study included a highly selected population of children with severe problematic asthma from a third-line reference centre, using relatively high doses of ICS. Hence, the findings may not be applicable to other populations of children with more common forms of asthma. There are no paediatric studies on the clinical application of soluble components in sputum.

In summary, induced sputum as a means to diagnose or monitor children with inflammatory airway disease is still a research tool and, until now, no clear benefit of measuring any sputum component in children has been documented.

The methodology is demanding and time-consuming, and requires considerable expertise, which makes the place for induced sputum in paediatric clinical practice a limited one.

Exhaled breath analysis

Exhaled breath condensate (EBC) has been studied for many years as an attractive vehicle for soluble components from the lower airways that can be obtained in a noninvasive way. A large number of measurements have been described in exhaled air condensate, including inflammatory mediators and cytokines, pH, hydrogen peroxide and other markers of oxidative stress, and molecules derived from microorganisms. Substances in breath condensate are generally present in trace amounts, which are near or well below the detection limits of most routine analytical techniques, and require extremely sensitive detection methods. The reproducibility of the measurements remains an issue of concern.

A promising new approach is the study of ''metabolomics'' in EBC, which makes use of spectrometric techniques and detects thousands of components, separated on the basis of molecular mass and/or charge, which can be associated with a clinical trait of interest in a hypothesis-free manner. An excellent overview of the present state-of-the-art regarding biomarkers in EBC is provided in a recent *European Respiratory Monograph*.

Methodology of EBC Various methods have been recommended to collect EBC samples, and equipment for EBC collection is commercially available. The methodology for EBC collection was reviewed and recommendations provided in an American Thoracic Society Task Force report. The techniques vary from a simple tube system to be cooled in a refrigerator before use, to more sophisticated devices that use cooled containers through which the exhalate passes and in which EBC is retained. A nose clip and saliva trap are recommended, and the material of tubing and condenser should be inert for substances of interest.

Unfortunately, the methods employed in EBC research to date have the inherent difficulty that the air from the lower airways passes through the pharynx and mouth, where contamination may easily occur. Saliva is an important potential source of contamination as it contains molecules of interest in vastly higher quantities than EBC. In addition, the equipment itself may be a source of contamination and either rigorous cleaning of all parts of the equipment that come into contact with the airstream or disposable tubing and containers are needed to avoid contamination.

Clinical application of EBC in children A lot of studies have reported associations of molecules in EBC and clinical disease in children and adults. Examples include:

- pH, which tends to be lower in severe or acute asthma but not in mild and stable disease;
- hydrogen peroxide and nitric oxide metabolites that are elevated in asthma;
- hydrogen cyanide, which is produced by *Pseudomonas* and detectable in EBC of CF patients;
- 8-isoprostane, a marker of oxidative stress in CF and asthma;
- a large number of inflammatory mediators and proinflammatory cytokines in relation to wheezing or asthma.

What is lacking for most potential biomarkers in EBC are studies into the clinical methodology, especially short- and long-term reproducibility studies and studies associating meaningful changes in disease activity to changes in biomarkers. In general, the overlap with findings in healthy subjects has been considerable, and studies that did assess reproducibility have been disappointing. No paediatric studies have been published that showed clinical benefit of measuring components in EBC in individual patients.

Conclusion

Noninvasive biomarkers of airway inflammation in exhaled air are of great interest as they may provide information on an important aspect of disease that is otherwise difficult to assess in children.

In theory, a reliable marker of airway inflammation would allow for better diagnosis and selecting the appropriate treatment in the lowest possible dose that suppresses airway inflammation. In practice, it has proven exceedingly difficult to substantiate these expectations. Of all noninvasive biomarkers of airway inflammation, only F_{ENO} has developed into a useful clinical tool with many applications, but also with limitations and pitfalls that one should be aware of. Induced sputum requires more time and effort, and has limited feasibility and repeatability in children, especially at a younger age. As adult studies have clearly demonstrated benefits of induced sputum-based monitoring of asthma, it remains desirable to pursue sputum induction further for application in children. At present, induced sputum mainly seems useful for obtaining microbiological specimens in suspected airway infection, but also the evidence for added value is scanty. Assessing biomarkers of inflammation in EBC has been an exciting and promising development for many years now. Despite a growing number of studies, development into clinical practise is hampered by methodological difficulties related to the extremely low concentrations of potential markers in EBC, a low reproducibility and a high risk of contamination in the upper airway. Sensitive and robust detection methods and better equipment for collection, all well standardised, may sooner or later reveal the true clinical potency of EBC biomarkers.

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Pulmonary function testing in infants and preschool children

Enrico Lombardi, Graham L. Hall and Claudia Calogero

Measuring lung function in infants (first year of life) and preschool children (2–5 years old) represents a major challenge in paediatric respiratory medicine. Infants cannot voluntarily perform the manoeuvres required for pulmonary function tests (PFTs) used in older children and adults. The majority of lung function tests in infants and young children up to 2 years of age require sedation to ensure acceptable and repeatable results. The most commonly used sedative is chloral hydrate (80–100 mg·kg^{-1}, maximum 1 g); however, this sedative is no longer available in the USA. Infant lung function tests performed during tidal breathing (such as tidal breathing measurements and the multiple breath washout) are more readily used without sedation, although test success rates will decrease with increasing age. While PFTs in this age group are possible and equipment is commercially available, infant PFTs are less suitable for routine clinical testing. A recent survey cited the ''need for sedation'' and the ''uncertainty about how data actually impacts patient care'' as limitations for the use of infant PFTs. Infant PFTs have been standardised by the American Thoracic Society (ATS) and European Respiratory Society (ERS).

Key points

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

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

This section will describe some of the most frequently used PFTs in infants and preschool children. Other fundamental PFTs for infants and preschool children, such as the washout techniques and the forced oscillation technique, are described in great detail separately in this section of the *Handbook*.

Raised volume rapid thoracic compression The measurement of forced expiratory flow and volumes in infants is obtained using the raised volume rapid thoracic compression (RVRTC) technique and international testing guidelines that are available. The RVRTC technique is demanding in terms of staffing and equipment resources, as well as the training required to ensure high-quality measurements are obtained. Briefly, the technique involves applying repeated inflation breaths to the sedated infant, *via* a facemask, to a pressure of 30 cmH_2O. An inflatable jacket is used to rapidly compress the infant's thorax and abdomen to produce the forced expiratory flow–volume curves. The jacket inflation pressure is increased progressively until there are no further increases in forced expiratory flow (FEF), suggesting flow limitation has been achieved. The reported RVRTC outcomes are FVC, $FEV_{0.5}$ and FEF at a defined proportion of FVC. Technically acceptable and repeatable outcomes are influenced by laboratory experience. The most commonly used reference equations may no longer be suitable for the current generation of commercially available equipment and it is not clear what changes in RVRTC outcomes constitute a clinically meaningful difference, primarily due to the difficulties associated with repeated sedation and changes with lung growth over time. These place further limitations on the use of RVRTC for the management of lung disease in individual patients.

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

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

Infant plethysmography The use of body plethysmography in infants to measure functional residual capacity (FRC_{pleth}) operates on the same principles as plethysmography in older children and adults. The primary difference is that the infant or young child is sedated, lying supine and breathing through a facemask that is sealed over the nose and mouth using silicon putty. Infant plethysmography measurement guidelines have been published. The success in obtaining FRC_{pleth} is generally high and is influenced by sedation success and experience of the personnel. Reference data in healthy infants are available; however, the validity of these data in using currently available equipment has been questioned. There are very few data on the repeatability of FRC_{pleth} over time and a clinically meaningful change in response to treatments (such as bronchodilators) or deterioration in clinical status is not known. Considered together these limit the ability of infant plethysmography to be used in a meaningful way in individual infants with chronic lung diseases.

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

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

PFTs in preschool children

Preschool spirometry In individuals >5 years of age, spirometry is the most commonly used lung function technique, while it is thought that preschool children are not able to perform acceptable spirometry manoeuvres. Recent studies have highlighted that spirometry in preschool children has a good feasibility (between 47% and 92%), especially when an incentive software is used. A lower feasibility (as low as 21%) has been found in children aged ⩽4 years and in those with neurodevelopmental disabilities (such as children with BPD).

Standardisation of spirometry for adults and children aged ⩾6 years requires that subjects inhale up to TLC and forcefully exhale for at least 3 s (for children <10 years of age) or at least 6 s (for children >10 years of age) until residual volume (RV) is reached, so that FEV_1 and FVC can be accurately measured. The manoeuvre should also have a good start, meaning an extrapolated volume <5% of FVC or <0.150 L. This manoeuvre needs to be repeated until at least three manoeuvres are obtained with the two largest values of FVC and FEV_1 within 0.150 L of each other.

Several studies have shown that preschool children have difficulty in meeting such acceptability criteria for spirometry. Preschool children are physiologically different from older children and adults: they have smaller lung volumes and larger airways with respect to lung volume when compared with older children. Therefore, spirometric manoeuvres in preschool children are completed more quickly than in older children, sometimes even in <1 s. As a result, FEV_1 is not always measurable and indices such as $FEV_{0.75}$ or $FEV_{0.5}$ are more reasonable in this age group. It has been shown that extrapolated volume is lower and extrapolated volume/FVC is higher in preschool children than in older children and adults. For these reasons, acceptability criteria for spirometry in preschool children are different from those used in older children and adults.

Figure 1 shows a preschool child performing spirometry. The ATS/ERS statement for lung function testing in preschool children has provided appropriate recommendations for spirometry in this age group, which can be summarised as follows:

- the child should have time to familiarise themselves with the equipment and operator,
- incentive software may be used, although this is not mandatory,

- the child's posture (seating or standing) and the use of a nose clip should be reported,
- if the extrapolated volume is >80 mL or 12.5% of FVC, the curve should be inspected again but not necessarily rejected,
- in case of early termination of expiration, it may be possible to record $FEV_{0.5}$, $FEV_{0.75}$ and FEV_1, but not FVC,
- a minimum of two acceptable manoeuvres should ideally be obtained, where the second largest FVC and FEV values are within 0.1 L or 10% of the highest value; however, poor repeatability should not be a reason for automatic rejection of data.

Several reference values for spirometry in preschool children have been reported and these data are now included in the recently published reference values of the ERS Global Lung Function Initiative. Clinical data on the usefulness of spirometry in preschool children have also been published.

Interrupter technique The interrupter technique is a suitable method to measure lung function in preschool children.

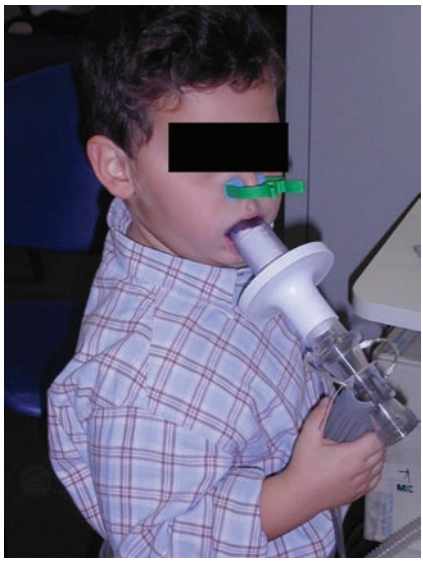

Figure 1. Preschool child performing spirometry.

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

- mouth pressure will equilibrate with alveolar pressure,
- the valve closure time will minimise leak,
- compliance of the upper airway is negligible.

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

The test procedure, technical aspects and data analysis for the classical interruptor technique have been fully described previously. The child should be seated, breathing quietly through a mouthpiece and bacterial filter, wearing a nose clip and with the cheeks supported (fig. 2). Each occlusion

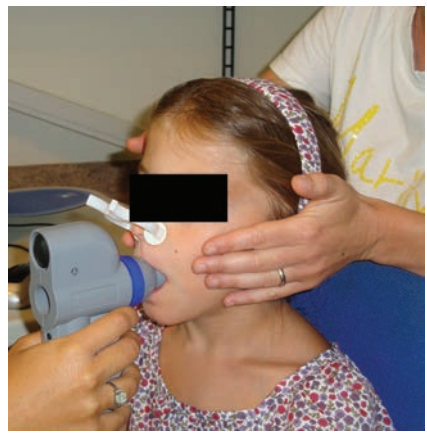

Figure 2. Preschool child performing R_{int}.

should be triggered during expiration by a flow set to coincide with peak expiratory flow and 10 interruptions should be recorded, with the aim of obtaining a minimum of five acceptable manoeuvres. At the end of the test the median value of all technically acceptable interruptions should be reported.

International reference equations for males and females have been recently published. Measurements of R_{int} have been shown to have a good intra-measurement and between-test repeatability.

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

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

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

Several indices for sR_{aw} have been proposed, such as:

- total specific resistance ($sR_{aw,tot}$), which is the slope of the line between the two points of inspiratory and expiratory pressure;
- resistance at the peak of flow ($sR_{aw,peak}$);
- effective specific resistance (sR_{eff}), which is the least-squared regression of pressure and flow throughout the breathing cycle.

Being a product of a volume and a resistance, an abnormal value can indicate changes in both components. It has been recently recommended that sR_{eff} should be calculated since it measures sR_{aw} over the entire breathing cycle.

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

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

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

Conclusion

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

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

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

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Single- and multiple-breath washout techniques

Sophie Yammine and Philipp Latzin

Inert-gas washout (IGW) has been re-established in recent years as one of the most sensitive lung function tests for assessing small-airway function. It can be performed over a single tidal breath, termed single-breath washout (SBW), or over a series of tidal breaths, termed multiple-breath washout (MBW). Recent developments have led to commercially available and user-friendly washout equipment, mirroring the increasing interest in a transition of IGW tests from research into clinical routine.

Key points

- IGW is based on washing in and out inert tracer gases to assess the gas mixing efficiency of the lung.
- The most important outcome parameter of MBW is the LCI, calculated as the cumulative expired volume needed to clear the lungs of the tracer gas divided by the lung size (FRC).
- IGW seems most sensitive in children with CF for detecting early lung disease; its role in other disease groups is currently less well examined.
- After early studies demonstrating the feasibility and usefulness of washout measurements in children, commercially available equipment, and new guidelines for standardisation will now enable the implementation of MBW in routine clinical practice.

Anatomical and physiological background

The dichotomous branching structure of the lung, resulting in $>100\ m^2$ of lung surface, has evolved to facilitate gas exchange. In the conducting airways (generations 0–16), gas transport mainly occurs by convection, and in the intra-acinar airways (generations 17–23), mainly by diffusion. In the transition zone at the entry to the acinus, both mechanisms show a similar contribution. The definition of small airways is derived from *post mortem* adult data and includes all airways with a luminal diameter of <2 mm (corresponding to generations 8–23). Pathological processes such as mucus impaction, hyperinflation, obstruction and bronchiectasis affect these gas transport mechanisms and lead to inefficient gas mixing, which can be detected and quantified using IGW.

Evolution of IGW

The IGW technique was introduced in the 1950s. Most data from the last 15 years have been obtained using sulfur hexafluoride as the inert tracer gas. However, because of its potent greenhouse gas effect, in many countries, sulfur hexafluoride is no longer available. Furthermore, bulky and expensive mass spectrometers, the gold standard for sulfur hexafluoride analysis, are not suited to routine clinical use. This has led to a renaissance of nitrogen washout using 100% oxygen, which had previously been abandoned, for observing alterations in infant breathing patterns. An ultrasonic flow meter nitrogen MBW setup is now commercially available. It is based on the measurement of oxygen, carbon dioxide and molar mass with indirect calculation of the

nitrogen concentration. Nitrogen MBW measurement has been demonstrated to be safe and feasible at school and preschool age, whereas in infants, sulfur hexafluoride is currently still standard.

SBW technique and parameters

SBW is classically performed using a vital capacity (VC) manoeuvre (fig. 1) but can also be done during tidal breathing, which has the advantage of being feasible even in children younger than 10–12 years. The SBW expirogram shows the tracer gas concentration over expired volume, where phase III represents the expired gas from the alveolar zone (fig. 1). The main outcome parameter of SBW is the slope of phase III (SIII), representing the efficiency of gas mixing in the small airways.

MBW technique and parameters

MBW is better established than SBW. As a tidal breathing test, it is easy to perform in children. It requires an adequate mouthpiece/facemask seal and a regular

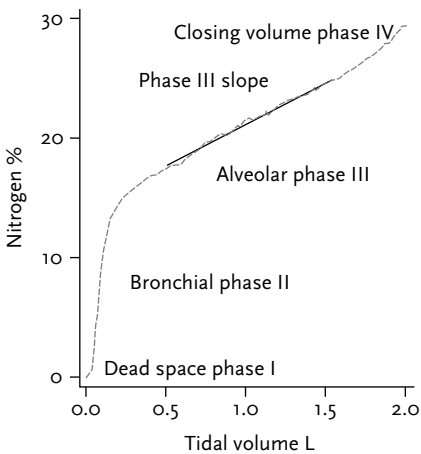

Figure 1. Classical VC nitrogen SBW in a normal subject. The four sequential phases of the expirogram are: phase I, representing the absolute dead space; phase II, the bronchial phase; phase III, the alveolar phase; and phase IV, delimiting the closing volume (in tidal-breath SBW, phase IV is missing). The slope of phase III is calculated by linear regression over phase III (%·L^{-1}).

breathing pattern. After reaching equilibration of the exogenous washed-in gas, the gas is switched off and the washout is started. For nitrogen MBW, the test starts directly with the washout by switching into 100% oxygen (fig. 2). The washout is terminated when the end-tidal gas concentration reaches values below 1/40 of its starting concentration. The current standard requires at least two, ideally three, valid test runs. New guidelines for IGW measurement extended for all age groups have just been published.

The main outcome parameter of MBW, reflecting overall ventilation inhomogeneity, is the lung clearance index (LCI), calculated as the cumulative expired volume needed to clear the lungs of the tracer gas divided by the functional residual capacity (FRC). Based on SIII analysis of washout breaths, more specific indices have been developed reflecting the convection-dependent inhomogeneity (S_{cond}) and diffusion–convection-dependent inhomogeneity (S_{acin}). Abnormalities in these indices allow assignment of ventilation inhomogeneity to proximal, conducting (increase in S_{cond}) or distal, intra-acinar (S_{acin}) airways.

Clinical application of inert gas washout

Normative data The advantage of LCI as an outcome parameter of MBW is an intrinsic correction for variations in lung size, with FRC as the denominator. This is reflected in the consistency of LCI normative data ranges across wide age groups. The normal range is surprisingly constant, with LCI values <8. The availability of commercial nitrogen MBW equipment and the effort for standardised operating procedures will contribute to a more uniform normative data set for LCI.

In a tidal breathing test, it is important to appraise the range of normal variability as a prerequisite to distinguishing pathological values. Within-test repeatability is well documented for LCI, with reported coefficients of variation between 3% and 8% in health and disease. Current guidelines recommend FRC/LCI variability ideally be $<10\%$ for the three test runs with acceptable

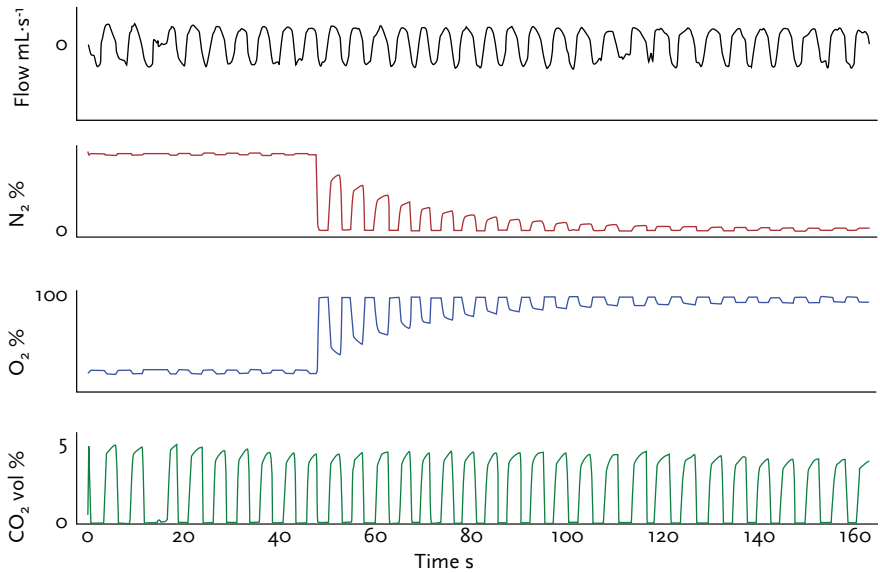

Figure 2. A nitrogen MBW test in a healthy adolescent. The raw signals flow (black), oxygen (blue) and carbon dioxide (green) are plotted against time. The nitrogen concentration (brown) is calculated indirectly as 100-([O_2]+[CO_2]+[Ar]).

FRC variability up to 25% if technical reasons are ruled out. Data on reproducibility over longer time periods are scarce and show variability comparable to the within-test repeatability. This is important to consider for reliable clinical use of LCI as an outcome parameter and for longitudinal tracking.

Clinical utility The majority of paediatric MBW studies have focused on CF. Few paediatric studies exist in other disease groups, such as asthma or bronchopulmonary dysplasia (BPD).

Airway involvement without clinical symptoms is an early component in children with CF due to infectious and inflammatory lung disease. Compared to HRCT, it has been shown that MBW is sensitive to early changes in children with CF, with clear superiority over spirometry and other lung function tests. In all cross-sectional studies, LCI was significantly higher in the CF group compared to healthy controls, with increasing differences with age. Whether this reflects changes in small or medium-sized airways is still debated. Regarding the clinical utility of LCI, longitudinal tracking could be demonstrated throughout childhood. Most importantly for future studies, two randomised controlled trials studying mucociliary clearance regimens in subjects with mild CF lung disease have shown that LCI was a sensitive study end-point and superior to spirometry outcomes.

Few promising results exist in children with CF using both VC and tidal SBW of tracer gases. Those methods still represent research tools requiring further development.

In adult asthmatics, SIII analysis from MBW and SBW has shown promising results with regards to predicting the response to dose titration of inhaled corticosteroid and demonstrated that different bronchoprovocative agents exhibit their effects at different sites in the airways. In children, only a few studies exist, yielding less clear results. Future findings will help to better understand the physiological processes of different phenotypes in asthma

and might provide new insights into specific diagnostic and therapeutic effects.

Data in infants with BPD are controversial. On one hand, a pattern of increased ventilation inhomogeneity and decreased FRC was described in a group of infants at term using nitrogen MBW. On the other hand, in two larger groups of infants at later gestational age, no effect of BPD was found on LCI or FRC using sulfur hexafluoride MBW. Several points may explain these different findings: differences in washout equipment and gases, especially the imprecision of the older nitrogen analysers; the use of sedation; and changes in the pathophysiology of BPD over time. The utility of MBW in BPD thus remains unclear and needs further study as well as longitudinal follow-up.

In adults, parameters of IGW (SIII of SBW and MBW) showed a high sensitivity in detecting the early stages of bronchiolitis obliterans syndrome, a well-known complication after haematopoietic stem cell transplantation. Preliminary data in children confirm these findings.

Future directions and open questions

The widespread application of IGW has the potential for early detection of diseases and more specific monitoring in children. MBW is on the verge of being implemented in CF clinics, opening the field for investigation of the immediate and long-term benefits of its application. One important question will be whether LCI-directed treatment can change disease outcome in patients with CF. SBW in children still represents a research tool and needs further development regarding robustness and standardisation.

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Forced oscillation techniques

Shannon J. Simpson and Graham L. Hall

Theoretical background

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

Key points

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

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

Use of the FOT in young children

The FOT is ideal for use in young children who are unable to adequately cooperate during traditional lung function tests and has been applied in children as young as 2 years of age with success rates >80% in young children. Commercially available FOT devices are currently available and guidelines have been established for the use of FOT in young children.

Data collection and repeatability The child should be seated in the upright position with a neutral head position, a nose clip in place and a good seal around the mouthpiece. The cheeks and floor of the mouth must be firmly supported to minimise the upper airway

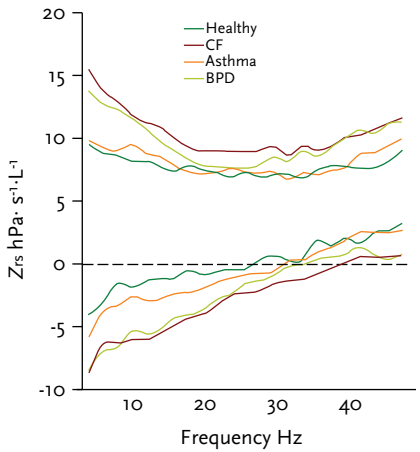

Figure 1. Impedance spectra in a healthy child and in young children with lung disease. The components of respiratory system impedance, resistance (top) and reactance (bottom) are shown across the medium frequency range. An average of three impedance measurements were obtained from four boys aged 4.4 years and 105 cm tall for comparison between disease states. Differences in Rrs, Xrs, AX, fres and fdep are evident, to varying extents, in commonly encountered paediatric diseases when compared to a typical healthy child.

shunting of input flows. Measurements should be obtained over several breathing cycles with no leak, vocalisation, swallowing, glottic closure or movement and the average of three to five acceptable measurements should be reported.

Within a testing session, the coefficient of variation for R_{rs} has generally been reported as <10%, while the coefficient of repeatability (twice the standard deviation of the difference between two measurements taken 15 min apart) ranges between 1.1 and 2.6 $hPa \cdot s^{-1} \cdot L^{-1}$ for R_{rs} and equates to a relative change of 12–30% with similar repeatability reported over a 2-week period and in children with CF and bronchopulmonary dysplasia (BPD). The repeatability of X_{rs} is reported as absolute values and ranges from 1.2 to 2.0 $hPa \cdot s^{-1} \cdot L^{-1}$.

Reporting of outcomes and normative data
The upper and lower limits of normal are defined, although differences in oscillatory signal and the frequencies of reported outcomes can make a comparison difficult. In addition, much of the available reference data has been collected in Caucasian populations. The majority of published reference equations use height as the only predictor of FOT outcomes, although sex was shown to contribute to R_{rs}, X_{rs} and the area under the X_{rs} curve (integrated area of reactance below the resonant frequency (AX)) in a recently published large study.

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

Clinical utility

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

Asthma and wheeze The majority of research using the FOT has been performed in young children with recurrent wheeze. The ability of the FOT to sensitively distinguish between healthy and wheezy preschool children before or after the administration of bronchodilator remains unclear.

Some studies have shown no difference in baseline lung function and bronchodilator responsiveness between healthy and wheezy children, while others have shown significant differences, even between different wheezing phenotypes. Several studies have defined the response to bronchodilators in healthy populations with relative cut-off values (derived from the 5th to 95th centiles) in the range of -33– -42% for R_{rs}, 61–70% for X_{rs} and 81% for AX, regardless of the salbutamol dose; although most studies administered 200 µg of salbutamol.

The FOT has been used to assess bronchial hyperresponsiveness in young children, with significant increases in R_{rs} and decreases in X_{rs} reported during both direct and indirect bronchial challenge tests. The FOT outcome most useful for monitoring bronchoconstriction during bronchial provocation is yet to be defined. The respiratory system admittance, the reciprocal of Z_{rs}, is more sensitive to bronchoconstriction than the commonly used R_{rs} due to the elimination of the upper airway artefact. Previous studies have used various changes in R_{rs} to define a positive response to bronchial provocation and the most appropriate cut-off for a positive response is yet to be validated. The development of shortened protocols for challenge tests using the FOT, such as for adenosine 5′-monophosphate, may help to overcome the shorter attention span of young children.

Cystic fibrosis CF begins in the peripheral airways and lung function tests sensitive to small airway dysfunction are likely to be best at monitoring early CF lung disease. The role of the FOT in monitoring CF lung disease is unclear with some studies reporting that the FOT fails to adequately identify airway obstruction in young children with CF. In contrast, increased R_{rs} and decreased X_{rs} have been reported in young children with CF particularly in the presence of respiratory symptoms.

Bronchopulmonary dysplasia Despite the observation that R_{rs}, X_{rs}, f_{res} and f_{dep} are frequently abnormal in children with BPD, the FOT has been used less extensively in young children born preterm. Further studies to examine the changes to FOT outcomes during development following preterm birth would be particularly beneficial.

Other/potential clinical utility The FOT has also been used to examine the temporal changes in respiratory mechanics, although primarily as a research tool rather than in clinical practice. Such studies have examined temporal changes over the normal breathing cycle as a method of detecting expiratory flow limitation, the effect of deep inspiration on respiratory mechanics and the monitoring of upper airway patency during sleep. The technique also has potential for the noninvasive assessment of respiratory mechanics in patients receiving mechanical ventilation for acute respiratory failure. While perhaps underutilised in this area, the FOT is able to detect and quantify upper or central airway diseases including tracheal stenosis, tracheo-oesophageal fistula, laryngeal obstruction and vocal cord dysfunction; although separation of inspiratory and expiratory impedances to examine the flow dependence during each phase of the respiratory cycle would likely yield most information in this group of patients.

Future directions

The measurement of respiratory system impedance has the potential to provide a great deal of information on a variety of conditions during the early years of life; however, further work is required if the FOT is to reach its full clinical potential. In the short term it is important to explore other FOT outcomes in addition to the traditionally reported R_{rs} at a single frequency with the knowledge that the pathophysiological mechanisms of many respiratory diseases exhibit strong peripheral lung involvement during early life. For example, measures of X_{rs} or AX may be more sensitive at monitoring the course of those respiratory disorders. We must also work towards understanding which FOT outcomes are most relevant for particular pathologies as one outcome for all disease

approach may not be appropriate. In the longer term it is important to gain an understanding of how respiratory mechanics alter longitudinally during development and what kind of deviation from this path requires intervention.

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Polysomnography

Sedat Oktem and Refika Ersu

Evaluation of children with suspected sleep disorders is primarily based on a thorough history. In appropriate cases the diagnostic process includes performance of polysomnography (PSG), most commonly for characterisation of breathing during sleep. Because PSG is a relatively expensive procedure requiring significant time and healthcare resources, understanding the strengths, limitations, and clinical utility of PSG is necessary to ensure optimal utilisation.

Respiratory indications for PSG in children

Diagnosis for sleep-related breathing disorders
PSG is indicated when:

- the clinical assessment suggests a diagnosis of OSAS in children;
- the clinical assessment suggests a diagnosis of congenital central alveolar hypoventilation syndrome or sleep-related hypoventilation due to neuromuscular disorders or chest wall deformities (it is indicated in selected cases of primary sleep apnoea in infancy);
- there is clinical evidence of a sleep-related breathing disorder in infants who have experienced an apparent life-threatening event.

Pre-operative PSG is indicated in children being considered for adenotonsillectomy to treat OSAS.

Assess response to treatment Children with mild OSAS pre-operatively should undergo clinical evaluation following adenotonsillectomy to assess for residual symptoms. If there are residual symptoms of OSAS then PSG should be performed.

Key points

- Clinicians should enquire whether the child or adolescent snores and, if so, obtain a PSG.
- PSG is the gold standard for the diagnosis of sleep-disordered breathing in children.
- If PSG is not available, then clinicians may order alternative diagnostic tests, such as nocturnal video recording, nocturnal oximetry, daytime nap PSG or ambulatory PSG.
- Paediatric PSG should be performed in a sleep laboratory equipped for children and staffed by qualified personnel following the American Thoracic Society standards for testing.
- Age-adjusted rules for the scoring and interpretation of PSGs should be used for children.

PSG is indicated following adenotonsillectomy to assess for residual sleep-related breathing disorder in children with pre-operative evidence for moderate-to-severe OSAS, obesity, craniofacial anomalies that obstruct the upper airway and neurological disorders (*e.g.* Down syndrome, Prader–Willi syndrome and myelomeningocele). It is also indicated after treatment of children for OSAS with rapid maxillary expansion to assess for the level of residual disease and to determine whether additional treatment is necessary. Children with OSAS treated with an oral appliance should have clinical follow-up

and PSG to assess response to treatment.

PSG is indicated for positive airway pressure titration in children with OSAS and for noninvasive positive pressure ventilation titration in children with other sleep-related breathing disorders.

Follow-up PSG in children on chronic positive airway pressure support is indicated to determine whether pressure requirements have changed as a result of the child's growth and development, if symptoms recur while on positive airway pressure, or if additional or alternative treatment is required.

Children treated with mechanical ventilation may benefit from periodic evaluation with PSG to adjust ventilator settings. PSG for the management of oxygen therapy is not routinely required in children treated with supplemental oxygen. Children treated with tracheostomy for sleep-related breathing disorders benefit from PSG as part of the evaluation prior to decannulation. These children should be followed clinically after decannulation to assess for recurrence of symptoms of sleep-related breathing disorders.

Respiratory diseases PSG is indicated in the following respiratory disorders, but only if there is clinical suspicion of an accompanying sleep-related breathing disorder:

- chronic asthma,
- CF,
- pulmonary hypertension,
- bronchopulmonary dysplasia,
- chest wall abnormalities, such as kyphoscoliosis.

Clinical evaluation alone does not have sufficient sensitivity or specificity to establish a diagnosis of OSAS. Clinical parameters such as history, physical examination, audio or visual recordings, and standardised questionnaires do not consistently identify the presence or absence of OSAS when compared with PSG.

Polysomnography

PSG in children should be performed in the proper setting. In young children, this will mean that the study has to be attended during the whole night by a trained technician to ensure the quality of the study. It is equally important to note that none of the current polysomnographic systems can generate accurate automated reports on paediatric polysomnographic studies. An automated report can both underestimate and overestimate the clinical condition. For this reason, paediatric polysomnographic studies should be reviewed manually using the raw data by trained physicians with knowledge on paediatric polysomnographic studies. The accuracy and agreement of manual scoring is dependent on the training background and the experience of the physicians. In the best hands, an interscorer agreement of at least 70–80% is expected.

In general, the result from a single night's study is sufficient for the diagnostic purpose of children with suspected OSAS. A ''first night effect'' has been described in adults, whereby sleep differs during the first night in a sleep laboratory compared to subsequent nights. Two studies assessing ''first night effect'' in children have shown that the parameters are no different between the first and second nights.

Technique Standard PSG consists of electroencephalogram, electromyogram (submental and tibial), electrooculogram (right/left), oximetry, end-tidal carbon dioxide tension ($P_{et}CO_2$), oronasal airflow (thermistor), nasal pressure sensor, respiratory inductance plethysmography, electrocardiography and a body position sensor. Children are also monitored and recorded on an audio/videotape using an infrared video camera. Each child is continuously observed by a technician trained in paediatric PSG who also records sleep behaviour and respiratory events (table 1 and fig. 1).

Electroencephalogram The international 10–20 system of electrode placement is used to determine surface electrode placement. The American Academy of Sleep Medicine (AASM)

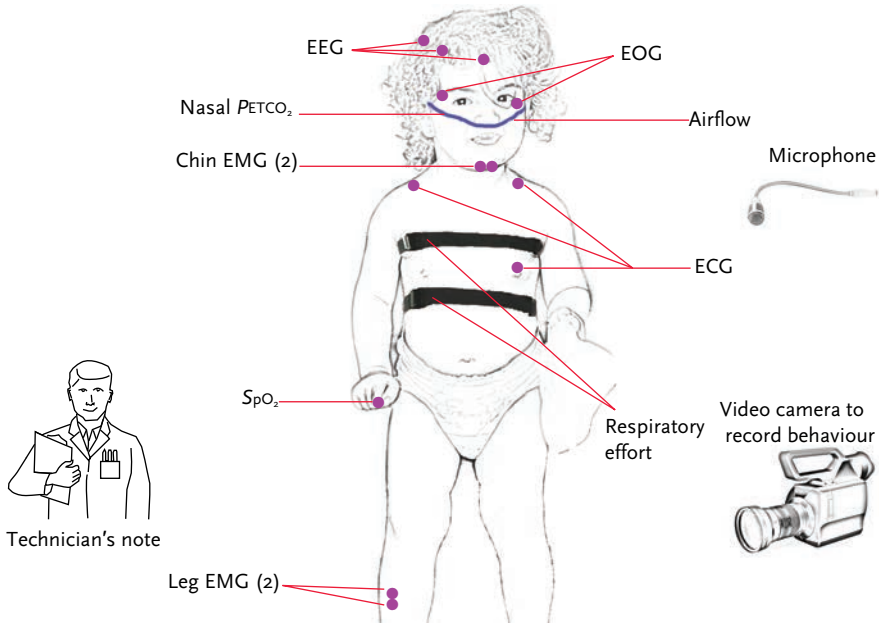

Figure 1. Components of PSG in children.

Table 1. Components of PSG in children

Electroencephalogram activity: current AASM recommendations are F4-M1, C4-M1 and O2-M1 with backup (F3-M2, C3-M2 and O1-M2), and are a change from the previous recommendation of C3 or C4 referenced to A1 or A2
Eye movements (electrooculogram) from electrodes placed near the outer canthus of each eye
Submental electromyographic activity from electrodes placed over the mentalis, submentalis muscle and/or masseter regions
Rhythm ECG with one lead II electrode or more chest leads at the discretion of the provider
Respiratory effort by chest-wall and abdominal movement *via* strain gauges, piezoelectric belts, inductive plethysmography, impedance or inductance pneumography and endo-oesophageal pressure (Note: the AASM does not recommend strain gauges or piezoelectric belts)
Nasal–oral airflow *via* a thermistor, nasal pressure transducer or pneumotachograph, or inductance plethysmography
S_{pO_2} including waveform with an averaging time of $\leqslant 3$ s
P_{etCO_2} or P_{tcCO_2}
Body position *via* sensor and direct observation
Limb movements (right and left legs) *via* electromyogram
Snoring recording or vibration (frequency and/or volume)
Audio/video recording by infrared or low-light equipment

recommends F4-M1, C4-M1 and O2-M1. Since children frequently displace leads during sleep, contralateral leads are typically applied as well (F3-M2, C3-M2 and O1-M2). Children have high-amplitude brain waves; thus, electroencephalogram recordings may need a sensitivity of 10–15 $\mu V \cdot mm^{-1}$, as compared to 5 $\mu V \cdot mm^{-1}$ in adults.

Electrooculogram Eye movements are detected by placing surface electrodes near the outer canthus of each eye. The electrooculogram electrodes should be offset from horizontal, one slightly above and one slightly below the horizontal plane to detect both horizontal and vertical eye movements. As infants and young children have smaller heads than adults, electrooculographic leads may need to be placed 0.5 cm from the outer canthi.

Electromyogram Two surface electrodes are placed either on the mentalis or submentalis to detect muscle activity. Again, as infants and young children have smaller heads than adults, chin electromyogram electrodes may need to be placed 1 cm apart rather than 2 cm apart.

Rhythm electrocardiogram A simple single lead ECG should be used to monitor cardiac rate and rhythm to enable cardiac arrhythmias and changes resulting from respiratory disturbances to be assessed.

Respiratory effort Chest and abdominal wall motion can be measured in a number of ways. Respiratory inductance plethysmography is the preferred method. Other sensors that have been used include piezoelectric belts, which are provided with many commercial PSG systems, intercostal electromyogram and oesophageal pressure monitoring. In one nonrandomised study of normal children, paradoxical breathing was seen much more commonly with piezoelectric belts than with respiratory inductance plethysmography.

Oesophageal pressure monitoring is rarely used as it is invasive, and the nasal pressure flow signal is often used as a surrogate when the upper airway resistance syndrome is suspected.

Nasal-oral airflow This is best measured and/or monitored by nasal pressure transduction and continuous monitoring of the capnography waveform. Thermistor application has been the standard technique in adult laboratories but might not be as sensitive a measure of airflow as pressure is in children.

Oxygen saturation The sensor is incorporated into a soft cuff that fits around a finger or toe or clips to an ear lobe. Children tend to move frequently during sleep, so the monitoring of the pulse waveform in addition to the saturation value is helpful in distinguishing motion artifact from true desaturation. This output can also be used for more sophisticated analyses, such as the measurement of pulse transit time.

Carbon dioxide Measurements of carbon dioxide have been used in two contexts during PSG:

- $P_{et}CO_2$ as an indicator of airflow obstruction and, hence, apnoea;
- measurement of end-tidal or transcutaneous carbon dioxide ($P_{tc}CO_2$) as a quantitative measure of hypoventilation during sleep.

Monitoring carbon dioxide has also been considered of potential value in diagnosing sleep hypoventilation syndrome. In addition, the measurement of carbon dioxide is useful in children with chronic lung disease or those receiving ventilatory support. It is especially important to measure carbon dioxide when supplemental oxygen is initiated in the sleep laboratory, as some patients may be dependent on their hypoxic drive to breathe. Adding oxygen without monitoring carbon dioxide may lead to worsening hypoventilation, and clinical deterioration of the patient.

$P_{et}CO_2$ can be measured directly from a tracheostomy or endotracheal tube, or as a side-stream measure from a nasal cannula. $P_{et}CO_2$ values maybe inaccurate in patients with obstructive lung disease with long time constants, such as in patients with advanced CF.

An alternative measurement option for evaluating hypoventilation is $PtcCO_2$. The transcutaneous electrode warms the skin, thereby arteriolising the capillary blood flow. The sensor must be moved during the night to prevent skin burns. Transcutaneous measurements may be preferable to end-tidal measurements in children with advanced obstructive lung disease, infants with rapid respiratory rates, children who breathe through their mouth and children receiving CPAP, in whom the CPAP airflow may interfere with end-tidal measurements.

Although most studies comparing $PetCO_2$ and $PtcCO_2$ to arterial samples have been performed in the intensive care unit or during anaesthesia, these studies show a good correlation.

Body position is frequently measured during PSG, although the measurement of body position is less important in young children than in adults, as OSAS is less positional.

Oesophageal pH is occasionally measured to determine whether gastro-oesophageal reflux is contributing to night wakenings, apnoea or desaturation. pH probe insertion is more invasive than the rest of the leads on a polysomnogram and takes specialised skill; placement must be confirmed by radiography. The percentage of total sleep time with pH <4 and the number and length of pH drops <4 can be quantified, and reviewed for an association with respiratory disturbances.

Video and sound recording Good quality video recordings are an important component of a clinical sleep study, and can be made using infra-red or low-light cameras and appropriate microphones. Video and sound recordings can provide useful information on sleep behaviour, snoring, sleep disturbance and breathing patterns.

Limb movements Gross body movements and limb movements may be assessed from direct observation, a video recording or from a peripheral electromyogram recording. These may be of use in detecting the extent of sleep disturbance or arousal frequency, and are necessary for assessment of sleep state in infants. Monitoring the electromyogram from a leg muscle (conventionally tibialis anterior) is a useful measure of peripheral skeletal muscle tone and allows assessments of gross body movements and arousals during sleep.

Interpretation of the PSG in children

Standard duration of the study A study of the whole night is the recommended investigation to assess sleep-disordered breathing. A minimum of 6 h sleep is desirable. The timing of the studies is also important. The study timing should be set to mimic the child's bedtime as closely as possible. The sleep study should then be conducted during the late evening and early morning.

Sleep stage analysis It is helpful to quickly review the patient's sleep architecture by viewing the hypnogram. A hypnogram is a graphical summary of the different sleep stages achieved (fig. 2). It is important to review the sleep architecture in terms of what is to be expected for the patient's age.

Components of sleep architecture should be assessed including percentage of total sleep time (TST) spent in stage I/II, stage III, rapid eye movement (REM) stage and wakefulness. These percentages should be compared with age-appropriate normals. Stage I sleep occupies 4–7.7% of TST, and stage II occupies 36–49% of TST, with the combination of stage I and II in each study ranging from 41% to 53% of the TST. Slow wave sleep occupies 14–32% of the TST, whereas stage REM occupies 17.4–21.1% of the TST. Timing of sleep stages can be

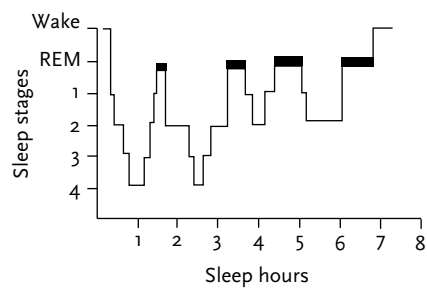

Figure 2. Hypnogram.

noted by review of the hypnogram. Children usually have a short period of stage I/II after sleep onset, and then enter stage III (slow wave sleep). Stage III sleep will predominate early in the night, with regular cycling between the stages I/II, stages III and REM. REM sleep will usually cycle every 60–120 min, with a wide range of timing between REM periods. Sleep latency, the time after lights out until sleep is achieved, should also be noted. Sleep latency is generally <25 min. It may be prolonged if the child has recently had a nap, and it may be shortened in certain sleep disorders.

Sleep efficiency is a measurement of the amount of the total time in bed that the patient spends asleep, and should also be noted. Sleep efficiency in children is usually >89%.

REM latency, the time from onset of sleep to the first epoch of REM sleep, is also noted. REM latency can be prolonged if the first REM period is difficult to detect by the scoring technician. Length of time spent in REM is short earlier in the night, with lengthening of REM episodes as the night progresses.

Arousal summary Arousals are scored by the scoring technician based on the appearance of the electroencephalogram tracing. An arousal is scored when there is an abrupt change in the electroencephalogram lasting 3 s, following at least 10 s of continuous sleep. Arousals can be attributed to preceding events, including respiratory events, leg movements, snore events or technician presence in the room, or may occur without an obvious trigger. Arousals are reported using the arousal index, which is the number of arousals divided by the hours of sleep. Studies of normal children have found mean arousal indices of 8.8–9.5.

Heart rate/rhythm The ECG should be reviewed for evidence of brady or tachy rhythms, as well as abnormal ECG rhythms. Respiratory events may be associated with a decrease in heart rate, with subsequent increase in heart rate after the event has resolved or in association with arousals.

Leg movements The scoring technician will score leg movements that meet criteria for periodic leg movement. Criteria for periodic leg movements include leg movements noted in either or both legs that are at least one quarter of the amplitude noted during the biocalibration lasting 0.5–5 s. Leg movements must be separated by at least 5 s, but not >90 s, and must occur in clusters of at least four to be considered periodic leg movements. These leg movements should not be related to other events, such as respiratory events or arousals. The periodic leg movement index is calculated by dividing the total number of periodic leg movements by the number of hours of sleep. A periodic leg movement index of ≥ 5 is considered abnormal.

Gas exchange should be reviewed carefully for the entire tracing. The pulse oximetry tracing should be reviewed for desaturation, with careful attention to whether the desaturation is associated with a respiratory event, arousal or leg movement. In general, oxygen saturation should be >92% in normal studies. Median baseline S_{pO_2} at preterm, term and infancy was approximately 98%, 98% and 96% respectively.

In children outside infancy a normal oximetry recording should have:

- a median S_{pO_2} level $\geq$ 95%,
- no more than four desaturations of $\geq$4% per hour,
- no abnormal clusters of desaturation.

Carbon dioxide tracing should be reviewed as well. Baseline carbon dioxide levels before sleep onset should be noted. Children may have a pattern of obstructive hypoventilation with OSAS, resulting in increases of carbon dioxide without significant oxygen desaturation. Abnormal levels of carbon dioxide vary, with some studies reporting >25% of TST being spent with carbon dioxide >50 Torr as abnormal, and some reporting that in normal children 2.8 ± 11.3% of TST was spent with carbon dioxide $\geq$50 Torr.

Respiratory events Respiratory scoring in children is different from that in adults. Paediatric scoring must be used for children $\leq$12 years of age. Small studies indicate

Table 2. Description of respiratory events

Obstructive apnoea	Drop in thermal sensor amplitude by ⩾90% baseline ⩾2 missed breaths ⩾90% duration meets amplitude reduction criteria Continued or increased inspiratory effort during reduced airflow
Central apnoea	Drop in thermal sensor amplitude by ⩾90% baseline Either duration ⩾20 s OR ⩾2 missed breaths and associated with arousal, awakening or ⩾3% desaturation Absent inspiratory effort
Mixed apnoea	Drop in thermal sensor amplitude by ⩾90% baseline ⩾2 missed breaths ⩾90% duration meets amplitude reduction criteria Absent inspiratory effort initially, then resumption of effort during latter part of event
Hypopnoea	Drop in nasal air pressure transducer amplitude by ⩾50% ⩾2 missed breaths ⩾90% of duration meets amplitude criteria Associated with arousal, awakening or ⩾3% desaturation
RERA	⩾2 missed breaths Flattening of nasal air pressure transducer waveform Increased work of breathing Sequence leads to arousal Drop in amplitude <50%
Periodic breathing	>3 episodes of central apnoea lasting >3 s separated by ⩽20 s of normal breathing
Apnoea index	Number of obstructive and/or central apnoeic events per hour of sleep
Obstructive apnoea index	Number of obstructive apnoeic events per hour of sleep
Hypopnoea index	Number of hypopnoeas per hour of sleep
AHI	Sum of the apnoea index and hypopnoea index
Obstructive AHI	Sum of obstructive apnoeic events and hypopnoeic events per hour of sleep

that adolescents have breathing patterns similar to those of younger children and the use of paediatric scoring criteria would be appropriate for adolescents. Adult criteria are used for patients aged ⩾18 years. Respiratory related arousals (RERA) are not scored in all laboratories. Definitions of respiratory events are summarised in table 2. Examples of snoring, central apnoea, obstructive apnoea and hypopnea are shown in figures 3–6.

Normal values of PSG and treatment indications

There are very few studies assessing the polysomnographic predictors of morbidity in children. Table 3 shows normative data for the different polysomnographic variables. These are statistical norms rather than clinical criteria upon which to base treatment decisions. It is generally accepted that OSA is mild if the obstructive AHI is ⩽5 events·h^{-1}, and moderate if it is >5 events·h^{-1} but <10 events·h^{-1}, and severe if it is >10 events·h^{-1}. It is generally accepted that if the snoring child has moderate or severe OSA they should be treated. Treatment indications for children with mild OSA are less clear. One review suggested that treatment should be considered if the child is at increased risk of having OSA and fulfils at least one of the following criteria.

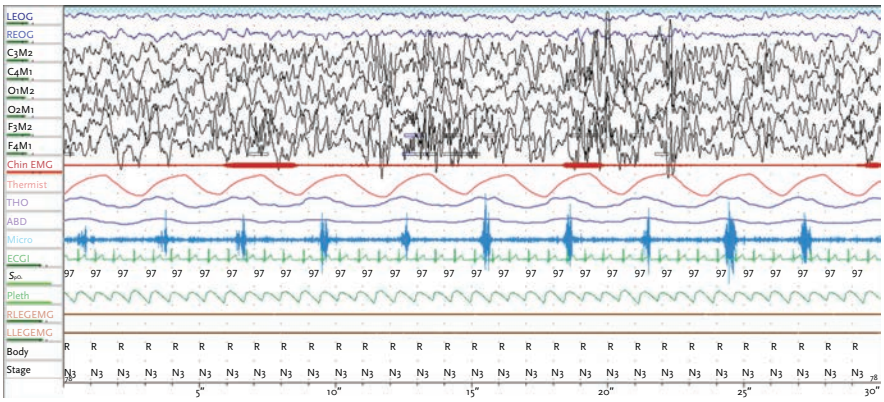

Figure 3. Snoring.

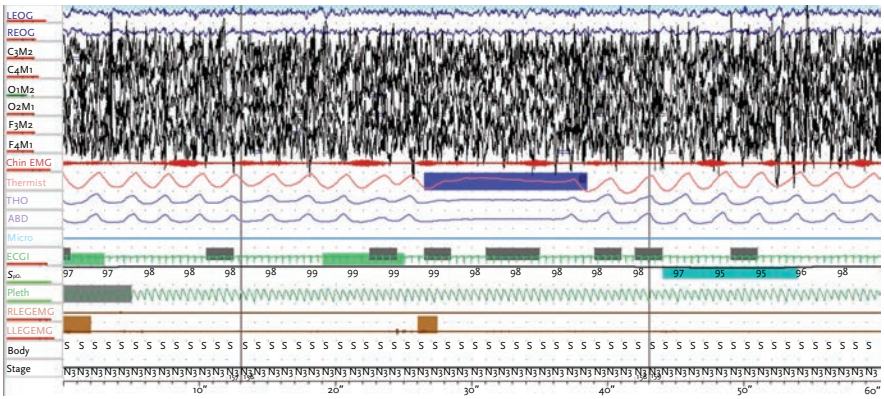

Figure 4. Central apnoea.

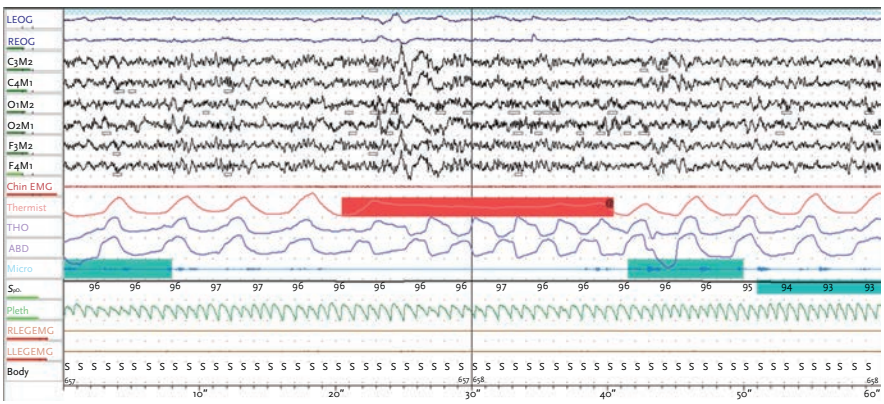

Figure 5. Obstructive apnoea.

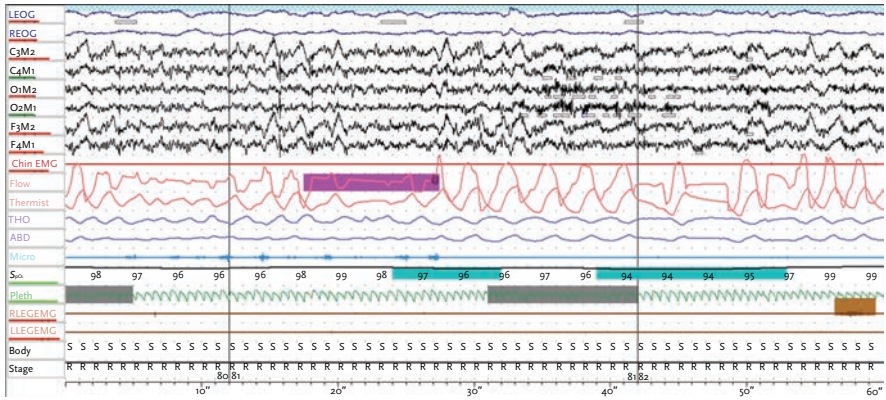

Figure 6. Hypopnoea.

- AHI 1–5 events·h^{-1} and systolic or diastolic blood pressure consistently >95th percentile for sex, age and height, or documented pulmonary hypertension.
- AHI 1–5 events·h^{-1} and morbidity from the central nervous system (excessive daytime sleepiness, hyperactivity, inattention and academic difficulties).

Table 3. PSG values in normal children

	Montgomery-Downs (2006)		Verhulst (2007)	Uliel (2004)	Traeger (2005)
Subjects n	542		60	70	66
Age range years	3–5[#]	⩾6[¶]	6–16	1–15	2.5–9.4
Sleep latency min	24.1±25.6	23±25.3	45.6±29.4		
Sleep efficiency %	90±7	89.3±7.5	80.5±8.5	90.8±6.5	89± 8
Arousals events·h^{-1}	9.3±4.8	6.1±1.8			8.8±3.8
RERA events·h^{-1}	0.92±2.0	1.2±1.0			
Hypopnoea index^{+} events·h^{-1}	0.03±0.07	0.10±0.18			0.3±0.5
Apnoea index events·h^{-1}	0.86±0.75	0.5±0.52			
Obstructive apnoea index events·h^{-1}	0.03±0.10	0.05±0.11	0.06±0.16	0.02±0.1	0.1±0.03
AHI events·h^{-1}	0.9±0.78	0.68±0.75	1.98±1.39		0.4±0.6
Obstructive AHI events·h^{-1}	0.08±0.16	0.14±0.22	0.08±0.17		
% TST SpO_2 >95%	99.6±0.95				
SpO_2 nadir %	92.7±4.5	92.6±3.6	91.8±2.7	94.6±2.2	92±3
SpO_2 lower limit %	84	85	86	90	86
ODI events·h^{-1}	0.29±0.35	0.47±0.96	0.8±0.9		
$PetCO_2$ % TST >50 mmHg	4.0±15.3	2.0±7.1		0.29±0.24	

Data are presented as mean±SD, unless otherwise stated. ODI: oxygen desaturation index. [#]: n=173; [¶]: n=369; [+]: with desaturation (3–4%) and/or arousal.

- AHI 1–5 events·h^{-1} and inadequate somatic growth.
- AHI 1–5 events·h^{-1} and nocturnal enuresis.
- AHI 1–5 events·h^{-1} and presence of risk factor(s) for persistence of OSA in adolescence.
- AHI 1–5 events·h^{-1} and diagnosis of muscular or neuromuscular disorders (*e.g.* Duchenne muscular dystrophy or cerebral palsy), or major craniofacial abnormality (*e.g.* midface hypoplasia or mandibular hypoplasia), or a combination of pathogenetic mechanisms (*e.g.* Down syndrome).
- Nocturnal pulse oximetry with three or more S_{pO_2} decreases $<$90% and three or more clusters of desaturation events. Alternatively, oxygen desaturation ($\geqslant$3%) of haemoglobin index $>$3.5 episodes·h^{-1}.

In conclusion, paediatric PSG is the gold standard for evaluation of children with chronic snoring both for diagnosing and assessing severity of OSA. Response to various treatment modalities are also objectively evaluated by PSG. It is also used to evaluate cardiorespiratory function in infants and children with alveolar hypoventilation, chronic lung disease or neuromuscular disease when indicated. Paediatric PSG should be performed in a child-friendly environment and should be evaluated according to the paediatric rules.

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Flexible bronchoscopy

Jacques de Blic

Bronchoscopy has become an invaluable tool for the diagnosis and treatment of many lung disorders in infants and children (Midulla *et al*., 2003; Schellhase, 2002; Wood, 1984). Since its introduction in the mid-1970s, an increasing number of flexible bronchoscopies are performed each year. The diagnostic value of flexible bronchoscopy is now widely accepted; it can be used to visualise the lower airways directly and to take samples, particularly of bronchoalveolar lavage (BAL). Its indications are not limited to exploring stridor, persistent atelectasis or recurrent pneumonia in ambulatory patients; more severely ill children, who are in an unstable respiratory status, may require bronchoscopy, sometimes under mechanical ventilation, in neonatal or paediatric intensive care units (ICUs).

Equipment

Bronchoscopes Two technologies are used to transmit light and images: glass fibres and charge-coupled devices (CCD).

- The classic fibreoptic bronchoscope uses fine filaments of flexible glass fibres. With this technology, the larger the bronchoscope, the better the image obtained because of the higher number of fibres.
- In a bronchovideoscope, the CCD is incorporated into the distal extremity of the instrument; it doesn't contain an eyepiece, needs a video screen and allows for a very high image quality.
- The hybrid bronchofibrevideoscope combines these two technologies. A CCD is located in the body of the instrument, which improves the quality of images.

Key points

- Cleaning and disinfection of flexible bronchoscopes are a major concern to prevent cross infection and contamination.
- Stridor is a common indication for flexible bronchoscopy in infants and laryngomalacia is the most frequent observed abnormality. Direct visualisation of the airways is necessary in all children with persistent stridor because lower airway lesions are frequently associated with upper airway lesions.
- In older children all pathological respiratory situations, especially persistent or recurrent clinical symptoms and/or radiological abnormalities, should lead to endoscopic airway exploration.
- Measures to prevent complications include: detection of high-risk children; nebulisation of β_2-agonists if there is pre-existing bronchial hyperresponsiveness; careful local anaesthesia to prevent laryngospasm; large oxygen supplementation; use of the lowest flexible bronchoscope diameter; appropriate anaesthesia; and training.
- Post-BAL fever may occur in up to 50% of cases.

Table 1 summarises the main characteristics of the different instruments available for children. External diameter determines the presence

(and size) or absence of a working channel. The 2.2-mm flexible bronchoscope does not have a working channel and is limited to visualisation of airways in ventilated neonates. The 3.4–3.6-mm flexible bronchoscopes have a 1.2-mm working channel, which allows suction and BAL to be performed, and is wide enough to allow the use of instruments such as a cytology brush or biopsy forceps (but the procedure is more difficult and the specimen very small). The 4-mm and 4.9-mm flexible bronchoscopes have a 2-mm working channel, which allows excellent quality biopsies and transbronchial biopsy.

The choice of the flexible bronchoscope is made according to the age of the patient and the diameter of the cricoid, but also according to the procedures that are to be performed. In general, the smallest instrument available should be used to minimise obstruction of the airways. It is assumed that there must be at least a 2-mm difference between the external diameter of the flexible bronchoscope and the diameter of the narrowest point of larynx, the cricoid cartilage. In paediatric and neonatal ICUs, it may be necessary to pass the flexible bronchoscope through the endotracheal tube, and the recommended difference in diameter is at least 1 mm.

Endoscopy room It needs to be fully equipped with:

- an operating table;
- a workstation, including a bright light source (some equipment uses a battery-operated system), a video system centre (with adaptor for older broncho-fibrescopes), a flat-screen LCD monitor, a keyboard and recording equipment;
- a trolley containing room temperature saline, a syringe, cytology brushes and biopsy forceps, trap for BAL, *etc.*;
- monitoring equipment (ECG, pulse oximeter and blood pressure monitor);
- an oxygen supply system;
- high-power suction sources;
- equipment and drugs for intubation and resuscitation.

Cleaning, disinfection and storage After each use, flexible bronchoscopes must be cleaned and disinfected to prevent cross infection and contamination. Disinfection may be performed by immersion in an appropriate disinfectant (2% alkaline glutaraldehyde) or in a washing machine. Checks for microorganism colonisation should be performed once a week with a culture of saline solution used for rinsing the flexible bronchoscopes. Flexible bronchoscopes should always be stored in a dedicated storage cabinet, hanging in a straight vertical position to prevent development of unwanted curves. Finally, flexible bronchoscopes should be regularly tested for leaks before cleaning to prevent permeation of any fluids into the optical system.

Table 1. Available bronchoscopes

External diameter mm	Imaging technique	Age years	Working channel mm	BAL	Biopsy	TBB	Brushing
2.2	BF	Neonate	No	No	No	No	No
2.7–2.8	BF/HFV	0–2	1.2	Yes	Yes (not easy)	No	Yes
3.4–3.6	BF/BV	2–5	1.2	Yes	Yes (not easy)	No	Yes
4	HFV	2–5	2	Yes	Yes	Yes	Yes
4.9–5.1	BF/BV	>5	2.2–2	Yes	Yes	Yes	Yes
5.9–6	BF/BV	>15	2.2–2.8	Yes	Yes	Yes	Yes

TBB: transbronchial biopsy; BF: bronchofibrescope; HFV: hybrid bronchofibrevideoscope; BV: bronchovideoscope.

Procedure

- The procedure may be performed under conscious sedation or general anaesthesia.
- Endoscopy is performed either at the head or at the bedside of the child.
- The flexible bronchoscope is usually passed through the nose.

Once the bronchoscope is inserted into the upper airway, the vocal cords are inspected. The instrument is advanced to the trachea and further down into the bronchial system and each area is inspected as the bronchoscope passes (fig. 1).

Indications

Airway endoscopy provides two different types of information, one by direct anatomical observation and the other through the samples taken during the procedure (mainly BAL, brushing and biopsies). Indications for bronchoscopy in children are listed in table 2.

In children, the main indications are the search of airway obstruction. Stridor is one of the most common indications, especially in neonates and infants. Inspiratory stridor is indicative of narrowing of the larynx, while biphasic, inspiratory and expiratory stridor suggests tracheal obstruction. In older children all pathological respiratory situations, especially persistent or recurrent clinical symptoms and/or radiological abnormalities, should lead to endoscopic airway exploration.

Information

Upper airways At the upper airways level, laryngomalacia is the most frequent observed abnormality. Endoscopy identifies collapse of the epiglottis and/or aryepiglottic folds and/or arytenoids into the glottis. Direct visualisation of the airways is necessary in all children with persistent stridor; lower airway lesions are frequently associated with upper airway lesions. The examination must be carried out carefully, and the airways should be monitored during

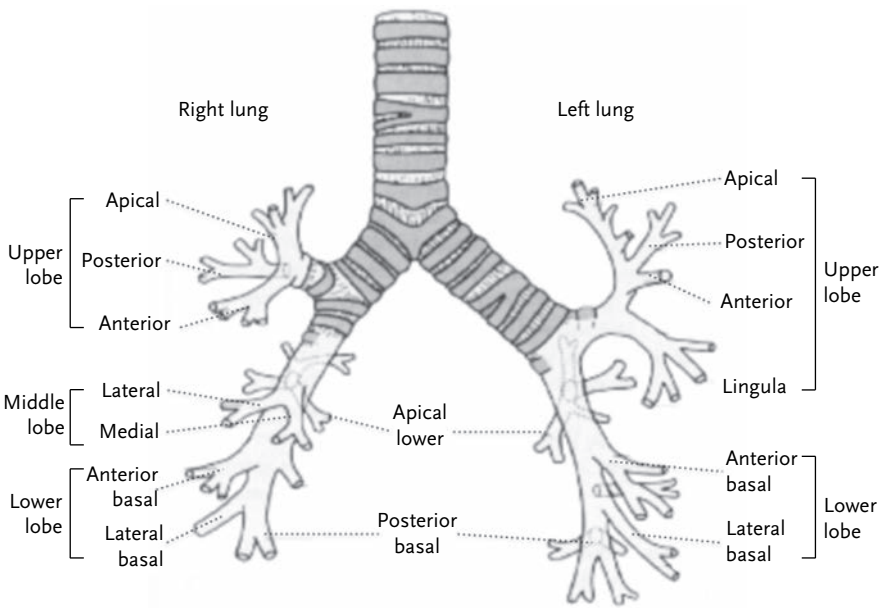

Figure 1. Segmentation of the tracheobronchial tree.

Table 2. Main indications for endoscopy in children

Airway obstruction
Suspected foreign body aspiration
Stridor (inspiratory and/or expiratory), noisy breathing
Severe recurrent/persistent wheezy bronchitis
Severe unexplained chronic cough that is unresponsive to therapy
Persistent/chronic productive cough
Recurrent bronchopneumonia
Recurrent/persistent consolidation
Localised hyperinflation
Bronchiectasis
Mediastinal adenopathies
Chronic interstitial pneumonitis
Infectious diseases
Immunocompetent children
TB
Severe acute pneumonia, severe acute interstitial pneumonia (that does not respond to standard broad-spectrum antibiotic therapy within 48 h)
Immunocompromised children
Acute onset of diffuse interstitial pulmonary infiltrates
Acute focal infiltrates (that do not respond to standard broad-spectrum antibiotic therapy within 48 h)
Chronic interstitial pneumonitis
Chronic recurrent bronchopneumonia in HIV-infected children (if organisms are not found by less invasive techniques)
In association with TBB in lung transplant recipients, as part of a routine surveillance programme and/or for the diagnosis of suspected lung disease
Haemoptysis

TBB: transbronchial biopsy.

the various stages of sedation. Local anaesthesia may worsen laryngomalacia (Nielson *et al.* 2000). Other abnormalities include the following.

- Subglottic stenosis: this may be congenital with membranous (or diaphragmatic) stenosis and symmetrical narrowing, or acquired after prolonged endotracheal intubation and appear irregular with granulation tissue, ulcerations and cysts.
- Vocal cord paralysis (unilateral or bilateral): this must be evaluated when the child is awake or under light sedation.
- Haemangioma presenting as an asymmetrical subglottic mass.
- Laryngeal cysts, laryngeal papillomatosis, laryngeal web or laryngeal cleft.
- Vocal cord dysfunction characterised by paradoxidal adduction of the vocal cord during inspiration, or both inspiration and expiration: diagnosis may be difficult even during endoscopy of the upper airways without sedation.

Lower airways At the lower airway level, endoscopy provides information on airway distribution, mechanical or dynamic obstruction, inflammation and secretions.

Proximal airway pattern is usually stable in humans. Most of the abnormal bronchi are 'variant' and supply normal lung parenchyma. Tracheal bronchus, which is observed in 1% of flexible bronchoscopes, is the most common. In this case, the bronchus originates from the right lateral wall of the trachea, above the carina. It may supply the entire right upper lobe or only the apical segments. Abnormal airway distribution includes situs inversus (associated with primary ciliary dyskinesia), left or right isomerism (two right or two left bronchial patterns, frequently associated with congenital heart cardiopathy), and lung agenesis/aplasia. In the latter a more or less rudimentary bronchus is observed at the main carina. Finally, opening of a tracheo-oesophageal fistula can be found on the posterior tracheal wall. Fistula can be confirmed by injecting methylene blue into the fistula and detecting its presence in the oesophagus (the same results is obtained when injecting methylene into the oesophagus to view the trachea).

During mechanical and dynamical airway obstruction, airway patency may be affected by intrinsic or extrinsic lesions.

Intrinsic obstructions include inhaled foreign bodies, stenosis (may be congenital with complete tracheal rings or acquired post-intubation), diaphragm, granuloma, endobronchial tumour or bronchial cast (also known as plastic bronchitis).

Extrinsic obstructions include compression by congenital malformation (such as bronchogenic cyst or duplication), adenopathies (*e.g.* malignancy or TB), tumour or vascular compression. The most frequent vascular compression is vascular ring (right-sided aortic arch and double aortic arch) (Chapotte *et al.*, 1998; McLaren *et al.*, 2008). A double aortic arch causes obstruction of the distal trachea and left main stem bronchus. A right-sided aortic arch with an aberrant left subclavian artery and enlargement of the Kommerell diverticulum appears with an anterior and posterior compression of the right wall of the distal trachea and the right main stem bronchus. The trachea is distorted in the shape of comma or drop, with the narrowest part directed to the right. Pulmonary sling obstructs the distal trachea and the origin of the right main stem bronchus. Pulmonary sling is strongly associated with congenital tracheal stenosis. Congenital heart disease with left to right shunt and enlarged pulmonary arteries may compress the right main stem and right middle lobe bronchus. Left main stem bronchus may be compressed by heart enlargement. The left main stem bronchus may also be compressed between right pulmonary artery and descending aorta. Absent pulmonary valves is associated with enlarged pulmonary arteries, which compress distal trachea, both the main stem bronchi and troncus intermedius. Significant anterior compression by anomalous innominate artery associated with tracheomalacia is rare. Likewise, posterior tracheal compression of an aberrant subclavian artery is usually not clinically relevant.

In dynamical obstruction, tracheomalacia and bronchomalacia are defined as an abnormal collapse (>50%) of the trachea or the main bronchi during spontaneous breathing, expiration or cough, due to a localised or generalised weakness of the airwall (Boogaard *et al.*, 2005). They may be congenital or acquired, and are mainly seen in children with vascular malformation and oesophageal atresia and/or tracheo-oesophageal fistula.

Inflammation and secretions In children, the bronchial mucosa appears thicker than in adults and the mucosa is salmon pink. The mucosa can be pale, erythemic, thinned or thickened. Endoscopy can also identify granulations, for example in swallowing disorders or sarcoidosis. Secretions should be characterised as moderate or abundant, localised or diffuse, being renewed or not after aspiration, mucous, muco-purulent, purulent or haemorrhagic.

Bronchoscopy in paediatric ICUs

Children in paediatric ICUs may require a bronchoscopy for a primary airway problem or a secondary complication (Bar-Zohar *et al.*, 2004; Efrati *et al.*, 2009; Koumbourlis, 2010,

Manna *et al.* 2006). These children are unstable and/or ventilator dependent. In these situations, sedation should be increased appropriately, the procedure should be fast, and should be performed by an experienced bronchoscopist, assisted by an intensivist. Flexible bronchoscopes are useful for diagnosing and assessing therapy in very sick children. Adverse effects of bronchoscopy in paediatric ICUs include hypoxia, hypercapnia, inadvertent positive end-expiratory pressure, hypotension, raised intracranial pressure and prolonged hypoxaemia following BAL (Morrow *et al.*, 2001). Main contraindications are severe hypoxaemia, bleeding diathesis, severe pulmonary hypertension, cardiac failure, cardiac instability/hypotension and procedures that provide no additional information. Indications for bronchoscopy use in paediatric ICUs are listed in table 3.

Bronchoscopy in neonatal ICUs

Persistent radiological airway obstruction is a constant concern in the neonatal ICU and the rapid evaluation of the airways is a major requirement for determining whether flexible bronchoscopy is needed or not. Sudden unexplained deteriorations in the respiratory status also provide reasons for endoscopic evaluation.

Table 3. Main indications of endoscopy in paediatric and neonatal ICUs

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

In spontaneously breathing infants, classic flexible bronchoscopy carries the risk of inducing respiratory failure, particularly in small patients ($\leqslant$2500 g) or those with a borderline respiratory status. A 2.2-mm flexible bronchoscope can be passed through a 2.5 mm endotracheal tube in intubated infants, but it has no working channel. A 2.8-mm flexible bronchoscope can be passed through a 3.5 mm endotracheal tube and has a working channel for bronchoaspiration and BAL. Similar to paediatric ICUs, an experienced paediatric bronchoscopist must perform the procedure quickly in an ICU; the heart rate, blood pressure, oxygen saturation and temperature should be constantly monitored throughout the procedure. The absence of an operator channel with the ultra-thin flexible bronchoscope prevents the suctioning of secretions, and the administration of anaesthesia or normal saline. However, careful suctioning prior to ultra-thin flexible bronchoscopy adequately prepares the airways for the procedure. Risks of complication are increased, including the risks of hypothermia, hypotension, hypoxia, apnoea, bradycardia and intra-cranial haemorrhage.

Flexible bronchoscopy may reveal endoluminal abnormalities (*e.g.* granuloma and inflammatory stenosis), malformation (tracheal bronchus), severe extrinsic compression, or severe tracheo and/or bronchomalacia (de Blic *et al.*, 1991; Koumbourlis, 2010). These airway anomalies can exist simultaneously, and their correct diagnosis is paramount to the management of these patients, also providing information for possible surgical intervention.

Tolerance and complications

Data show that flexible bronchoscopes are well tolerated in most cases and that the risk of major complications remains low (de Blic *et al.*, 2002). However, the potentially dangerous nature of these complications necessitates careful analysis of indications and clinical status for each patient and proper monitoring during the procedure. Moreover, the skill of the bronchoscopist and

anaesthesiologist may also decrease the incidence of complications, demonstrating the value of training. These complications can be divided into physiological, mechanical, infectious, anaesthetic and post-BAL fever.

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

Mechanical complications These include epistaxis, haemoptysis (which may be favoured if coagulopathy is present or if the platelet count is <20 000 cells·mm^{-3}), pneumothorax and post-flexible bronchoscope subglottic oedema.

Infectious complications These complications are rare and, by default, are related to the cleaning of the bronchoscope. The spread of infection appears to be a very rare complication.

Anaesthetic complications The most life threatening adverse events during flexible bronchoscopy involve drug overdose, inadequate monitoring or inappropriate sedation.

The following will reduce the risk of complications:

- detection of high-risk children (aged <2 years, with known or suspected laryngotracheal abnormalities);
- nebulisation of β_2-agonists, if there is pre-existing bronchial hyperresponsiveness, to avoid bronchospasm;
- careful local anaesthesia to prevent excessive cough and laryngospasm;
- large oxygen supplementation;
- using the lowest flexible bronchoscope diameter;
- use of appropriate anaesthesia;
- training.

Post-BAL complications Fever is observed in up to 52% of cases (Fonseca *et al.*, 2007; Picard *et al.*, 2000; Schellhase *et al.*, 1999). Post-BAL fever usually begins a few hours after the examination, with spontaneous defervescence occurring within 24 h. It has been attributed to the release of biologically active mediators, such as cytokines, and to transient bacteraemia. Factors such as young age, a positive bacterial culture and abnormal bronchoscopic findings, including whether a topical anaesthetic and saline are administered, are related to a higher risk of developing post-BAL fever. A recent study showed that the use of intramuscular dexamethasone in immunocompetent children prior to the procedure caused a significantly greater reduction in the incidence of fever than placebo, favouring inflammatory cytokine-induced fever (Picard *et al.*, 2007).

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Bronchoalveolar lavage

Fabio Midulla, Raffaella Nenna and Ernst Eber

Definition

Bronchoalveolar lavage (BAL) is a procedure used to recover cellular and noncellular components of the epithelial lining fluid from the alveolar and bronchial airspaces.

Techniques

Bronchoscopic BAL involves the instillation and immediate withdrawal of pre-warmed sterile 0.9% saline solution through the working channel of a flexible bronchoscope, which has been wedged into a bronchus with a matching diameter. Generally, paediatric bronchoscopes with external diameters of 2.8, 3.5 or 3.7 mm and a working channel of 1.2 mm are used in children <6 years of age, whereas instruments with external diameters of 4.6–4.9 mm and a working channel of 2.0 mm are used in children >6 years of age. The preferred sites for bronchoscopic BAL are the middle lobe or the lingula because, being the smallest lobes of the respective lungs, they offer better fluid recovery. When lung disease is localised, BAL must target the radiological or endoscopically identified involved lobe or segment. In patients with CF, samples from multiple sites should be obtained in order to avoid underestimation of the extent of infection.

Alternatively, a nonbronchoscopic BAL can be performed by inserting a catheter through an endotracheal tube. Unfortunately, this method does not allow visualisation of the lavage site, although turning the child's head to the left predictably directs the catheter into the right lung.

To avoid contamination, BAL must precede any other planned bronchoscopic procedure.

Key points

- BAL is a procedure used to recover cellular and noncellular components from the alveolar and bronchial airspaces.
- Clinical applications involve microbiological studies and/or evaluation of cellular components.
- BAL is performed for diagnostic and therapeutic indications.

Two methods are used for calculating the amount of sterile saline for lavage and the number of aliquots required to obtain samples that are representative of the alveolar compartment. Some authors choose to use two to four aliquots of equal volume (10 mL per aliquot for children <6 years of age and 20 mL per aliquot for children >6 years of age), irrespective of the patient's body weight. Others suggest the use of three aliquots, each consisting of 1 $mL \cdot kg^{-1}$ body weight for children weighing up to 20 kg, and three 20-mL aliquots for heavier children. While maintaining the tip of the bronchoscope wedged at the selected site, gentle manual or mechanical suction (3.3–13.3 kPa, *i.e.* 25–100 mmHg) is applied in order to collect the lavage specimen in a syringe or in a dedicated collection trap. BAL is considered technically acceptable if >40% of the total saline instilled is recovered and the lavage fluid (except for the first sample) contains few epithelial cells.

Processing

BAL specimens should be processed as soon as possible. To optimise cell viability, BAL fluid must be kept at 4°C until analysed. The first unfiltered BAL aliquot is usually processed separately for microbiological studies. Bacteria, fungi, protozoa and viruses are detected by direct light microscopy after centrifugation or alternatively by smears. Special stains such as Gram, Papanicolaou, Gomori-Grocott or tolouidine blue are used in air-dried preparations. In addition, the samples that are to be cultured for fungi, protozoa and viruses are centrifuged first, whereas those for bacterial cultures are processed without centrifugation. The rest of the aliquots are filtered through sterile gauze to remove mucus; then they are pooled and submitted for cytological studies and analysis of BAL solutes.

BAL fluid can be prepared in two ways by:

- obtaining cytospin preparations of the whole BAL fluid,
- re-suspension of the cells pellet in a small amount of medium.

At least three to four slides should be prepared for each patient. The number of cells per mL of the recovered BAL fluid is counted with a cytometer on whole BAL specimens stained with trypan blue or with a cytoscan. Slides can be stained with May–Grünwald, Giemsa or Diff-Quick stains for differential cell counts and the evaluation of cellular morphological features. In particular situations, slides can also be prepared with specific stains, *e.g.* oil red O stain to detect lipid-laden macrophages, iron stain to identify iron-positive macrophages in patients with alveolar haemorrhage, and periodic acid–Schiff (PAS) to identify glycogen. Immunocytochemical staining of lymphocyte surface markers is used to differentiate lymphocyte subsets in specific clinical situations, such as chronic diffuse parenchymal lung disease (DPLD).

The parameters measured include the percentage of the instilled normal saline that is recovered (as compared to the amount of saline instilled), as well as various BAL fluid cellular and noncellular components (table 1). The mean BAL fluid total cell count ranges from 10.3 to 59.9×10^4 cells·mL^{-1}, with a range of 81.2–90% for macrophages, 8.7–16.2% for lymphocytes, 1.2–5.5% for neutrophils and 0.2–0.4% for eosinophils. The BAL fluid neutrophil percentage appears to be higher in children aged <12 months as compared to children aged 13–36 months. Normal values of BAL fluid lymphocyte subsets in children resemble those found in healthy adults, except for the CD4/CD8 ratio, which is lower in children. Establishing reference values for noncellular components is a complex task owing to the absence of valid BAL fluid dilution markers. Studies designed to investigate noncellular BAL fluid components have few clinical indications and are more important in the research setting.

Indications

BAL is performed for diagnostic and therapeutic indications. Clinical indications for BAL include nonspecific chronic respiratory symptoms, nonspecific radiological findings and clinical signs and symptoms suggestive of chronic DPLD. Clinical applications involve microbiological studies and/or evaluation of cellular components.

Microbiology BAL is an important tool in the diagnosis of lung infection in both immunocompromised and immunocompetent patients, including children with chronic pneumonia, CF and suspected TB. BAL is diagnostic when pathogens not usually found in the lung are recovered, such as *Pneumocystis jirovecii, Toxoplasma gondii, Legionella pneumophila, Histoplasma capsulatum, Mycobacterium tuberculosis, Mycoplasma pneumoniae* and respiratory viruses. Other infectious diseases, in which isolation of the infectious agent from BAL fluid is not diagnostic, but may contribute to their diagnosis and management, include infections with herpes simplex virus, cytomegalovirus, *Aspergillus*, *Candida albicans*, *Cryptococcus* and atypical mycobacteria. The presence of $>10^4$ colony-forming units per mL BAL fluid will identify patients with bacterial pneumonia with

Table 1. Total and differential cell counts in BAL fluid from control children

	Clement (1987)	Ratjen (1994)	Riedler (1995)	Midulla (1995)	Tessier (1996)
Alveolar macrophages					
Mean±SD	89.7±5.2	81.2±12.7	NR	86±7.8	89.9±5.5
Median	89	84	91	87	92.5
Range	82–99	34.6–94	84–94#	71–98	77–98
Lymphocytes					
Mean±SD	8.7±4.6	16.2±12.4	NR	8.7±5.8	8.9±5.6
Median	10	12.5	7.5	7	8
Range	1–17	2–61	4.7–12.8#	2–22	2–22
Neutrophils					
Mean±SD	1.3±0.9	1.9±2.9	NR	5.5±4.8	1.2±1.2
Median	1	0.9	1.7	3.5	1
Range	0–3	0–17	0.6–3.5#	0–17	0–3
Eosinophils					
Mean±SD	NR	0.4±0.6	NR	0.2±0.3	NR
Median	NR	0.2	0.2	0	NR
Range	NR	0–3.6	0–0.3#	0–1	NR

NR: not reported. #: first interquartile to third interquartile.

reasonable accuracy. Hence, the physician must consider this cut-off together with the underlying disease and the overall clinical picture. Furthermore, in children who present with chronic wet cough, a positive culture with $>10^4$ colony-forming units per mL is indicative of a protracted bacterial bronchitis.

Cellular components The evaluation of BAL fluid cellular components may have important clinical indications in children with chronic DPLD, a group of disorders that are characterised by alveolitis, tissue remodelling, fibrosis or a combination thereof. In these patients BAL may be a useful tool for characterising the alveolitis and for monitoring the patient during treatment, follow-up and in reaching or confirming a specific diagnosis (table 2). Three different forms of alveolitis can be identified (fig. 1):

- lymphocytic,
- neutrophilic,
- eosinophilic.

Findings from BAL may help in providing a specific diagnosis in children with alveolar proteinosis, pulmonary haemorrhage, pulmonary Langerhans cell histiocytosis, chronic lipoid pneumonia and pulmonary alveolar microlithiasis.

Because BAL fluid recovered from infants with alveolar proteinosis contains PAS-positive, diastase-resistant, basophilic and mucin-negative amorphous material it typically appears milky. Electron microscopy of the BAL fluid sediment discloses abundant extracellular, multilamellar bodies and tubular myelin structures consistent with abnormal surfactant forms. Differential cell counts predominantly show lymphocytes with alveolar macrophages, which, on electron microscopy, have an enlarged foamy cytoplasm containing numerous extracellular, concentrically lamellar surfactant bodies (lamellar bodies).

When the BAL fluid appears bloody or orange pink in children with anaemia and infiltrates on chest radiographs the suspected

Table 2. Forms of alveolitis in children with respiratory disorders

Lymphocytic alveolitis	Neutrophilic alveolitis	Eosinophilic alveolitis
Prevalence of CD4 cells	IPF	Eosinophilic pneumonia
Sarcoidosis	BOOP	Diffuse parenchymal lung diseases
Crohn's disease	Wheezy bronchitis	Asthma
Prevalence of CD8 cells		
Exogenous allergic alveolitis (hypersensitivity pneumonitis)		
Histiocytosis X		
Diffuse parenchymal lung diseases associated with collagen diseases		
BOOP		

BOOP: bronchiolitis obliterans organising pneumonia; IPF: idiopathic pulmonary fibrosis.

diagnosis is alveolar haemorrhage. The BAL fluid characteristically becomes progressively bloodier with each sequential sample. Specific haemosiderin staining detects haemosiderin in alveolar macrophages (fig. 2). When haemosiderin-laden alveolar macrophage percentages exceed 20%, the diagnosis of diffuse alveolar haemorrhage is usually confirmed. The diagnosis can sometimes be delayed because haemosiderin-laden macrophages may take >48 h to appear after bleeding.

In patients with pulmonary Langerhans cell histiocytosis, Langerhans cells can be identified in BAL fluid through immunostaining for S-100, CD1a and langerin. The threshold of 5% CD1a-positive cells in BAL fluid used for diagnosing pulmonary Langerhans cell histiocytosis has excellent specificity, but low sensitivity.

BAL has also been used to document the diagnosis of pulmonary alveolar microlithiasis by demonstrating microliths in the BAL fluid, which stain pink with PAS stain. Well-formed microliths stain black with von Kossa stain because they have a high calcium content.

A cytological examination showing vacuolated alveolar macrophages indicates chronic lipoid pneumonia (fig. 3). The diagnosis

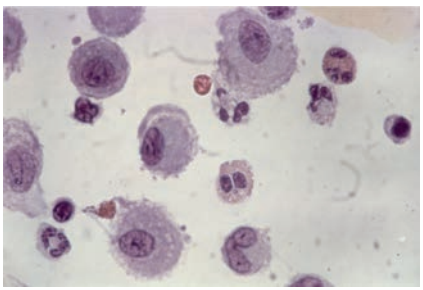

Figure 1. BAL fluid cytology features in eosinophilic alveolitis (May–Grünwald Giemsa stain, ×100 magnification).

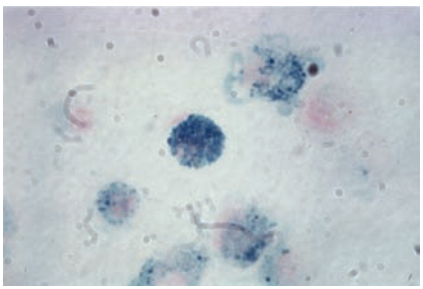

Figure 2. Haemosiderin–laden alveolar macrophages in the BAL fluid of a patient with alveolar haemorrhage (Prussian blue stain, ×100 magnification).

can be confirmed by specific staining with oil red O. Lipid-laden macrophages can be quantified with the lipid-laden macrophages index assigning to each lipid-laden macrophage a score ranging from 0 to 4 according to the amount of cytoplasmic lipid. A lipid-laden macrophage index >100 has 100% sensitivity, 57% specificity, a negative predictive value of 100% and a false-negative rate of zero.

BAL remains the procedure of choice to diagnose chronic pulmonary aspiration by determining the lipid-laden macrophage index and/or by measuring gastric pepsin concentrations. A lipid-laden macrophage index >100 is considered positive for aspiration. With respect to other potential biomarkers, tracheal pepsin has been used as a marker of reflux aspiration. Pepsin detection in the BAL fluid has been shown to have high sensitivity and specificity for reflux-related pulmonary aspiration.

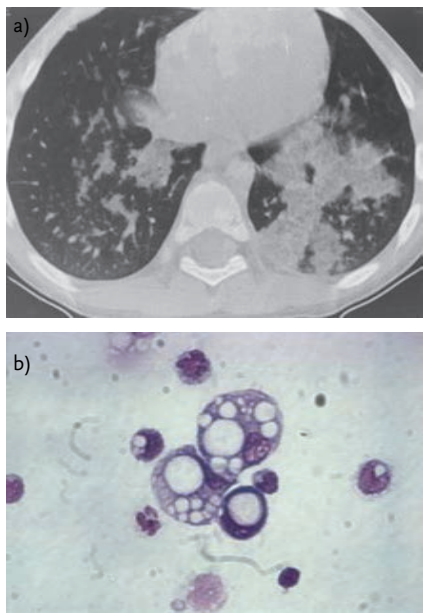

Figure 3. Lipoid pneumonia. a) Contrast-enhanced CT scan of the chest showing lipoid material in the lungs. b) BAL fluid cytology showing vacuolated alveolar macrophages (May–Grünwald Giemsa stain, × 100 magnification).

Therapeutic BAL BAL has a major role in the therapy of certain lung diseases, in the form of total lung lavage (alveolar proteinosis) or mucus plug removal (persistent atelectasis). In particular, children with persistent and massive atelectasis, especially CF patients, seem to successfully undergo selective lavage with DNase or surfactant.

Complications and contraindications

BAL is a well-tolerated and safe procedure; however, on occasion fever, cough, transient wheezing and pulmonary infiltrates have been observed, which usually resolve within 24 h.

The most frequent complication, usually lasting <24 h, is fever; the only treatment needed is antipyretics. In immunocompromised patients antibiotic therapy must be performed for at least 48 h.

BAL may cause hypoxaemia, hypercapnia, or both. Severe bleeding, bronchial perforation, mediastinal emphysema, pneumothorax and cardiac arrest are extremely rare. Contraindications to the procedure include bleeding disorders, severe haemoptysis and severe hypoxaemia that persists despite oxygen treatment.

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Bronchial brushing and bronchial and transbronchial biopsies

Petr Pohunek and Tamara Svobodová

Flexible bronchoscopy allows detailed examination of the bronchial tree down to, at least, the segmental and subsegmental bronchi. Visual examination is the main part of the examination; it provides information about the anatomy and intraluminal lesions, and allows assessment of airway stability and patency. Visual assessment of the bronchial mucosa gives some basic information about possible inflammation, swelling or atrophy. If we want to examine the processes occurring in bronchial mucosa in more detail, visual information alone is not sufficient. For detailed information about the inflammatory or structural changes in the mucosa some additional methods are needed. For sampling of bronchial mucosa tools are available that can be passed through the working channel of the bronchoscope.

Key points

- Bronchial brushing is a useful complementary method for assessing cytological changes in the superficial mucosal layer.
- Endobronchial biopsy allows more detailed evaluation of inflammation and structural damage of the bronchial wall. It also allows direct histological analysis of an endobronchial lesion, *e.g.* a tumour.
- TBLB samples lung parenchyma without the need for thoracoscopy or thoracotomy.

Bronchial brushing

Bronchial brushing is a method used for sampling superficial samples of bronchial mucosa. Basically, two methods can be used. A protected brush is a brush enclosed in a plastic tube that covers the brush and prevents unwanted contamination during passage of the brush through the working channel (fig. 1). Only after the brush is fully passed through the channel is it pushed out of the cover. It is then used for sampling of the desired area before being withdrawn back into the covering tube. The whole instrument is then pulled back out of the channel, the brush is pushed out of the cover and sampled cellular material washed in appropriate medium or smeared on a slide for further examination. The use of a protected brush is limited by the size of the working channel. The minimum channel diameter needed for protected brushing is 2.0 mm. When using a smaller paediatric bronchoscope (3.6 mm or 2.8 mm) we are left with a small working channel with a diameter of 1.2 mm. Only a thin unprotected brush can be passed through this channel. Unprotected brushing is usually performed as a final method before the end of the bronchoscopy. An unprotected brush is passed through the channel and then, under visual control, the mucosal surface is sampled by gently scratching the surface with the brush. The main difference to protected brushing is that the unprotected brush is then withdrawn into only the tip of the bronchoscope just to be hidden in the channel. Then, with the brush left in place, the whole bronchoscope is withdrawn from the patient, The brush is then pushed out of the channel and either cut and dropped into

a vial containing the appropriate medium, washed in the medium or smeared on a slide. This method allows proper sampling with minimum contamination or loss of collected material during the passage of the brush through the working channel.

Bronchial brushing is a useful method of sampling mucosa for cytology and has been successfully used both for clinical and research purposes.

Main indications Usually, bronchial brushing is performed from mucosa within the visual reach of the bronchoscope and sampling is performed from the visible lesion or from the unselected mucosal surface in expected general pathologies. Cytology from visible lesions may provide a specific diagnosis; cellularity of mucosa in general conditions can be evaluated with an assessment of possible mucosal dysplasia or metaplasia, providing contributory information about the intensity and type of inflammation. Bronchial brushing is also used for sampling epithelial cells for an evaluation of ciliary function or structure in suspected primary ciliary dyskinesia. In selected situations, blind sampling can be performed, such as a deep sondage for cytology or culture from a peripheral lesion. Sampling into culture media allows collection of material under visual control for targeted culture.

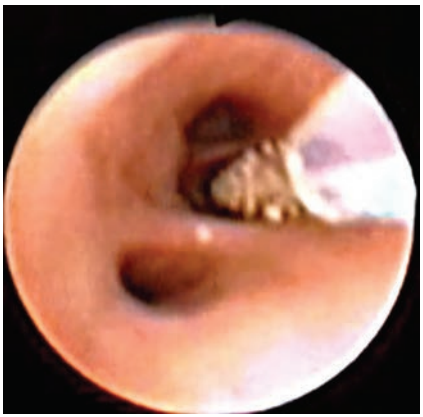

Figure 1. Protected bronchial brush.

Bronchial brushing is generally safe, as it is limited just to the mucosal surface. Minor superficial self-limited bleeding can be seen. In a deep blind sondage there is a possible risk of pneumothorax and the patient should be properly monitored post-procedure with this possibility in mind. Routine follow-up chest radiography is not necessary after a bronchoscopy with bronchial brushing.

Bronchial biopsy

Bronchial (or endobronchial) biopsy is a method allowing sampling of a small piece of bronchial mucosa for histological examination.

Main indications Targeted biopsy is essential for histological diagnosis in focal intraluminal processes, such as tumours, mucosal nodules, granulation tissue, *etc*. Biopsy is also often indicated as a supplementary method for the evaluation of diffuse pathological processes in the bronchial wall (*e.g.* asthma, CF, chronic bronchitis and primary ciliary dyskinesia). Bronchial biopsy only provides information about processes occurring in the superficial layer of the bronchial wall; however, a properly obtained biopsy usually comprises all the relevant structures involved in most pathological processes. In a bronchial biopsy, bronchial epithelium, basement membrane, the subepithelial layer with mucus glands and vessels, and, usually also, the smooth muscle bundles are visible. Various staining methods can be used to increase yield of the method, including immunohistochemistry and specific staining for structural proteins (*e.g.* trichrome)

The size of bronchial biopsy depends on the size of biopsy forceps. Larger paediatric bronchoscopes, with a diameter of 4.9 mm, or hybrid flexible bronchoscopes, with a diameter of 4.0 mm, have a 2.0 mm working channel. This allows most standard biopsy instruments to be used. Biopsy forceps are available in different sizes and shapes. The most commonly used type for a standard bronchial biopsy is an oval fenestrated cup forceps (fig. 2). This forceps allows appropriate embedding in bronchial mucosa and sampling without undesired

damage to the sample. Various other types are available, including alligator shape forceps. These are usually not used for standard biopsy as more damage to the sample might occur. For a standard paediatric bronchoscope with a diameter of 3.6 mm or 2.8 mm with a 1.2-mm channel only limited types of biopsy forceps are available (fig. 2). These are usually provided as an oval non-fenestrated cup with or without a rat tooth. These small instruments are generally much less efficient in obtaining a proper sample of bronchial mucosa and their use, and especially handling of the tiny samples, requires experience.

Bronchial biopsies in general processes are usually taken from some secondary or tertiary carina. It is not recommended to sample from the main carina as the mucosa at this level could carry some nonspecific changes. Sampling from the carina is technically rather easy as there is good possibility to position the forceps, close and grab, and then withdraw the closed forceps carrying the sample between the closed branches (fig. 3). The forceps are then pulled out of the channel and handed to an assistant who places the sample into a vial containing appropriate fixation medium. The sample can usually be liberated from the branches by vigorous shaking of the forceps in the medium. Sometimes a small needle might need to be used to get the

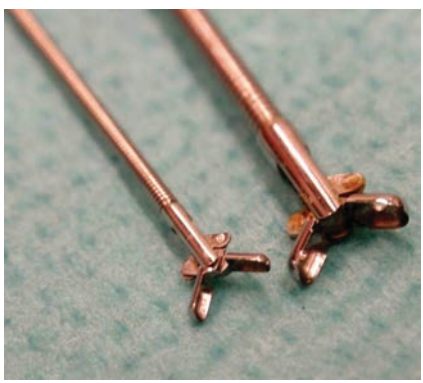

Figure 2. Left: oval cup forceps for a thin paediatric bronchoscope (1.2-mm working channel). Right: oval fenestrated cup forceps.

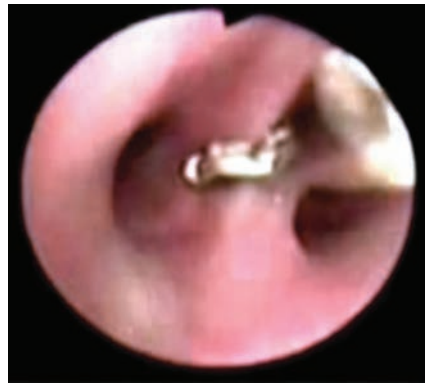

Figure 3. Position of the biopsy forceps for sampling from a secondary carina.

sample off the forceps branches. Depending on a visual assessment of the sample size and quality, biopsy is repeated to guarantee a sufficient sample for further diagnostic evaluation.

If the focal pathology is located in the bronchial wall and therefore sampling from a carina would not be helpful, a different technique must be used. Using the flexion of the tip of the bronchoscope, the forceps must be pressed against the wall with the branches open parallel to the wall and the pathological structure kept between the branches. The forceps are then closed and the mucosa grabbed between the branches. If this is not successful, the positioning must be retried and sampling repeated.

Bronchial biopsy is generally a very safe method. As it samples only a superficial layer of bronchial wall, bleeding is negligible in most cases and a risk of pneumothorax is almost zero. It has been shown to be safe even in children with CF whose bronchial mucosa is generally inflamed and hyperaemic. Even in very young children evaluated for recurrent wheezing bronchial biopsy has been shown to be safe and effective. There was one case of pneumothorax as a complication of bronchial biopsy in a large series (de Blic *et al.*, 2002). In this case, the biopsy was taken from an existing pathology that may have caused some pre-existing lesion of the

bronchial wall. It is recommended to take bronchial biopsies from one lung only to avoid theoretical risk of a bilateral pneumothorax.

Logically, any supplemental procedure prolongs the time required to perform bronchoscopy. Sampling of three adequate biopsy samples requires ~5 min and this should be taken into account when planning a procedure.

Transbronchial lung biopsy

Transbronchial lung biopsy (TBLB) is a special procedure that allows sampling of pulmonary tissue *via* endobronchial approach.

Main indications A main and well-established indication for TBLB is evaluation of rejection in patients with transplanted lungs. Less often, TBLB has been used for diagnostic evaluation of diffuse parenchymal lung diseases or for evaluation of infection. Successful diagnostic TBLB has been documented mainly in homogeneous pathologies, such as pulmonary sarcoidosis and hypersensitive pneumonitis. The main advantage of TBLB is its repeatability as there is no need for video-assisted thoracoscopy or open thoracic surgery (now used much less often). It has been recommended to target the TBLB using preceding HRCT. This helps to increase yield especially in non-homogenous pathologies.

The technique of TBLB is relatively simple; however, it needs experience and practice. TBLB is performed using standard biopsy forceps, preferably with an oval fenestrated cup. Use of alligator forceps is generally not recommended as it may cause more complications. Use of larger instruments through the 2.0-mm channel has better yield; however, successful TBLB can be obtained even with thin forceps used through a small paediatric bronchoscope. For TBLB, the bronchoscope is positioned into a relevant segmental or sub-segmental bronchus. Biopsy forceps are then inserted through the working channel and gently pushed into the periphery beyond direct vision. Fluoroscopy is mandatory as it helps to position the forceps and allows monitoring of the whole procedure, including possible immediate complications, such as pneumothorax (fig. 4). Once the closed forceps are wedged with an elastic resistance, the forceps are withdrawn ~10 mm, opened and pushed down with the aim to break the bronchial wall and accumulate adjacent lung parenchyma between the branches. The forceps are then closed and withdrawn back through the channel. A marked elastic resistance should be felt, which signals a good position of the forceps and predicts an adequate sample. A quick release of the resistance occurs when the sample is detached from the lung and the whole closed forceps can then be withdrawn through the channel. Three to six samples from one side are usually taken to ensure sufficient tissue to evaluate. Sampling from both sides may lead to bilateral pneumothorax and severe respiratory compromise and should, therefore, be avoided. Any bleeding from the area should be carefully monitored using the bronchoscope, which should be left in place for ~3 min after the last sampling to ensure that no major haemorrhage has occurred. If significant bleeding occurs the bronchoscope can be wedged into the relevant sub-segmental bronchus to help to stop the bleeding.

Compared to endobronchial biopsy, TBLB carries higher risk of complications. The most frequent are bleeding and

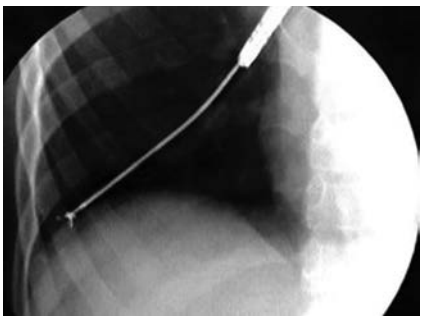

Figure 4. Biopsy forceps during TBLB as shown on the fluoroscopy.

pneumothorax. Overall, the frequency of any complications has been shown to be <10%.

Conclusion

Sampling of bronchial mucosa and pulmonary parenchyma is now a well-established part of a diagnostic process in many respiratory diseases. Cytology and, mainly, histology significantly contribute to diagnosis and therapeutic decision. Biopsy is generally safe but every procedure should be properly planned in advance with possible risks kept in mind and with a decision as to what samples are required for diagnostic evaluation. As endobronchial biopsies contribute significantly not only to immediate diagnosis but also to general understanding of pathological processes, it is now considered ethically acceptable to use part of the biopsy material for research. Of course this must be based on an appropriate protocol, informed consent of legal representatives of the patient and approval by the Institutional Review Board.

Acknowledgements

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Rigid and interventional endoscopy

Thomas Nicolai

Rigid bronchoscopy was the first method described to visualise the lower human airway. In 1897, Kilian removed an airway foreign body using rigid bronchoscopy. The technique was simple and has, in principle, remained unchanged. A rigid hollow tube is used to intubate the trachea or a bronchus. Ventilation can be maintained through this tube, and direct vision was used initially to inspect the airway. The tube was illuminated internally with a prism. Later improvements included a rigid telescope introduced into the hollow bronchoscope tube (table 1). These telescopes are fibreglass rods protected by a metallic covering, with a lens at the distal and an eye piece at the proximal end. Light is transmitted through this instrument with a coupling device from an external light source. Today, the eye piece at the proximal end can be connected to a charge-coupled device camera; thus, the image can be converted to a digital signal and displayed on a video screen.

Key points

- Rigid bronchoscopy is indicated for foreign body retrieval and pre-operative diagnostic workup of subglottic lesions.
- With the necessary precautions the procedure is quite safe.
- Teaching the necessary skills to future generations of paediatric bonchoscopists is a challenge.

Technical considerations

The use of the rigid endoscope for the trachea and bronchi is only possible if the larynx can be exposed and the bronchoscopy tube can then be advanced into the airway. In children with difficult airways, such as in Pierre Robin sequence and other malformations, this may sometimes be impossible.

As the introduction of a rigid tube into the airways is very irritating, full anaesthetic is always necessary. Because the ventilation of the patient has to be performed through the rigid tube, appropriate connectors are necessary and different sizes of rigid tubes are used to intubate differently sized airways to achieve a reasonable seal and allow ventilation of the patient. The rigid endoscope has smooth edges at the distal end but could still potentially damage the airway. Therefore, the rigid tube can only be advanced safely if its distal edge is visible during its movement. If this principle is adhered to, rigid bronchoscopy is a very safe procedure.

If the rigid tube is advanced into the lower airways, care must be taken to smoothly align the long axis of the rigid tube with the airway. This is achieved by turning the head to the right when intubating the left bronchial system, and conversely on the right side.

The bronchoscope tubes have small lateral slits that allow the passage of air into the more proximal airways, even when the tip of the bronchoscope has been advanced into the distal bronchi or when it may be occluded by a foreign body during an extraction procedure. So-called

Table 1. Rigid bronchoscopes for children

Tubes: internal diameter mm	Telescopes: outer diameter mm
3.0	1.8
3.5	2.0
4.0	2.7
4.5	3.4
5.0	4.0
5.5	
6.0	

These are typical examples, exact actual sizes may vary for different manufacturers; typical lengths are 28, 30 and 35 cm.

tracheoscopes are rigid tubes with the same diameter as the bronchoscopes but without lateral openings to avoid a loss of ventilation pressure when the tip of the tracheoscope is placed in the trachea, when, the lateral openings of a bronchoscope would still be proximal to the larynx.

The rigid bronchoscope allows for the use of various instruments through its lumen (fig. 1); these can be:

- forceps,
- suction catheters,
- special magnets,
- biopsy needles.

Specialised bronchoscopes even allow the transmission of a carbon dioxide laser through a set of mirrors and make laser surgical procedures in the lower airways possible with no deeper or transmural tissue damage.

Indications

Today, most diagnostic indications are covered by the use of a flexible bronchoscope. However, a few clear indications for rigid bronchoscopy remain, and foreign body removal is the most frequent (fig. 2). The guidelines of the American Thoracic Society clearly advocate rigid bronchoscopy for foreign body removal in children.

Even today the advantage of rigid bronchoscopy is a secure airway during the procedure and the possibility to introduce various instruments. In particular, if a large and potentially occluding foreign body has to be extracted, the rigid technique allows the bronchoscopist to reposition or push the foreign body if it is lost during the procedure, giving more safety to a potentially life-threatening operation. In addition, bleeding or secretions can be controlled or suctioned. This is often impossible when a foreign body retrieval basket has been advanced through the thin suction channel of a flexible scope. Also, with a flexible bronchoscope, ventilation through a mask or laryngeal mask is necessary while the bronchoscope obstructs part of the airway. The possible ventilation pressure is limited to 20–25 cmH_2O with this technique. If the foreign body or bodies cause increased airway resistance, sufficient ventilation pressure may not reach the lung, leading to dangerous hypoventilation and respiratory instability. However, small distally positioned foreign bodies may be more easily extracted with a combination of both methods (flexible through rigid).

Other indications include the recanalisation of airways, *e.g.* in TB, the use of a carbon dioxide laser for surgical interventions and, rarely, the placement of silicone stents. The removal of bronchial casts in plastic bronchitis or solidified airway secretions in severe bacterial tracheobronchitis are also best performed with a rigid bronchoscope.

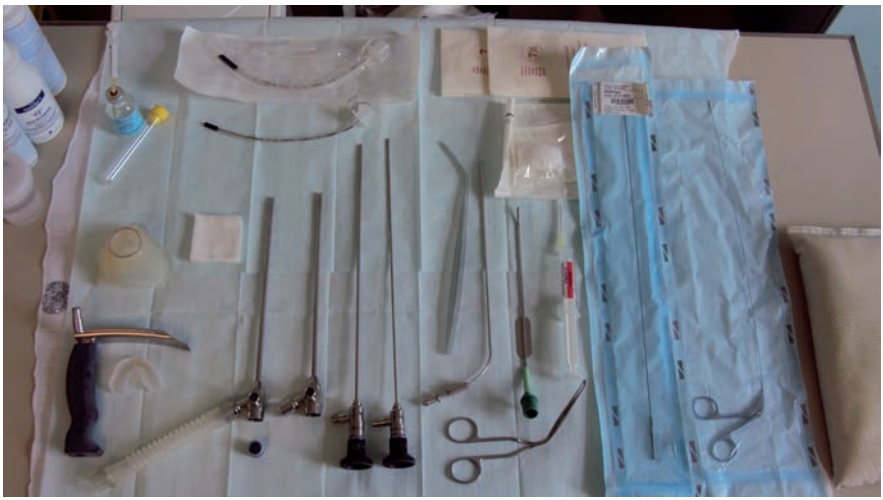

Figure 1. Instrument tray for rigid bronchoscopy in children, including bronchoscopy tubes, telescopes and suction tubes.

Bronchoscopy using only a rigid telescope

A variant of rigid laryngo-tracheo-bronchoscopy that is quite useful in children consists of the use of a rigid telescope alone (without a rigid bronchoscopy tube) to intubate and inspect the airways.

The technique involves exposing the larynx with a laryngoscope. If a more complicated examination or intervention is planned, the laryngoscope can be fixed to the operating table with a special device, thereby freeing the left hand of the bronchoscopist (suspension laryngoscopy) (fig. 3). During a period of apnoea, the rigid telescope is then advanced through the level of the vocal folds into the lower airways. Great care is taken not to touch the airway surface. This technique gives extremely detailed pictures of the glottis, subglottic region and trachea and can be used for preoperative documentation and instrumentation if laryngeal or subglottic surgery is planned. It also allows for the use of instruments, apart from the telescope, without the limitations of space within the rigid bronchoscopy tube. Measurements of distances can be made with great accuracy. This method is particularly suited to directly inspect the subglottic region, even in cases such as laryngitis, without touching the airway surface. This is useful to exclude a foreign body in the diagnostic workup of atypical or persistent cases of croup. The procedure lasts only seconds and can be performed under short anaesthetic such as for an intubation procedure, even in a respiratory-unstable patient.

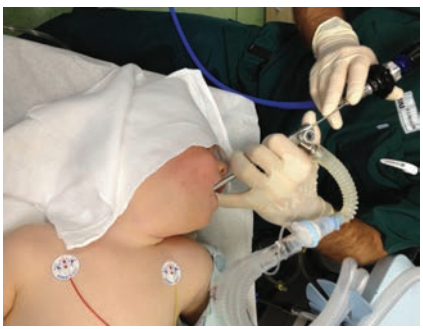

Figure 2. Rigid bronchoscopy for the removal of a foreign body.

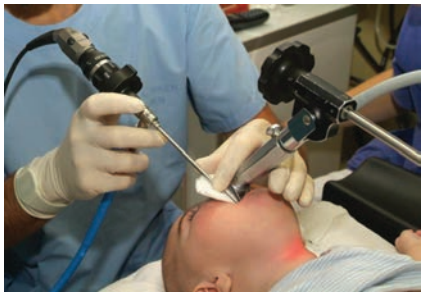

Figure 3. Rigid laryngoscopy with a telescope and laryngoscope blade fixed to the operating table (suspension laryngoscopy).

This method may also be used to inspect the damage to the larynx in children with intubation stenosis or glottic inflammation by retracting the endotracheal tube, inspecting the subglottic region and immediately reintroducing the tube. This technique allows optimal diagnosis and even local therapies, such as laser resection or infiltration of laryngeal papillomas with substances like cidofovir.

Contraindications and difficulties

Contraindications to rigid bronchoscopy obviously include an airway that cannot be intubated with a rigid bronchoscopy tube without excessive force or when the use of laryngoscope exposing the larynx is contraindicated, such as in vertebral instability.

A bleeding diathesis or severe thrombocytopenia makes the use of a rigid endoscope more dangerous, without being an absolute contraindication. Bacteraemia may ensue with rigid bronchoscopy and, therefore, the recommendations for antibiotic coverage in children with congenital heart disease must be followed.

Rigid laryngoscopy and bronchoscopy will not allow the diagnosis of any dynamic or functional features such as airway malacia, vocal cord paralysis or pharyngeal instability and may, therefore, be insufficient in the diagnosis of stridor. In these cases, it may be combined with flexible endoscopy as indicated.

Future developments

It will be necessary to keep teaching future generations of bronchoscopists rigid bronchoscopy to ensure airway foreign body extraction remains a safe procedure. This poses a real challenge to paediatric bronchoscopists because almost all diagnostic bronchoscopies will be flexible, with few indications remaining for rigid endoscopy except foreign body removal. Usually, ENT surgeons have the necessary skills and a paediatric bronchoscopist who wants to learn this technique would be advised to participate in (at least adult) rigid bronchoscopies, followed by a hands-on simulation course in paediatric rigid bronchoscopy and supervised foreign body extractions.

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General anaesthesia, conscious sedation and local anaesthesia

Jacques de Blic and Caroline Telion

The diagnostic value of bronchoscopy is now widely accepted to directly visualise the lower airways and obtain samples, particularly by performing bronchoalveolar lavage. Performing a safe and successful examination and sampling of the airways depend on the experience and skill of the operator and on the comfort of the child. Bronchoscopy, like any invasive technique, may induce anxiety, fear, pain and unpleasant memory of the experience. Paediatric patients should almost always be sedated for bronchoscopy. The available techniques are general anaesthesia for babies or young children and moderate sedation for children, teenagers or patients with ASA III–V status, according to the American Society of Anesthesiology classification.

Key points

- Appropriate sedation is important for a well-tolerated bronchoscopic procedure; available techniques include general anaesthesia and moderate sedation.
- Various protocols may be used during flexible bronchoscopy that involve the administration of a single drug or drug combination (midazolam, meperidine, propofol, ketamine, remifentanil, *etc.*), or inhalation agents (premixed 50% nitrous oxide and oxygen or sevoflurane).
- Rigid bronchoscopy should always be performed under general anaesthesia.
- Whatever the choice of sedation and technique of oxygen delivery (nasal prongs, face mask, laryngeal mask or endotracheal intubation) it is essential to maintain and preserve spontaneous ventilation.

Pre-bronchoscopic procedures

A detailed history and a complete physical examination should be performed. Pre-operative assessment of the child is essential, including:

- general history,
- allergies and previous adverse drug reactions,
- current medications,
- sedation/anaesthesia history with focus on complications and airway problems,
- history of upper airway problems and sleep-disordered breathing or snoring,
- major medical illnesses,
- physical abnormalities and neurological problems,
- recent acute illnesses (*e.g.* upper respiratory infection, fever, *etc.*).
- written fully informed consent.

Minimum fasting periods prior to the procedure are usually 2 h for clear liquids, 4 h for breast milk, 6 h for formula or light meals and 8 h for full meals.

The need for premedication is at the discretion of the anaesthetist. In general it is unnecessary; however, if the child is distressed or unable to cooperate then premedication is advisable.

Oral atropine (0.01–0.02 $mg \cdot kg^{-1}$) minimises bradycardia induced by vasovagal stimulation and also decreases airway

secretions. The utility and safety of oral or intramuscular atropine premedication has yielded conflicting results

Appropriate equipment in a dedicated bronchoscopy suite including pulse oximeter, blood pressure measuring device, electrocardiograhy, capnography, suction apparatus and, if possible, a temperature monitor is necessary.

General anaesthesia

General anaesthesia may be achieved either by an intravenous drug (propofol, ketamine or remifentanil) (table 1) or a volatile agent (halothane or sevoflurane). They can be used alone or in combination. The presence of a trained anaesthesiologist is necessary.

- Propofol is an intravenous sedative hypnotic agent administered in a dose of 2–5 $mg \cdot kg^{-1}$. It has a rapid onset and a short duration of action. The level of sedation and that of respiratory depression are dose dependent.
- The use of ketamine as an anaesthetic agent is less common in children. Ketamine has been associated with laryngospasm and bronchospasm. It should be used in combination with atropine and benzodiazepine in premedication. Ketamine can be used successfully, but requires attention to topical anaesthesia of the airway in order to reduce the risk of laryngospasm; the addition of a benzodiazepine is also recommended to prevent the emergence of hallucinations.
- Remifentanil is a synthetic opioid agent which is a strong analgesic. It has a short duration of action and a short half-life. Its adverse effects include respiratory depression, hypotension, vomiting and rigid chest syndrome. It is rarely used in anaesthesia for flexible bronchoscopy, but it is used in rigid endoscopy.

Inhalational agents are commonly used. Sevoflurane has a rapid onset of action, its effects quickly resolve after the discontinuation of drug administration, it has minimal cardiovascular and no bronchoconstrictive effects. It allows deep sedation with preservation of spontaneous ventilation. When using inhalational agents, the preferred technique for administration is usually *via* a face mask with the bronchoscope being passed through a port on the mask while the anaesthetic gas is delivered. An alternative technique is the use of a laryngeal mask.

Moderate sedation

There is no unique protocol for inducing conscious sedation. As for general anaesthesia, conscious sedation may be achieved either by an intravenous drug (*e.g.* midazolam or meperidine) (table 1) or a volatile agent (inhalation of premixed 50% nitrous oxide and oxygen). Combinations of agents are more effective than single agents. Sedation should be given in small incremental doses until the desired effect is obtained.

Midazolam is a water soluble benzodiazepine. It reduces anxiety and causes amnesia of the procedure. Flumazemil is used as an antagonist. Midazolam is not intended as a sole agent for paediatric sedation, but should be administered in association with an opioid or nitrous oxide *via* a face mask.

Meperidine is a synthetic opiate that produces both sedation and analgesia; it has the advantage of rapid onset of action and is easily reversible (naloxone). Mepiridine is preferably administered intravenously by fractional doses to achieve the desired effect with the minimum drug dose. The use of a benzodiazepine reduces the required dosage of meperidine. Known adverse effects include:

- respiratory depression that may last longer than other clinical effects,
- transient urticaria due to release of histamine,
- transient hypotension,
- nausea,
- vomiting.

Anxiolysis and analgesia may also be achieved with inhalation of premixed 50% nitrous oxide and oxygen administered *via* a face mask. Onset of action is 3 min and duration of action is 5 min. Side-effects,

Table 1. Main drugs used for sedation in paediatric flexible bronchoscopy

Drug	Actions	Dose	Onset of action	Duration of action	Antagonist
Midazolam	Anxiolysis Amnesia	*i.v.* (bolus): 75–300 $\mu g \cdot kg^{-1}$	1–5 min	90 min	Flumazemil 0.01 $mg \cdot kg^{-1}$
Meperidine	Analgesia	*i.v.* (bolus): 0.5–2 $mg \cdot kg^{-1}$	5 min	3–4 h	Naloxone 0.01 $mg \cdot kg^{-1}$
Ketamine	Analgesia Anaesthesia Amnesia	*i.v.* (intermittent bolus): 0.25–0.5 $mg \cdot kg^{-1}$	2–4 min	10– 20 min	
Propofol	Anaesthesia	*i.v.* (intermittent bolus): 0.5–1 $mg \cdot kg^{-1}$ *i.v.* (continuous infusion): 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	<1 min	30 min	
Remifentanil	Anaesthesia Analgesia	*i.v.* (intermittent bolus) 0.25-0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ Continuous infusion 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$	2–5 min	2–3 min	

especially nausea, may occur when it is administered for more than 15 min.

Local anaesthesia

Local anaesthesia is of particular importance when conscious sedation is used. 2–5% lidocaine is applied on the nose and the larynx and 0.5–1% below the larynx. Lidocaine may be instilled directly, sprayed or nebulised (1–5 mL of 2–4% lidocaine according to the child's weight). The total dose should not exceed 5–7 $mg \cdot kg^{-1}$, but the exact amount applied is difficult to assess as most of the lidocaine is removed by suction, spitting or swallowing. Insufficient topical anaesthesia will result in pain, cough, laryngospasm and/or bronchospasm due to vagal stimulation. Topical lidocaine may worsen laryngomalacia.

Techniques to ensure adequate ventilation during flexible bronchoscopy

Whatever the combination of drugs and the technique utilised to deliver oxygen, it is essential to maintain and preserve spontaneous ventilation. The techniques available include nasopharyngeal prongs, face or laryngeal mask, and endotracheal intubation.

Nasopharyngeal prongs are easy to pass down one nostril while the bronchoscope is passed through the other. They allow inspection of most of the upper airway and assessment of the airway dynamics.

Face masks allow the inspection of the entire airway and the assessment of its dynamics. This method permits application of positive end-expiratory pressure. The bronchoscope is passed through an adaptor on the face mask. Problems may arise if a complication occurs as the airway is shared during the entire process between the bronchoscopist and the anaesthesiologist (fig. 1).

Laryngeal masks allow a larger bronchoscope to be introduced, avoid tracheal intubation and are well tolerated. Airway control is better achieved than with the use of a face mask. Disadvantages are that the upper airways and vocal cord movement cannot be assessed (fig. 2).

Endotracheal intubation allows the bronchoscope to be re-passed easily and quickly when necessary. Disadvantages are that upper airways, vocal cord movement and airway dynamics cannot be assessed and that the endotracheal tube may limit the size of the bronchoscope.

Figure 1. Face mask.

Moderate sedation or general anaesthesia for flexible bronchoscopy

The technique of sedation used depends on:

- respiratory status,
- psychological and emotional status of the patient,
- underlying disease,
- available drugs,
- availability of an anaesthetist,
- procedures to be performed.

The principal objective of moderate sedation is to maintain spontaneous ventilation, but fibroscope insertion may induce cough reflex, laryngospasm or ventilatory depression. For these reasons if, in the past, most flexible bronchoscopies were performed under moderate sedation, most units have currently moved to general anaesthesia, which appears to be more comfortable for both the child and the medical team.

When sedation is used, the most frequent agents used are sevoflurane and propofol alone or in combination.

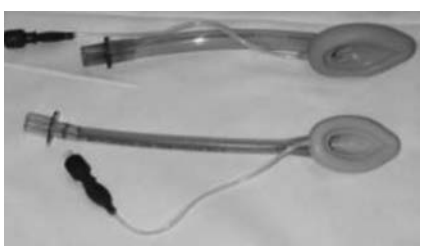

Figure 2. Laryngeal mask.

Sedation and anaesthesia in rigid bronchoscopy

Rigid bronchoscopy should always be performed under deep sedation. Induction of anaesthesia is similar to that of flexible bronchoscopy. Inhalational anaesthesia and oxygen delivery are maintained through a T-piece connected to the side arm of the rigid bronchoscope. Two modes of ventilation are routinely used: spontaneous ventilation or (preferably) positive pressure-controlled ventilation. The use of jet ventilation has also been reported. The use of a muscle relaxant (*e.g.* suxamethonium 1.5 $mg \cdot kg^{-1}$) has been proposed for cases when interventional endoscopy is performed; however, it appears to be less useful in children than in adults.

Recovery and post-procedural care

Upon completion of the procedure, the child must remain in the recovery area until cardiovascular and respiratory stability are assured and the child is awake and orientated. An intravenous line should be left *in situ* until the child is completely awake and tolerating oral fluids.

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Conventional radiography

Meinrad Beer

The role of chest radiography includes:

- primary diagnosis,
- monitoring of patients' progress, and
- assessment for interventional procedures.

Thorough consideration of radiation protection based on optimised equipment includes the protection of relatives and medical staff. Fluoroscopy allows the generation of functional information and should be available as an advanced diagnostic modality in special circumstances. Typical indications for chest radiography and fluoroscopy for different age groups are listed in table 1. Digital imaging has revolutionised chest radiography in the last decade. The increasing number of severely ill children (stem cell transplantation, very low weight preterm babies and polytrauma children) demands a well-equipped radiological unit and well-trained personal.

Key points

- Chest radiography is the backbone of the radiological diagnosis of chest diseases. The use of fluoroscopy is restricted to special clinical indications.
- The advent of digital imaging and pulsed fluoroscopy significantly improved the imaging quality of chest radiography and allowed a tremendous reduction of radiation dose.
- Careful attention is necessary for consideration of radiation protection and necessity of imaging (role of routine follow-up examinations).

Chest radiography

Technique For newborns and infants, the anterior–posterior (AP) view in supine and, later, the upright/sitting position is the accepted standard for conventional chest radiography, as the time-point for deep inspiration is better detectable. For newborns, specially designed holder systems are available, which allow the optimal positioning of the field of view (properly centred) and radiation protection. Moreover, movements of the children are minimised. The AP projection is also used in critically ill children at the paediatric intensive care unit (PICU) for bedside imaging. However, the technical capabilities of the bedside X–ray machines are limited, leading to decreased spatial resolution of images. Moreover, as in adults, heart size is increased and pleural effusions are more difficult to quantify.

The posterior–anterior (PA) projection is the accepted standard for conventional chest radiography in older children. Historically, this was the position that allowed the most exact judgement of the size of the heart. Moreover, the radiation dose is about one-third higher at the site of entry. Most radiosensitive structures and organs, such as eyes, thyroid glands, thymus and mammae, are on the far side from the X-ray machine, *i.e.* anterior. In rare conditions (exact location of basal pneumonias, oncological follow-up and scoring of CF), the PA projection may be combined with the lateral projection.

Table 1. Typical indications for chest radiography and fluoroscopy for different age groups

Age years	Radiography	Fluoroscopy
0–2	IRDS CLD Lines and wires Pneumonia Dysplasia	Oesophageal atresia
2–5	Pneumonia Aspiration Lines and wires	Foreign body aspiration
5–10	Pneumonia Asthma CF Lines and wires	Gastric reflux
10–18	Pneumonia Asthma CF Lines and wires	Gastric reflux

IRDS: infant respiratory distress syndrome; CLD: chronic lung disease.

However, the radiation dose of these lateral views is about two to three times as high as a standard PA view.

Table 2. Criteria for image quality and technical parameters

Size of focus	⩾0.6 to ⩽1.3 mm
Additional filtering	1 mm aluminium + 0.1–0.2 mm copper
Anti-scatter grid	None
Distance focus detector	100–120 cm (AP, children without the chance to cooperate) 140–160 cm (AP, children with the possibility to cooperate)
Tube voltage	60–80 kV
Automatic exposure control	Should not be used in infants; if used, then with both lateral detectors
Time of exposition	⩽20 ms
Radiation protection	Wrapped around, including the gonads (lead)

Chest radiography in the AP/PA projection from the newborn stage up to 10 years is shown as an example.

A direct readout matrix (conversion of X-ray intensity into electrical signals) is the hallmark of digital radiography. Direct (selenium based) are distinguished from indirect (scintillator/photodiode) systems. Both systems provide high-quality images with a resolution of ~10 pixels per millimetre (corresponding to 5 line pairs per millimetre) and allow a significant reduction of radiation dose of up to 50% (depending on the desired resolution). With the advent of dual-reading systems, the spatial resolution is now comparable to the older conventional radiographic systems. An individual optimisation of the software for image calculation is essential. Nevertheless, artefacts from extrafocal radiation may be exaggerated by the digital systems.

Criteria for image quality and technical parameters are listed in table 2. Correct adaption of tube voltage and current to age and to weight is an essential prerequisite for dose reduction as well as the age adapted use of filters. The distance between the child and tube should be not to narrow. Dose reference values allow an estimation of the correctness of the radiologist's own dose values. Most European national guidelines recommend a range for the radiation dose of chest X-rays from 0.3 (preterm child) to

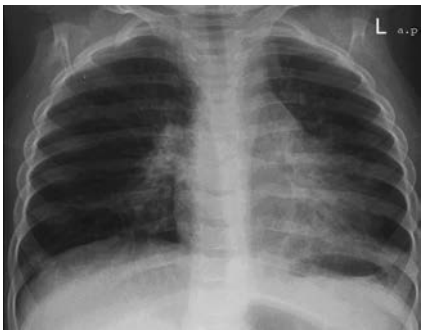

Figure 1. A 15-month-old girl with fever, coughing and wheezing. Pneumonia on both paracardial sides with pleural effusion on the left side.

4 cGy·cm^{-2} (10-year-old child). Whenever possible, shielding (of at least the gonads) should be adopted with appropriate materials. In addition, radiation protection of parents and/or medical staff and/or other children (*e.g.* in the PICU) are important.

Besides the exact positioning of the X-ray on the child, deep inspiration and minimal rotation are important quality factors. A straight run of the trachea is an indicator of a properly inspired X-ray image in newborns and infants. For older children, the scapulae should be rotated so that they are projected outside the lung parenchyma. The exposure to the X-ray generator should be as short as possible to reduce radiation exposure and minimise potential distortion caused by movements of the child.

Nowadays, special training programmes for chest imaging in infants and small children are available. Thus, even nonspecialist medical staff can learn a high standard of data acquisition prior to primary patient contact. This is especially important for low birth weight infants.

Clinical examples Most chest radiographs are taken for assessment of children with suspected infectious diseases of the lung, focusing on exclusion/verification of pulmonary opacities and pleural effusions, sometimes also of pulmonary hyperinflation (obstruction). There is lively discussion of whether chest radiography allows the differentiation between viral and bacterial infections. Moreover, some authors doubt the necessity of routine chest radiography in the assessment of ambulatory acute lower respiratory tract infection. Figure 1 shows the value of chest radiography in detecting complicated pneumonia with relevant pleural effusion in a young child. Ultrasound may be used as follow-up modality to reduce radiation dose.

For PICUs, the value of chest imaging is less debated. In critically ill newborns, it is used to assess the correct position of different lines and wires, such as tracheal and gastric tubes, temperature sensors, and central venous lines (fig. 2).

Conventional chest imaging plays an important role in the detection of the salient radiographic features of CF. Different scoring systems, such as the Brasfield or Crispin–Norman (CN) scores, have been developed to provide objective parameters for longitudinal assessment of potential disease progression. These scoring systems allow an objective assessment of disease severity with low interobserver variability. Included criteria encompass structural changes of the lung parenchyma/tracheobronchial system itself as well as secondary changes in thorax shape and displacement of adjacent organ systems (fig. 3).

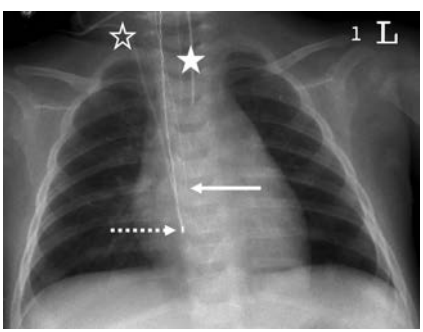

Figure 2. Newborn child at the PICU with fever. Opacities are seen centrally (pneumonia on both paracardial sides). The patient is intubated (closed asterisk), and has a gastric tube inserted too high (arrow), a correctly inserted temperature sensor (dotted arrow) and central venous catheter from the right jugular vein (open asterisk).

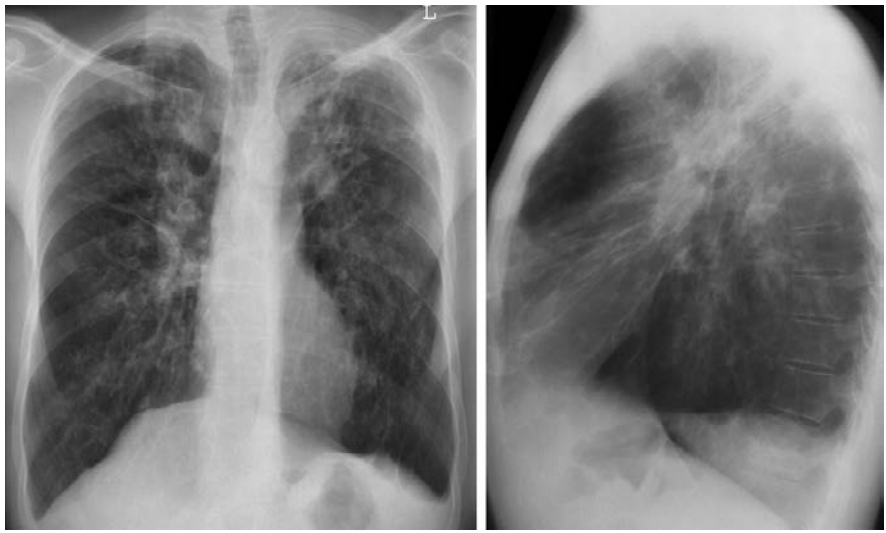

Figure 3. A 22-year-old male patient with CF. Increased lung volumes (obstruction) with a low diaphragm, increased retrosternal space and kyphotic thoracic spine are seen. Marked pulmonary round, linear and confluent opacities are also evident (CN score 27).

Complications of advanced CF such as atelectasis, mucous impaction, pneumothorax, pulmonary haemorrhage and cor pulmonale can be detected. However, CT is superior in detection of extent of bronchiectasis or special kinds of infections (*e.g.* allergic bronchopulmonary aspergillosis, ABPA). MRI is unique in the assessment of functional pulmonary parameters such as perfusion and ventilation.

Chest radiography also constitutes the first step in the radiological diagnosis of

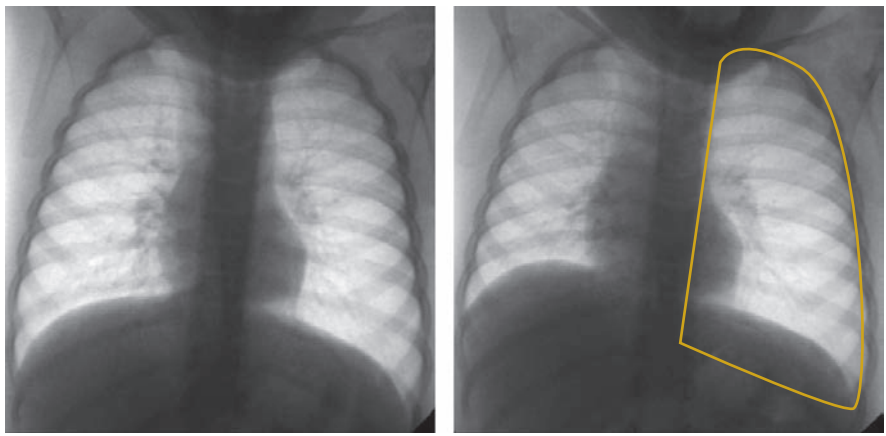

Figure 4. A boy with suspected aspiration of a foreign body. Fluoroscopy detected regional hypertransparency/hyperinflation in the left lower lobe, mostly due to a valve mechanism (increased volume on the left side in end-expiratory (right) compared to end-inspiratory (left) ventilation).

noninfectious chest diseases like tumours, trauma, malformation and foreign bodies.

Fluoroscopy

Technique The last decade also brought significant technical improvements for fluoroscopy. The most important was the advent of pulsed imaging. State-of-the-art fluoroscopy allows the option of different extents of pulse rates. Thus, functional imaging affording high (*e.g.* motility disorders of the oesophagus) and low temporal resolution (*e.g.* slow breathing) is possible with a reduction in radiation exposure of up to 70% (low temporal resolution and low pulse rate). However, functional radiography by fluoroscopy is only rarely used for post-operative complications or detection of fistulas.

Clinical example Determination of regional hyperinflation is one possible indication for chest fluoroscopy. Fluoroscopy allows the storage of a series of digitally acquired images ("cine-loop" and extended "last image hold"). Retrospectively, images in maximum end-inspiratory and end-expiratory phases can be selected to judge or rule out aspiration of foreign bodies (fig. 4).

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Computed tomography

Harm A.W.M. Tiddens, Marcel van Straten and Pierluigi Ciet

A wide spectrum of lung function tests has been developed to detect and monitor structural lung abnormalities+ in children. Over the past decade, chest computed tomography (CT) has gained importance as a more sensitive modality for diagnosing and monitoring such abnormalities. The radiation exposure needed for a volumetric chest CT has fallen substantially, which has lowered the threshold for its usage in children. In addition, CT scanners have become much faster making it feasible to perform a chest examination within a single breath-hold or even in free breathing. This section of the *Handbook* focuses on key issues needed for the optimal and safe use of chest CT in children. This information will be helpful both to fill in relevant information on the chest CT order form and to discuss the selection of the best protocol for the chest CT for children more efficiently with the paediatric radiologist.

Key points

- Use of chest CT in children requires special expertise of the radiologist to follow the "As Low As Reasonably Achievable" (ALARA) principle.
- A chest CT investigation requires a well-defined clinical question, detailed patient history, and deliberation with the radiologist prior to the investigation to maximise diagnostic yield and minimise radiation exposure.
- Careful instruction of the child prior to the investigation is important to reduce anxiety, optimise volume control during the procedure and reduce movement artefacts.
- Volume control during the chest CT should be considered whenever possible.

CT technology

Since their introduction in 1972, CT scanners and reconstruction algorithms have improved greatly. The time needed to obtain the information for reconstructing a cross-section has been reduced to the order of one second, and the spatial resolution has improved substantially. Most CT scanners use so-called fan beam geometry, meaning that the X-ray tube rotates around the patient and attenuation measurements are obtained with an array of detectors, which also rotates. Early scanners acquired data during full rotation of the X-ray tube, before the scanner table moved to scan the next longitudinal position (fig. 1a). This technique, called sequential scanning, was used for nearly two decades

In the late 1980s, a new technique, called spiral or volumetric CT, was introduced by the German physicist Willi Kalender. The patient moves through the CT scanner while simultaneously projection data are acquired from the continuously rotating X-ray source and detector array (fig. 1b). The performance of the spiral CT scanner was further improved by the introduction of scanners which measured multiple fans simultaneously. With multi-slice spiral CT, multiple fan measurements are made and an arbitrary number of slices can be reconstructed. (In the literature, a number of alternative terms can be found for this

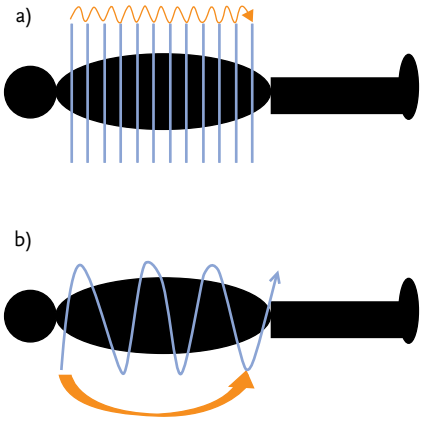

Figure 1. a) Noncontiguous sequential CT. Data are acquired during full rotation of the X-ray tube, and then the scanner table moves to scan the next longitudinal position. Typically thin (0.5–1.5 mm) slices at intervals of 0.5–2 cm are acquired using this technique. b) Volumetric or Spiral CT. The patient moves through the CT scanner while simultaneously projection data are acquired from the continuously rotating X-ray source and detector array.

technique, such as multi-section, multi-channel, and volumetric CT). The coverage in the longitudinal direction per fan measurement is given by the total beam collimation, *i.e.* the width of a single detector row times the total number of rows. Currently available CT scanners allow acquisition of 256–320 fans simultaneously with a beam collimation of up to 320 × 0.5 mm = 16 cm. Thanks to multi-slice CT, the time needed for a chest CT scan has been reduced dramatically, without decreasing the spatial resolution. More recently, scanners have been introduced with two X-ray tubes and two detector arrays rotating simultaneously. These dual-source scanners are capable of scanning the whole chest of a child in less than one second.

Volumetric or sequential scan

Multi-detector CT (MDCT) scanners allow imaging of the chest using either noncontiguous sequential CT scans or by continuous volumetric acquisition. Sequential CT techniques sample the lung by sequentially acquiring thin (0.5–1.5 mm) slices at intervals of 0.5–2 cm (fig. 1a). These are usually obtained in inspiration from the apex of the lung to the diaphragm. A disadvantage of this procedure is that acquisition time will be longer, requiring a longer breath-hold and thus more cooperation by the child. Furthermore, relevant information between the slices can be missed. Finally, for longitudinal follow-up it is unlikely that slices will be taken at the same anatomical levels, making comparison difficult. The only advantage of noncontiguous sequential scanning is a lower radiation exposure than volumetric scanning, which might be considered preeminent in specific cases. Using a volumetric acquisition mode the complete lung is scanned (fig. 1b). An important advantage of this mode is that the scanning procedure is faster. With modern scanners, the entire lung can be scanned in less than one second or only a few seconds, depending on the size of the child and the speed of the scanner. Scanning usually begins at the lung apices and works toward the diaphragm. In case of long breath-hold times, movement artefacts near the level of the diaphragm can be observed. When breath-hold times are critical, it can be considered to scan the lung starting at the level of the diaphragm up to the apices of the lung to reduce movement artefacts.

The major advantages of volumetric CT include comprehensive assessment of the lung structure, allowing reconstruction into multiple planes and of three-dimensional images. In addition it enables matching and sensitive comparison of slices at identical anatomical positions for longitudinal follow-up.

Resolution

The achievable spatial resolution of a scan depends on the scan speed and indirectly on the radiation dose. The scan speed is determined by the speed of table movement and the speed of rotation of the X-ray tube. The speed of table movement mainly depends on the "pitch value". The pitch is defined as table feed per full rotation of the X-ray tube divided by the total width of the collimated X-ray beam. The lower pitch

value, the more information is collected per unit length. Young children have small airway diameters, hence for detailed information of the lung a low pitch is required. When scanning is performed with a low pitch, thin slices can be reconstructed without interpolation artefacts. When scanning is done with a high pitch, reconstruction artefacts will appear. Spatial resolution will generally also improve when the rotation speed of the X-ray tube is lowered, because this allows for the acquisition of more detailed measurements.

The level of detail needed will primarily depend on the clinical question. For example, for CT angiography, high resolution is needed to allow the reconstruction of vessels in great detail. When trapped air on an expiratory scan is evaluated, a low resolution is often sufficient. High-resolution images have more image noise. This image noise can affect the visibility of the structures of interest despite the resolution improvement. Therefore more detailed information can only be acquired at the cost of higher exposure to ionising radiation. High-resolution volumetric datasets are required for (semi-) automated image analysis of lung parenchyma and airways.

Radiation

A disadvantage of chest CT scanning is the relatively high doses of ionising radiation needed compared to, for example, conventional chest radiography. It is assumed that exposure to ionising radiation in CT increases lifetime risk of cancer. This risk is higher in paediatric patients, who have a higher number of active dividing cells than adults. Hence, radiation dose should be justified and minimised to a level "as low as reasonably achievable" (ALARA principle). Since the effects of radiation are assumed to be cumulative, the number of CTs should be kept within acceptable limits. Care should be taken to tailor the CT protocol to the size of the patient and to use the minimum radiation dose that will produce images of diagnostic quality and allow sensitive image analysis. The risks related to exposure levels of state-of-the-art low-dose chest CT protocols are considered to be low. Radiation exposures for a combined inspiratory and expiratory chest CT protocol are in the order of 0.5–1 year of the annual background radiation in the USA. For an expiratory scan, a lower radiation dose protocol should be used than for an inspiratory scan. The required radiation dose can be in the order of half to one third of that for the inspiratory scan. An expiratory scan should only be requested when small airways disease and/or perfusion defects are suspected.

Contrast media

In order to image the vascular system of the lungs, administration of contrast is needed. Several issues complicate the administration of *i.v.* contrast media to neonates and children, including the use of small volumes of contrast medium, the use of small-gauge angiocatheters (for example, 24-gauge), and unusual vascular access sites (hand or foot). Ideally, angiocatheters should be inserted 0.5–1 hour prior to the chest CT so the child is not too upset to lie down quietly in the CT scanner. The dose of contrast media varies between 2–4 $mL \cdot kg^{-1}$ body weight, with very small volumes of contrast media typically administered to neonates and infants (typically 2 $mL \cdot kg^{-1}$). Since contrast media are cleared through the kidneys, a normal kidney function is required. In case of suboptimal renal function, the dose of contrast needs to be adjusted.

Adverse reactions to iodinated contrast media are classed as acute or late. The former occur within 1 hour of contrast medium injection and are further classified as mild, moderate or severe (table 1). For this reason, resuscitation equipment, a paediatric resuscitation protocol and qualified personal should be close at hand in case a severe allergic reaction occurs. Late adverse reactions occur 1 hour to 1 week after contrast medium injection and are represented by a variety of late symptoms (nausea, vomiting, headache, musculoskeletal pain, fever) or by skin reactions, which are usually mild and self-limited. While most minor physiological side-effects of *i.v.* contrast medium

Table 1. Classification of adverse reactions to intravenously administered contrast media

Mild	Nausea, mild vomiting Urticaria Itching
Moderate	Severe vomiting Marked urticaria Bronchospasm Facial/laryngeal oedema Vasovagal attack
Severe	Hypotensive shock Respiratory arrest Cardiac arrest Convulsion

administration in adults are of minimal significance, such events are often of increased importance in children. For example, local warmth at the injection site and nausea, generally regarded to be physiological side-effects to contrast medium administration, may cause a child to move or cry. Such a response to contrast medium injection may result in the acquisition of a nondiagnostic imaging study, necessitating repeat imaging and additional exposure to contrast medium and radiation.

There are several difficulties in interpreting the available literature on the incidence of allergic-like reactions to *i.v.* iodinated contrast media in children. Many studies fail to discriminate between physiological side-effects and allergic-like reactions. In addition, these studies lack agreement on what constitutes mild, moderate, or severe reactions. Finally, there is a lack of controlled prospective paediatric studies on the topic. Therefore, not surprisingly, the reported incidence of paediatric allergic-like reactions to contrast media is variable, and ranges 0.18–0.46%. It is generally agreed, however, that the incidence of allergic-like reactions in children is lower than that in adults.

Volume control

Lung volume, and configuration and orientation of airways, is highly dependent on the level of inflation of the lung. When the lung is well inflated, lung parenchyma is positioned between the heart and sternum. In addition the trachea has a round appearance and the contour of the diaphragm is flattened. For an optimal diagnostic result, volume control is important and should be aimed for whenever possible. Furthermore, it is important that movement of the subject and of the lungs is minimised. However, most young children below the age of 4 years are not able to perform a voluntary breath-hold at the correct volume level and at the correct moment. There are two methods available to scan the lungs in these young children.

The first technique is the noninvasive pressure-controlled ventilation (PCV) technique under general anaesthesia or sedation. The PCV technique starts off by hyperventilating the child by giving a short series of augmented breaths using high positive pressure applied *via* a facemask, laryngeal mask, or tube to recruit all lung areas and to allow for a respiratory pause. Next, for inspiratory images, the lung is inflated to a positive transpulmonary pressure of 25 cmH_2O and the lungs are imaged while pressure is maintained. For expiratory images, no pressure is applied, hence the lung will deflate to a volume level near functional residual capacity. PCV techniques have been shown to be highly reproducible. A disadvantage, however, is that atelectasis can develop within minutes in children under general anaesthesia. Atelectatic regions of the lung cannot be evaluated for the presence of bronchiectasis or other structural abnormalities. When high-resolution images are required, for example when interstitial lung abnormalities are suspected, PCV should be selected as the technique of choice.

The second technique to acquire a CT scan in children below the age of 4 years is to use an ultra-fast CT scanner that can obtain motion-free images of the lung in free-breathing children even without sedation or general anesthesia. A disadvantage of this method is that there is no strict control of lung volume. Spontaneous breathing will be

in a volume range between functional residual capacity and functional residual capacity plus tidal volume. Scans acquired during tidal breathing are less sensitive than those acquired using PCV in detecting bronchiectasis. However, the specificity of bronchiectasis detection is good. For children aged $\geqslant$4 years, chest CT can be carried out mostly without sedation or anaesthesia. Breath-hold instructions during the in- and expiratory CT scan are routinely given by a CT technician, often resulting in suboptimal volume levels. The inspiratory volume level of these radiographer-guided scans results in a lung volume in the range of 80% of TLC. The expiratory volume level of such scans is in most subjects near functional residual capacity, which is well above residual volume. For many years, it has been recognised that spirometer-controlled breathing manoeuvres during the CT scan result in improved standardisation of in- and expiratory volume levels and fewer movement artefacts and thus improve the diagnostic yield substantially. In this case, the patient can be trained by a lung function technician 30–60 minutes prior to the CT scan to perform the requested breathing manoeuvres in supine position using a spirometer. The same technician instructs the patient during the CT scan. The spirometer operated by the patient is connected to a monitor positioned in front of the window of the CT control room, and the lung function technician focuses on the patient during the CT scan while the CT technician can focus on operating the scanner. The lung function technician indicates when the CT acquisition can be started, taking into account the delay (1–4 s) between pushing the start button of the CT scanner and start of the actual acquisition. The sensitivity for the detection of trapped air of spirometer-controlled expiratory scans is superior to that of uncontrolled scans.

Inspiration and/or expiration scan

For many chest CT scan indications, acquisition of both inspiratory and expiratory chest CTs is relevant. An inspiratory CT scan near TLC is needed for the evaluation of lung parenchyma and for the detection of bronchiectasis (fig. 2a–c).

To diagnose bronchiectasis, the diameter of the airway is compared to the diameter of the adjacent or nearby pulmonary artery. When the bronchoarterial ratio exceeds 1.0, it is considered bronchiectasis. It has been shown that the airway:artery ratio is dependent on the inspiration level. The current consensus is that the diagnosis of bronchiectasis can best be made on an inspiratory CT near TLC. At lower lung volumes, the diameter of the airway is reduced more relative to that of the adjacent artery. Hence, at lower lung volumes the bronchoarterial ratio can be less than 1.0 even for a bronchiectatic airway. In addition, at low lung volumes the orientation of airways is different relative to that at inspiration, and airway length is reduced as well, making identification of abnormal widened airways cut in cross-section more difficult. Finally, at low lung volumes, a lower number of airways can be evaluated relative to an inspiratory scan. Similarly, to measure airway wall thickness a standardised volume level near total lung volume is needed. At lower lung volumes, the inner wall of the airway will fold into the lumen, which will appear as a thickened airway wall on a chest CT.

Expiratory scans can be important when perfusion defects and/or small airways disease are suspected (fig. 2d–f). While airways $<$1 mm in diameter are in general not visible on CT scans, small airway disease can be detected indirectly as lucent regions on expiratory scans. These lucent regions can be the result of trapped air with or without hypoperfusion. Trapped air areas can be distinct to the adjacent healthier deflated and normally perfused or hyperperfused dense parenchyma. When multiple lucent areas are present in the lung combined with normal or hyperperfused dense areas, the term mosaic attenuation pattern is used. Areas of trapped air can be differentiated from hypoperfused areas by comparing their density in inspiratory and expiratory scans. Trapped air areas without

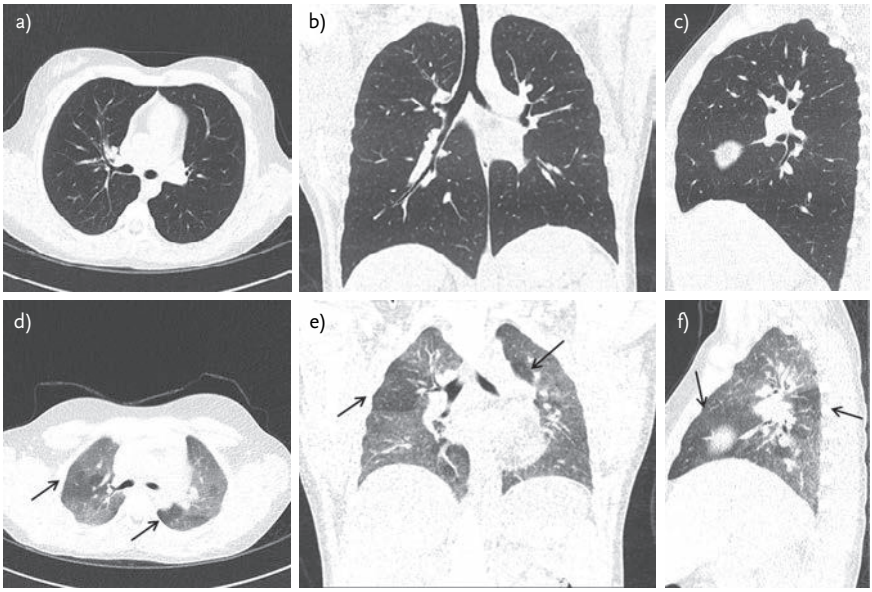

Figure 2. a–c) A spirometer-controlled inspiratory chest CT reconstructed in the axial (a), coronal (b) and sagittal (c) planes. Note that the lung is positioned between the heart and the sternum and that the lung is protruding between the ribs. d–f) A spirometer-controlled expiratory chest CT reconstructed in the axial (d), coronal (e) and sagittal (f) plane. Arrows indicate lucent regions of the lung caused by hypoperfusion and/or trapped air. The lucent areas are adjacent to normal dense regions, representing a mosaic pattern.

hypoperfusion appear lucent only on the expiratory scan. Optimal expiration to a volume level near residual volume increases the contrast between lucent regions and normal or hyperperfused healthier lung regions. However, lucent regions can be considered as trapped air areas only when they follow the distribution of a secondary pulmonary lobule (defined as the smallest unit of lung surrounded by fibrous septa). When up to five secondary lobules are involved, especially if positioned in the dependent regions of the lung (superior segments of the lower lobes, anterior parts of middle lobe and lingula), areas of trapped air are still considered physiological. However, reference studies to support this are lacking.

Dynamic *versus* static imaging

Dynamic cine-multidetector CT has been used to study the dynamic behaviour of central airways in adult patients. This method can be used as an alternative method to bronchoscopy to diagnose tracheomalacia. Unfortunately, dynamic information requires exposure to ionising radiation for the duration of the scan, which will increase the total radiation dose needed for the study. MRI is an alternative technique in development to acquire dynamic information. Hence, further research is needed to define whether cine-multidetector CT or MRI will become a competing technique for bronchoscopy in the near future.

Image processing

Generated images need to be reconstructed and stored in the correct way. After a chest CT has been performed, the raw data are post-processed to generate relevant series and specific reconstructions. The generated images are stored in the Picture Archiving and Communication System (PACS) system. Raw data are in general automatically

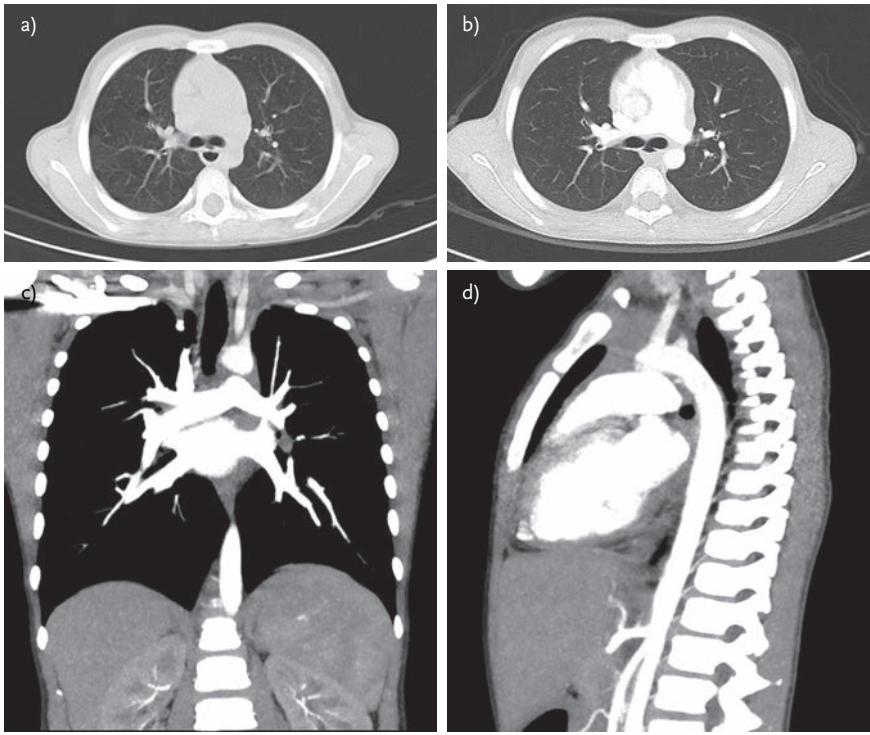

Figure 3. The effect of administration of an intravenous contrast medium. a) A slice (3 mm) in the axial plane acquired before the administration of a contrast medium. b) The same patient scanned after the administration of a contrast medium. Note that the contrast-enhanced image appears slightly sharper and noisier as compared to the native image because of a small change in reconstruction kernel and windowing. c and d) The lung reconstructed in the coronal (c) and sagittal (d) plane using a maximum intensity projection. Note that the contrast-enhanced blood vessels contrast clearly with the surrounding lung tissue.

deleted 1–2 weeks after the scan. Hence, it is important that all relevant series are reconstructed and stored before the raw data are deleted. The radiologist will determine scan protocol and reconstruction series needed based upon the clinical data and questions as defined on the order form. Reconstruction protocols define reconstruction planes (axial, coronal, sagittal), slice thickness (for example 0.65, 1, 1.25, 3, or 5 mm), windowing (parenchyma or mediastinum) and definition of reconstruction kernels (soft or hard). The reconstruction kernel, also referred to as ''filter'' or ''algorithm'' by some CT vendors, is one of the most important parameters that affect the image quality. Generally speaking, there is a tradeoff between spatial resolution and noise for each kernel. A smooth kernel generates images with lower noise but with reduced spatial resolution (fig. 3a). A sharp kernel generates images with higher spatial resolution, but increases the image noise (fig. 3b). Other important reconstruction algorithms are maximum intensity projection (MIP) (fig. 3c–d) and minimum intensity projection (MinIP) (fig. 4). MIP consists of projecting the voxel with the highest attenuation value on every view throughout the volume onto a two-dimensional image. This technique is normally used to detect lung nodules or in scans with contrast to improve vessel depiction. MinIP is a data visualisation

method that enables detection of low-density structures in a given volume. The MinIP algorithm is particularly useful for analysing the airways, which are hypodense compared the surrounding tissue. It is often worthwhile to discuss with the radiologist the case before the scan is made, especially for non-routine patients. At least one series of thin-slice images ($\leqslant$1 mm) in the axial plane should be stored using an appropriate predefined reconstruction kernel. These thin slices are needed to evaluate the airways and this series allows additional post-processing for example reconstruction of thicker slices in the axial, coronal or sagittal plane or for a three-dimensional reconstruction. Furthermore, thin slices are mostly required for commercially available image analysis platforms.

Image analysis

For clinical use, it is possible to monitor progression of structural lung changes on chest CTs. This can best be examined by comparing slice by slice the follow-up to the baseline examination in the axial or other planes. Most PACS viewers enable coupling of two examinations in a single window, with scrolling down through the lung from the apices to base. These comparisons should be performed both for the inspiratory and the expiratory CT scan. Slice-by-slice comparison enables determination of whether observed structural changes on the baseline CT have progressed, are stable, or have improved on the follow-up CT – or whether new abnormalities have developed. Ideally, structural changes on chest CT, such as bronchiectasis or trapped air, should be quantified when possible. To date for chest CT in CF, the method of choice has been scoring. A CT scoring system is a tool to describe the abnormalities that can be observed on the slices obtained from a single CT investigation in a semi-quantitative way. Several scoring systems have been developed (see de Jong *et al*., 2004). For all these systems, the reader identifies various abnormalities on the CT scans and assesses their severity. Important abnormalities that are included in most of the scoring systems are bronchiectasis, mucous plugging, airway wall thickening and parenchymal opacities. Other abnormalities such as small nodules, mosaic attenuation, sacculations and air trapping on expiratory images are included only in some of the systems. An advantage of scoring systems is that they are relatively insensitive to the CT scanner technique and protocol being used. Recently the CF–CT scoring system was developed. The CF–CT scoring training module includes clear definitions and reference images for the structural abnormalities that have to be scored and provides training sets. It has been used successfully in a number of studies. To date there are no validated automated image analysis systems available to quantify bronchiectasis, trapped air or emphysema on paediatric chest CT. It is likely that in the near future commercially available (semi-) automated systems will come to market and replace visual scoring. The use of such systems will require volume standardisation of the chest CT protocol. Semi-automated systems to compare airway:vessel ratios have been used in CF studies. In addition, programs to segment the lung parenchyma and the bronchial tree have been developed. These systems will be used in the near future to detect and quantify CF and non-CF bronchiectasis.

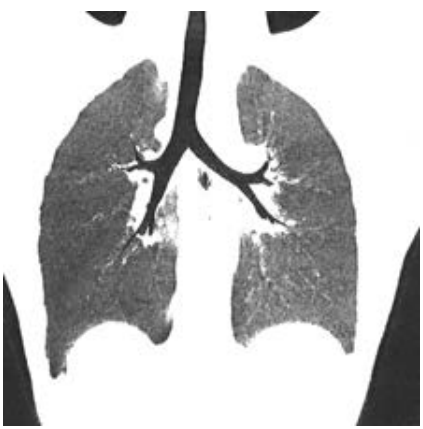

Figure 4. A slice of the lung reconstructed in the coronal plane using a MinIP algorithm which enables detection of low-density structures in a given volume.

Furthermore, systems have been developed to visualise and quantify trapped air. Ideally such a system should be able to compute the volume of trapped air expressed as a percentage of total lung volume. Similarly for chronic obstructive pulmonary disease, systems have been developed to quantify the volume of emphysema. It might be possible and useful to modify these systems to quantify emphysema for diseases such as bronchopulmonary dysplasia and congenital diaphragmatic hernia.

Conclusion

Chest CT technology has been developed to such a level that it has become an important tool for the diagnosis and monitoring of chest diseases in children. To optimally and safely use chest CT in children, a paediatric radiologist should be involved in defining the optimal protocol based on the clinical question. Furthermore, the referring clinician should carefully describe relevant clinical details and the clinical questions. Standardisation of lung volume is of key importance to optimise the diagnostic yield of the chest CT. Lung function technicians can play an important role in preparing children for a chest CT and in coaching and monitoring breath hold manoeuvres during acquisition.

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Magnetic resonance imaging

Lucia Manganaro and Silvia Bernardo

MRI of the chest is a new technique in the imaging of the lung. The lack of ionising radiation makes MRI an attractive alternative to CT in paediatric applications, in which repeated or serial scanning is required.

Paediatric lung imaging

Diseases of the respiratory system are of great importance in paediatrics. Imaging of the chest has led to improvements in the diagnosis and treatment of numerous medical conditions in children.

The first, and most widely used, modality is represented by radiographic imaging. It is fast and inexpensive and provides a good overview of anatomy and pathology.

For most paediatric pulmonary pathologies a plain film is the first, and only, step in the absence of complications and when the clinical course is regular. The best case is to avoid additional imaging, especially CT, if the diagnosis can be obtained by other means. CT is the gold standard in:

- the evaluation of congenital anomalies,
- parenchymal pathologies,
- the case of chronic airway disease for a morphological study,
- the assessment of the complications of inflammatory process,
- the staging of tumoural masses.

MRI is a radiation-free technique and offers alternative solutions to routine diagnostic challenges for the imaging of the lung. It is especially relevant to young patients and pregnant patients, as well as subjects who need to undergo multiple investigations. However, in the approach of lung diseases, the feasibility of MRI investigation is limited by several technical problems. Despite this, in recent years many efforts have been made and there have been significant advances.

MRI techniques For many years MRI imaging was considered useful in the evaluation of mediastinal abnormalities and not the lung parenchyma. However, the lack of radiation exposure makes MRI of the lung particularly attractive for paediatric radiology.

The subordinate role of MRI in the evaluation of lung is caused by different technical problems, especially:

- artefacts related to cardiac and breathing motion,
- the low signal-to-noise ratio because of low proton density of the lung,
- the susceptibility of artefacts because of air–soft tissue transition,
- the low-spatial resolution in comparison to CT.

Key points

- MRI techniques allow for fast and reliable assessment of pulmonary diseases in children.
- Thoracic MRI is a radiation-free method and can be performed frequently without contrast media application.
- The diagnostic value of MRI is shown in patients with infectious diseases, immunodeficiency, anatomic abnormalities, acquired chronic diseases and pulmonary tumours.

In addition, it is important to remember the heterogeneity of the paediatric population and that the time of acquisition of an MRI examination is longer than for CT.

More so than in radiography or CT, the image quality in MRI depends on patient compliance. It can be expected that some sequences may produce unsatisfactory results in very young patients. A drawback of MRI is that, in general, it requires a longer scan time than CT, something that is not much of an issue with older children but may preclude its use in non-sedated younger children. Lung MRI is generally performed with a high-field magnet system using ultra-short acquisition. Different types of sequences can be used.

The spoiled gradient echo (three-dimensional gradient-echo) sequence has multiple applications in lung MRI. For anatomical imaging, it can be used for two- or three-dimensional acquisitions with or without fat suppression pre- and post-contrast administration.

The balanced steady-state free precession (bSSFP) sequence has many applications, in particular in cardiac MRI, but it can also be applied to anatomical lung imaging.

The single-shot fast spin echo (SSFSE) sequence is advantageous for lung imaging for fast acquisition.

Diffusion-weighted imaging (DWI) provides qualitative and quantitative assessment of water diffusivity within tissues. In the thoracic field, DWI is more challenging due to respiratory and cardiac motion. Nevertheless, DWI can be used to evaluate pre-treatment cellularity and treatment responses of focal thoracic lesions.

Control of respiratory phase Respiratory motion of the diaphragm and chest wall can be reduced by respiratory triggering using a pressure-sensing belt. Recently, respiratory gating using a navigator echo has been widely used for the same purpose. Other motion-reducing methods, such as saturation bands, signal averaging and motion-insensitive pulse sequences, may be used in children.

Contrast media use (gadolinium chelates) allows for:

- better characterisation and extension of disease,
- evaluation of the process activity,
- studies of cardiovascular and perfusion performance.

As work in progress, MRI can assess various aspects of pulmonary function, including lung perfusion, blood flow, respiratory mechanics and, using an inhaled contrast agent, pulmonary ventilation. Thus, MRI is emerging as a versatile modality for morphological and functional imaging of the lung.

MRI perfusion imaging can be performed using two different techniques: contrast-enhanced MRI perfusion and noncontrast-enhanced MRI perfusion. In patients with pulmonary embolism MRI perfusion provides additional information about perfusion defects. Perfusion scintigraphy has been replaced by ultrafast CT (multiple-detector or volume CT with special child programmes) in the imaging of pulmonary embolism in children. Using CT as the gold standard, MRI perfusion shows a comparable high sensitivity and specificity for the detection of perfusion defects. In patients affected by pneumonia, MRI perfusion contributes important information for the differential diagnosis of pulmonary embolism.

MRI ventilation Because of the low proton density and high susceptibility of lung tissue, conventional proton MRI is not suitable for visualising lung ventilation, and alternative contrast mechanisms have to be used. Oxygen-enhanced MRI has been investigated for lung ventilation imaging and has a unique feature in which perfusion and diffusion also contribute to the oxygen enhanced MRI signals. An inhaled contrast agent, either oxygen or a hyperpolarised noble gas (hyperpolarised helium-3 is a gaseous MRI contrast agent that, when inhaled, provides a very high MRI signal from the airspaces), is required for MRI lung ventilation imaging. In clinical studies, MRI is able to differentiate between diseases with

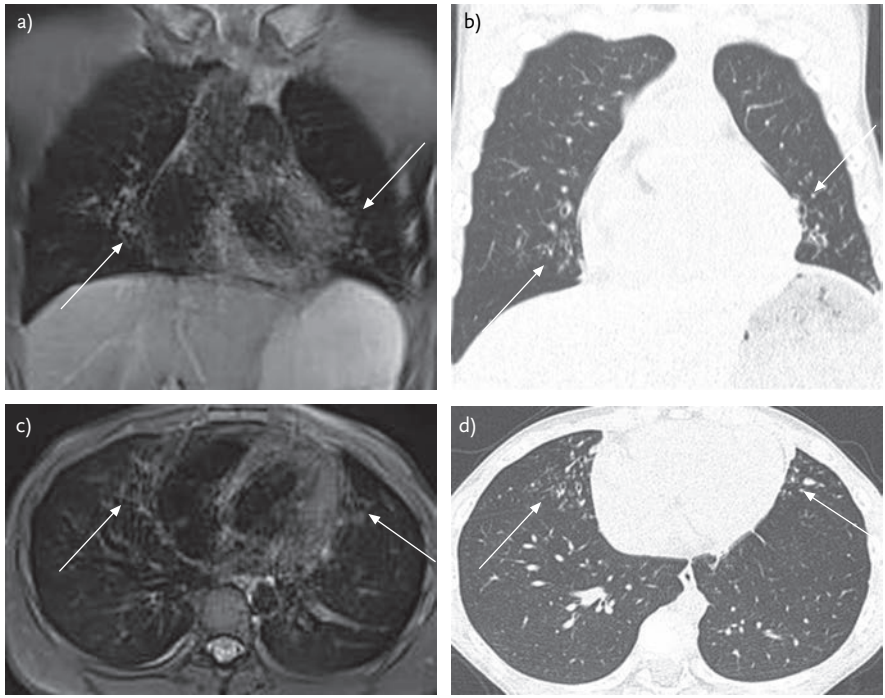

Figure 1. A CT scan from a 9-year-old boy with cough and dyspnoea of b) the coronal and d) the axial plane showed bronchiectatic areas and bronchial wall thickening next to the heart (white arrows). a, c) The same findings are visible on MRI sequences, confirming sensitivity of these protocols for bronchiectasis is at least similar to CT.

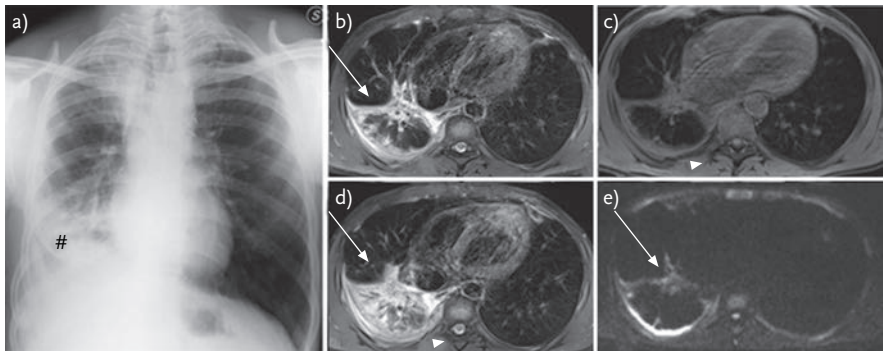

Figure 2. A 12-year-old boy with dyspnoea following lung transplantation. a) The chest radiograph showed an opacity in the right lung (#). b, d) T2-weighted fat saturation images clearly demonstrate a pneumonic infiltrate (arrows), e) confirmed with a particularly high signal in diffusion weighted imaging (arrow), associated with posterior hyperintensity in T2-weighted imaging (arrowheads) and c) hypointensity in T1-weighted imaging (arrowhead) indicating pleural effusion.

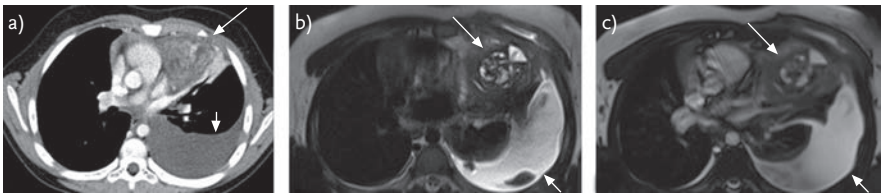

Figure 3. A CT scan, performed after a chest radiograph, in a 10-year-old girl with a history of progressive difficulty in breathing and chest pain. a) A dishomogeneous space-occupying lesion in the mediastinum (arrow) associated with pleural effusion (short arrow) from the upper mediastinal area, in front of the aorta and pulmonary artery, is visible. b, c) MRI confirmed the mediastinal mass causing a compressive effect on pulmonary vessels and parenchyma with almost total collapse of the left lung (arrow) and pleural effusion (short arrow). The signal intensity demonstrated the presence of water intensity cystic spaces with fat-fluid levels (specific for teratoma).

and without ventilation/perfusion mismatch (*V'*/*Q'*) and has shown high sensibility in comparison to gold standard references such as scintigraphy. However, its clinical application is limited by a low signal-to-noise ratio (the difference in signal intensity between the area of interest and the background) and difficulties in performing the examination. Further clinical studies in children are necessary to prove its great potential.

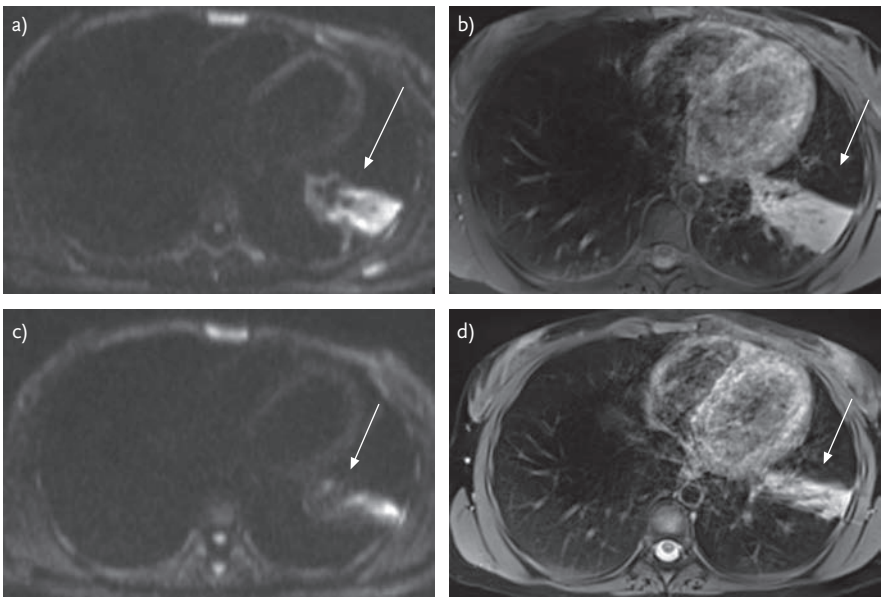

Figure 4. An 11-year-old girl with a history of fever and cough. Acute phase dorsal consolidations on the left are well represented as hyperintense focus in a) diffusion weighted imaging sequence b600 (arrow) and b) turbo spin echo (arrow). After 3 weeks of therapy the focus appears less hyperintense in c) diffusion weighted imaging sequence b600 (arrow) and d) turbo spin echo (arrow) showing a response to therapy (image courtesy of G. Morana, Department of Radiology, Ca Foncello Hospital, Treviso, Italy; personal communication).

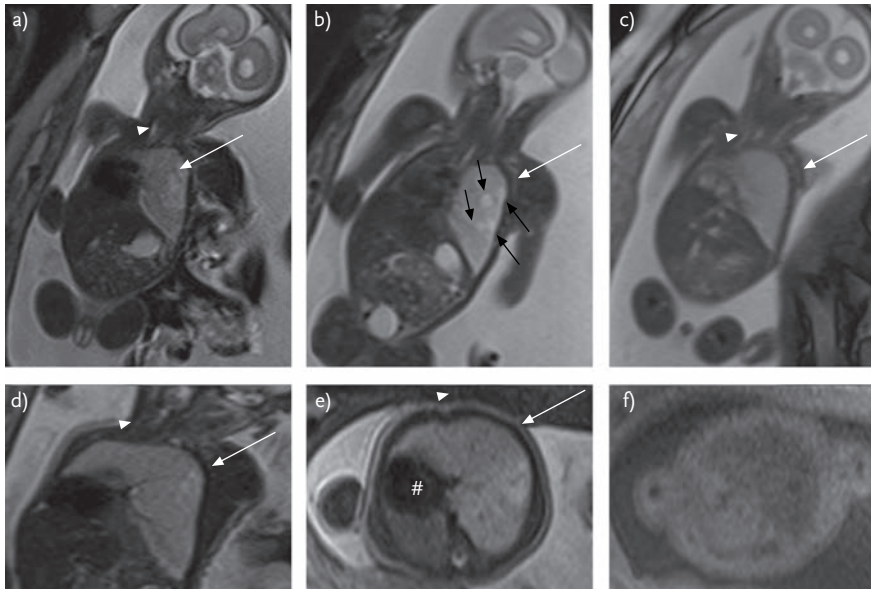

Figure 5. A fetus at 23 months +4 days of gestation. a–e) Hyperinflation of the left lung (arrows) associated with trans mediastinal hernia (arrowheads) and right medistinal shift (#). Many centimetric lesions are present in the pulmonary parenchyma (black arrows). f) These lesions are hyperintense in T2- and hypointense in T1-weighted fat saturation images, indicating cystic lesions suggestive of a Type II CPAM (Stocker classification).

Paediatric lung MRI: indications and features

Major clinical indications for MRI arise from three major fields:

- lung infections, CF, asthma and pulmonary hypertension (fig. 1),
- regular imaging in patients in whom radiation exposure should be avoided (fig. 2),
- mediastinal masses (fig. 3).

Lung infections The diagnostic value of MRI is shown in patients with infectious diseases. MRI detects pulmonary infiltrates, hilar changes and pleural or pericardial effusions as well as, or better than, chest radiography.

The predominant MRI findings are alveolar or interstitial parenchymal changes, pleural thickening and fluid and lymph node enlargement. It is very important to highlight the role of MRI in complicated pneumonia when there is the suspicion of empyema or lung abscess. In these cases MRI allows the complications and the extension of pleural empyema to be evaluated; it can also be repeated to evaluate the development and to monitor the response to treatment (fig. 4).

Some authors emphasise the role of MRI in the characterisation of pulmonary infiltrates, especially in patients suffering from neutropenic fever, although cost-efficiency has not been proven for this indication.

CF is the most common indication for MRI. By using common proton-MRI sequences it is possible to visualise the structural changes of CF lung disease such as:

- bronchial wall thickening,
- mucus plugging,
- bronchiectasis,
- air–fluid levels,
- consolidation,
- segmental/lobar destruction.

In patients with CF, bronchial wall thickening of the small airways enhances their detectability by MRI so that small airways with thick walls can be visualised in the lung periphery. Mucus plugging is also well visualised by MRI due to the high T2-weighted signal of its fluid content and is associated, in most cases, with bronchiectasis. The MRI appearance of bronchiectasis is dependent on bronchial level, bronchial diameter, wall thickness, wall signal and the signal within the bronchial lumen.

Another sign is consolidation, which is mainly caused by alveolar filling with inflammatory fluid. The visualisation of consolidation in MRI is based on the high T2-weighted signal from the inflammatory fluid. A developmental role of MRI in the patients affected by CF maybe related to follow-up after transplantation because it is radiation free.

Neoplasm Although not used routinely, MRI may be sensitive in the detection of pulmonary metastases. The sensitivity will depend on lesion size; the sensitivity in smaller nodules (<5 mm) remains to be established. Much work is needed to establish the role of MRI and its relationship with CT.

Other important indications are anatomic abnormalities such as pulmonary sequestration, acquired chronic diseases, pulmonary arteriovenous malformations (PAVMs), vascular malformations and fetal malformations.

Fetal lung MRI

Prenatal diagnosis of congenital lung anomalies has increased in recent years as imaging methods have benefitted from technical improvements. Fetal MRI offers several technical advantages over ultrasound, including:

- a larger field of view,
- fewer limitations due to maternal habitus,
- the ability to visualise fetal anatomy regardless of fetal presentation.

MRI plays a key role in the accurate diagnosis of congenital chest masses, allowing for accurate prediction of outcome, parental counselling, planning of pregnancy and newborn management.

Congenital bronchopulmonary malformations (BPMs) represent a wide spectrum of lung anomalies, including congenital pulmonary airways malformation (CPAM) (fig. 5), bronchopulmonary sequestration (BPS) and congenital lobar overinflation.

The normal fetal lungs demonstrate increasing relative signal intensity on fluid-sensitive sequences as the pregnancy progresses, secondary to the accumulation of fluid within the developing lungs.

A BPM can present with different features and can appear as solid, cystic or mixed lesions. Masses may appear as iso-signal or lower signal compared to normal lung tissue in the third trimester of pregnancy. A high-signal solid mass on MRI is not diagnostic for a specific type of BPM. The identification of a macroscopic cyst or systemic arterial blood supply to the mass improves specificity. MRI provides alternative or additional diagnoses compared with ultrasound in 38–50% of fetuses.

In conclusion, although spatial resolution is lower than CT, MRI has the advantage of being able to:

- evaluate different aspects of tissue,
- improve the characterisation of a pathological process,
- combine the morphological and functional findings in one study.

The absence of ionising radiation is the strength of MRI. For all these reasons, MRI in paediatrics is a major acquisition.

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Ultrasonography

Carolina Casini, Vincenzo Basile, Mariano Manzionna and Roberto Copetti

Newborns, infants and children present a similar clinical picture on lung ultrasound examination as adults. A high-resolution linear probe (7.5–12 MHz) is used for lung examination through longitudinal and transverse sections of the anterior, lateral and posterior wall of the chest.

Precocious exposure of infants and children to radiation may lead to a higher risk of developing malignancies later in life due to both the latency of the effect of radiation exposure on the cells and the fact that growing children are inherently more radiosensitive, because they have a larger proportion of dividing cells. Ultrasound avoids the use of ionising radiation.

The interest of the neonatal and paediatric community in lung ultrasound is growing very slowly. However, the use of ultrasound in respiratory diseases of the newborn and the child needs to be encouraged not just as a valid diagnostic alternative but as a necessary ethical choice (Cattarossi *et al*., 2011).

Key points

- A high-resolution linear probe is employed for lung ultrasound examination in children and infants.
- Lung ultrasound avoids the use of ionising radiation.
- Lung ultrasound demonstrates very good accuracy in several respiratory diseases.

Technique and ultrasound anatomy

The examination is performed with the child in a supine position. The probe is placed perpendicular, oblique and parallel to the ribs in the anterior, lateral and posterior (lower and upper) thorax. Posterior areas may be better viewed in lateral recumbence. The position with an erect trunk is practically never necessary.

The normal lung of the newborn does not differ substantially from that of adults. The pleural line is easily visualised beneath the ribs and it is easy to highlight the sliding movement of the pleural layers (sliding sign) (Lichtenstein *et al*., 1995).

The presence of horizontal reverberation artefacts of the pleural line (A lines) that are repeated at constant intervals below the pleural line is normal (fig. 1) (Lichtenstein *et al*., 1995).

At birth, is possible to observed vertical artefacts (B lines) pathognomonic of interstitial syndrome in adults (Lichtenstein *et al*., 1995, 1997; Reissig *et al*., 2003; Soldati *et al*., 2009), even in newborns who are absolutely healthy (Copetti *et al*., 2007) (fig. 2). The fetal lung is very rich in fluids and, therefore, B lines also can be seen in healthy term newborns born either vaginally or by caesarean section, but more frequently in the latter. This is due, in large part, to the greater quantity of liquid contained in the lung to prevent squeezing of the rib cage during passage through the birth canal. It can be more often seen on the right side without a typical localisation and disappears completely within 24–36 h.

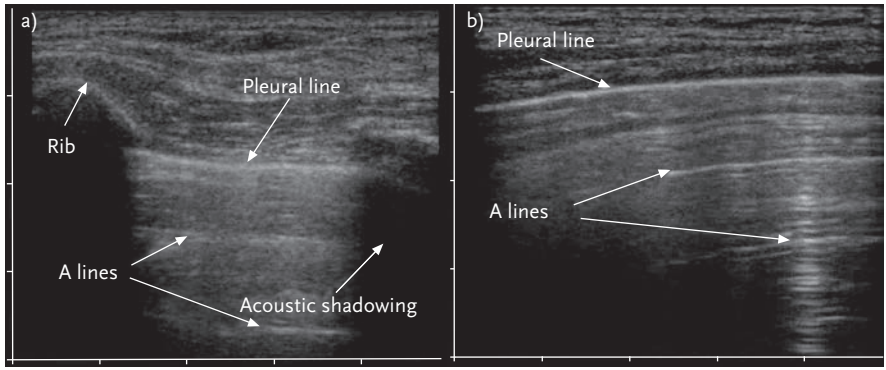

Figure 1. Normal lung. a) Longitudinal scan showing the ribs and their acoustic shadowing, the pleural line and A lines. b) Transverse scan showing the pleural line and A lines.

Transient tachypnoea of the newborn

Transient tachypnoea of the newborn (TTN) is a common cause of neonatal respiratory distress, which has a similar frequency all over the world. TTN has low morbidity but it can be severe and should be differentiated from other pulmonary or cardiac diseases (such as pneumothorax, pneumonia, sepsis, respiratory distress syndrome (RDS) and congenital heart disease).

All infants with TTN show, on the first ultrasound examination, bilateral coalescent B lines on the lung base (echographic ''white lung'') and a normal or near-normal appearance of the lung in the superior fields (Copetti *et al*., 2007). This finding is evident in both lungs, though not always symmetrically. The boundary between the inferior pulmonary fields, where the artefacts are coalescent, and the superior fields is so sharp that the lung picture is specific. It is important to note that the pleural line is normal in the areas of white lung. This ultrasound finding was named ''double lung point'' because it looks like two different contiguous lungs in the same patient (fig. 3).

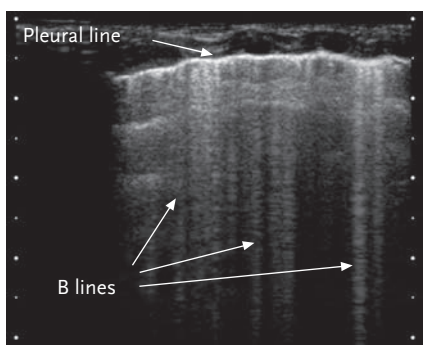

Figure 2. Transverse scan in a healthy newborn at birth. There is evidence of numerous B lines.

Respiratory distress syndrome

RDS, also known as hyaline membrane disease, is due, at least in part, to

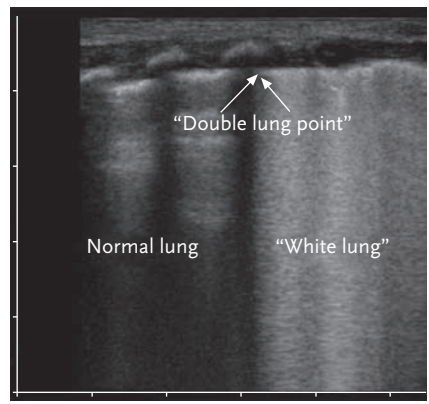

Figure 3. Longitudinal scan showing a clear sharp difference between the upper and lower lung fields (double lung point).

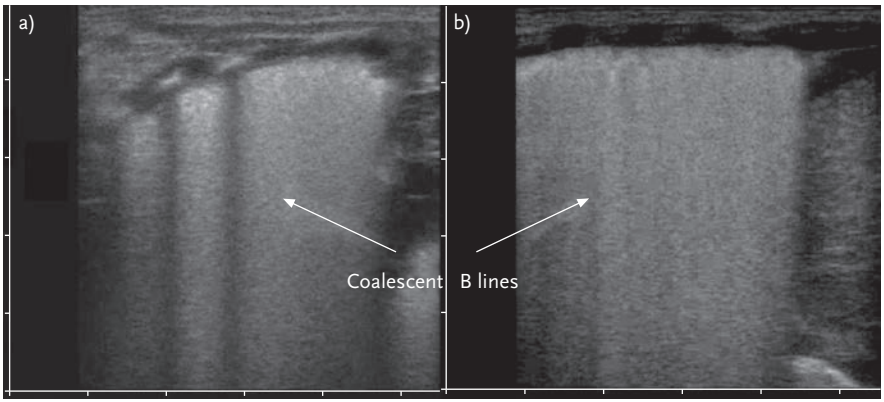

Figure 4. a) Superior and b) inferior field of the lung in a newborn with RDS. In both areas, there is evidence of coalescent B lines (white lung). The pleural line is poorly defined and coarse.

insufficiency of pulmonary surfactant and is mainly confined to preterm infants. All infants show B lines, which are coalescent, diffuse and symmetrically distributed in both lungs. This pattern is echographic white lung. The pleural line is always extensively thickened, irregular, poorly defined and coarse. Multiple subpleural hypoechoic areas, which are generally small, are observed mainly in the posterior and lateral scans, indicating lung consolidations. Larger consolidations with a tissular pattern and with evidence of air or fluid bronchograms may be observed more

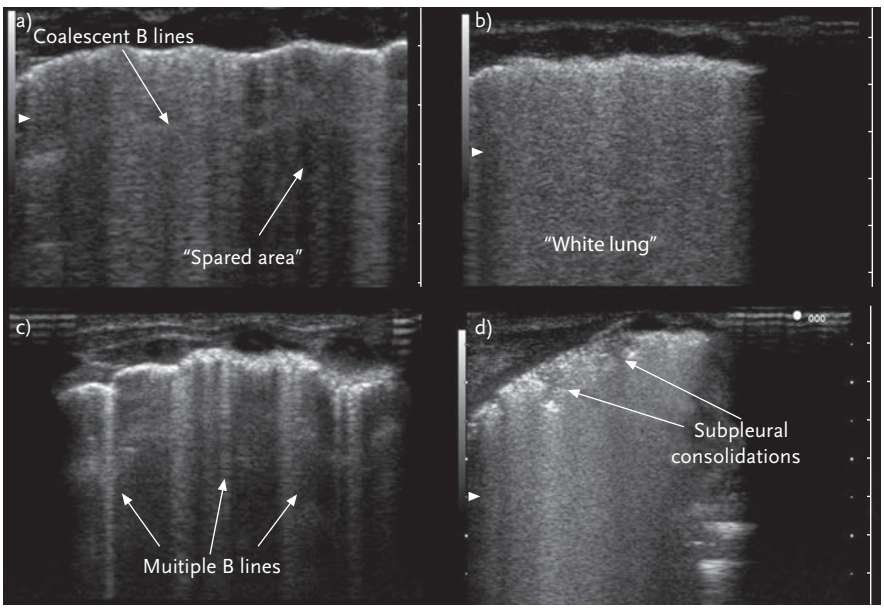

Figure 5. a) Evidence of a "spared area" in infant affected by BPD. b) Area of "white lung" in BPD. c) Area of interstitial syndrome in BPD. d) Subpleural consolidations in BPD.

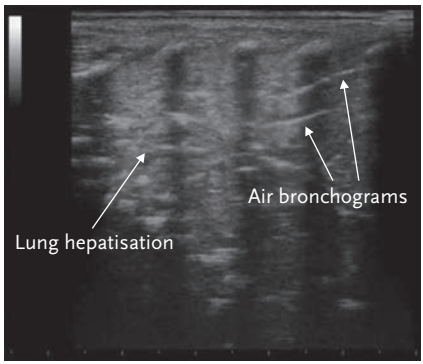

Figure 6. Liver-like appearance of the lung and parallel course of air bronchograms in pulmonary atelectasis.

frequently in the posterior fields. These findings are immediately present at birth before clinical deterioration (Copetti *et al*., 2008a). Scans of the anterior thoracic wall are sufficient for the diagnosis. The three most important signs for ultrasound diagnosis are:

- bilateral coalescent B lines involving all of the lung (white lung);
- absence of "spared areas" (areas of lung with a normal appearance); and
- pleural line abnormalities (fig. 4).

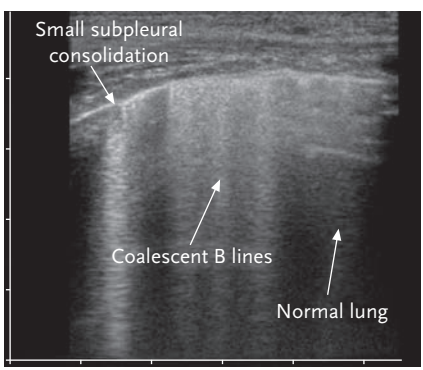

Figure 7. Typical picture of bronchiolitis with evidence of a small subpleural consolidations and an area of coalescent B lines near an area of normal lung.

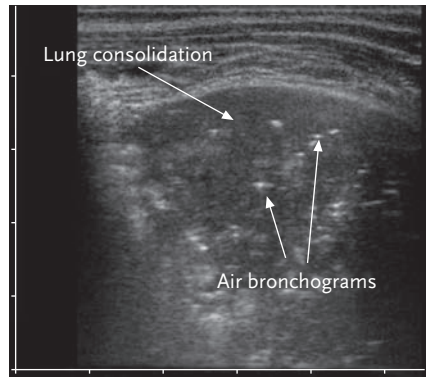

Figure 8. Typical ultrasound appearance of pneumonia in children.

Bronchopulmonary dysplasia

Bronchopulmonary dysplasia (BPD) is a form of chronic lung disease that develops in preterm neonates treated with oxygen and positive pressure ventilation. The diagnosis is made on the basis of oxygen requirement at 36 weeks gestation.

In infants with BPD, there is evidence of multiple B lines that have a nonhomogeneous distribution and diffuse changes in the pleural line, which is thickened with multiple small subpleural consolidations. Generally, there is evidence of spared areas and interstitial syndrome, and pleural line changes correlate to disease severity (fig. 5) (Copetti *et al*., 2008a).

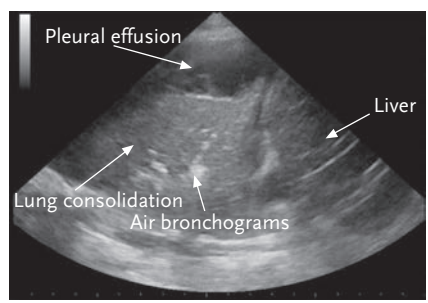

Figure 9. Lobar pneumonia in a child.

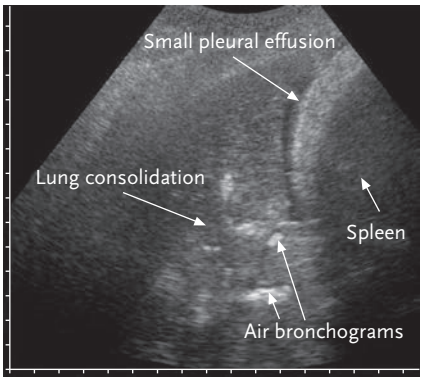

Figure 10. Left basal pneumonia in a child.

Pulmonary atelectasis

Pulmonary atelectasis is frequent in ventilated newborns. Often, chest radiographic diagnosis is difficult due to the underlying respiratory disease. The dynamic ultrasound signs are very useful for diagnosis and may be monitored at the bedside.

The ultrasound appearance of atelectasis is characterised by a liver-like appearance of the lung with "lung pulse" (Lichtenstein *et al.*, 2003), absence of lung sliding and a parallel course of air bronchograms, as described in adult patients (fig. 6). The evidence of dynamic air bronchograms rules out obstructive atelectasis (Lichtenstein *et al.*, 2009). This is very important because, often, lung consolidation may be caused by alveolar collapse (*i.e.* pulmonary haemorrhage and RDS) and, in ventilated newborns, by hypoventilation due to low ventilatory pressure.

Pneumothorax

Pneumothorax is frequent in newborns. Chest radiography has the same diagnostic limitation as in adults. Transillumination is the bedside procedure used by neonatologists. Ultrasound signs are the same as described in adults:

- absence of lung sliding;
- absence of B lines; and
- presence of "lung point" without massive pneumothorax (Lichtenstein *et al.*, 1995).

Bronchiolitis

Bronchiolitis is an acute, infectious, inflammatory disease of the upper and lower respiratory tract that may result in obstruction of the small airways. Diagnosis is made based on age and seasonal occurrence, tachypnoea, and the presence of profuse coryza and fine rales, wheezes or both upon auscultation of the lungs.

In our experience, the ultrasound findings are peculiar and this is important because in some patients with more severe symptoms, chest radiography may be avoided. In patients with bronchiolitis, we have consistently observed bilateral involvement of the lungs. Typically, areas of normal lung adjacent to areas with subpleural consolidations (1–3 cm) are observed, due to small atelectasis. These consolidations are surrounded by B lines that can also appear coalescent (fig. 7). Larger consolidations are less frequent and generally observed in more severe disease. Small pleural effusions can also be seen.

Recently, Caiulo *et al.* (2011) confirmed our observations and demonstrated that ultrasound can avoid the need for chest radiography.

Finally, unpublished observations made by V. Basile and P. Comes (San Giacomo General Hospital, Monopoli, Italy) showed that early, pulmonary paravertebral areas are affected by the appearance of B lines and small subpleural consolidations. These findings often anticipate the involvement of anterior areas.

Pneumonia

Children and infants with pneumonia may present with a number of clinical symptoms and signs such as fever, cough and tachypnoea. A minority of children present with fever of unknown origin and may have no respiratory symptoms or signs. Chest radiography is still considered to be the first imaging step for diagnosing pneumonia in children.

In children, pneumonia appears as a hypoechogenic area with poorly defined

borders and compact underlying B lines. Vertical artefacts are often seen in varying numbers, in areas adjacent to the consolidation. The pleural line is less echogenic in the area affected by lung consolidation. Lung sliding is reduced or absent. In the case of large consolidations, branching echogenic structures representing air bronchograms, are seen in the infected area. Dynamic air bronchograms can be observed. This finding rules out atelectasis. Multiple lenticular echoes, representing air trapping in the smaller airways, are also frequently present. Fluid bronchograms, described in post-obstructive pneumonia, are identified as anechoic tubular structures with hyperechoic walls, without a colour-Doppler signal. Pleural effusion is easily detected and appears as an anechoic area in the pleural space (fig. 8–10) (Copetti *et al*., 2008b).

In paediatric patients, as in adults, lung ultrasound demonstrates a diagnostic accuracy higher, or at least not inferior to, chest radiography (Volpicelli *et al*., 2012).

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Isotope imaging methods

Georg Berding

Background

Radiotracer methods allow physiological processes in the lungs to be visualised and the regional pathologic changes due to disease, resulting into functional impairment, to be detected. Most frequently, ventilation and perfusion of the lungs are investigated. Inhaled nuclides of inert gases that emit gamma rays or aerosols of fine particles (<1 µm) containing Technetium-99m (^{99m}Tc) are used to display the ventilated volume of the lungs. When injected intravenously, ^{99m}Tc-labelled albumin aggregates are retained in the capillary bed of the lungs and thereby visualise arterial perfusion of the parenchyma (*via* vasa publica). Other processes are less frequently investigated, *e.g.* mucociliary clearance function, which can be studied using aerosols of larger particles (>2 µm), or alveolar capillary membrane integrity which can be measured with water-soluble radiotracers. A more recent approach focuses on the detection of florid inflammation or vital malignant tissue in the lungs/thorax using fluorodeoxyglucose (^{18}F-FDG) and positron emission tomography (PET).

Key points

- The use of radiopharmaceuticals enables information on ventilated volume and regional perfusion of the lungs to be obtained.
- *V*′/*Q*′ scintigraphy enables accurate diagnosis of congenital abnormalities of the lungs, vessels and heart, as well as in patients with bronchiectasis or CF.
- *V*′/*Q*′ scintigraphy is easy to perform, typically without sedation, and causes only low-radiation exposure.
- A more recent method, ^{18}F-FDG PET/CT, contributes to the diagnosis of malignancies and inflammation.

Indications

In children, ventilation/perfusion (*V*′/*Q*′) scintigraphy is used to characterise primary/congenital abnormalities of the lungs and pulmonary vessels, as well as the heart and large vessels (fig. 1). Generally, *V*′/*Q*′ scintigraphy can be used to quantify lung function pre- and post-intervention. In particular, essential information can be provided by perfusion scintigraphy before and after:

- pulmonary arterioplasty,
- intravascular stent placement,
- coil occlusion of unwanted vascular communications,
- surgical creation of a shunt.

Notable per cent fractions of *V*′ and *Q*′ in the left and right lung can be determined. In the case of right-to-left shunts, these can be measured semi-quantitatively based on kidney and brain uptake during the lung perfusion scan. These measurements can be valuable in the assessment and treatment of patients with cyanosis, *e.g.* due to the tetralogy of Fallot or arteriovenous malformations. Assessment of suspected pulmonary embolism in children is, in contrast to adults, a rare indication. Damage to lung tissue due to infection can be

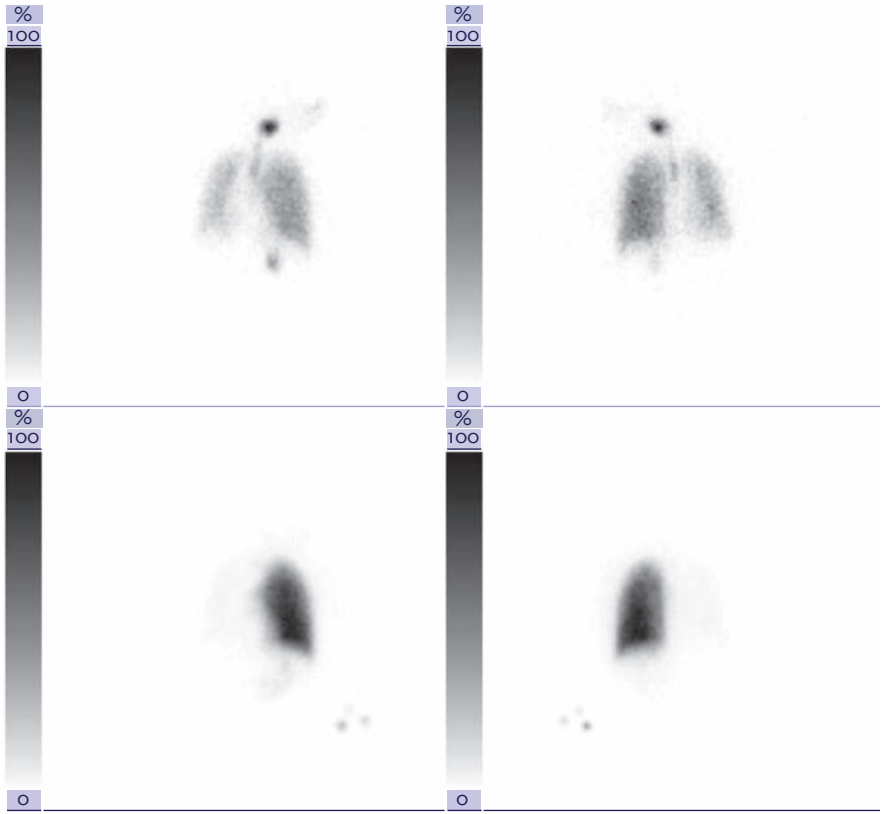

Figure 1. V′/Q′ scintigraphy in a 6-year-old boy with decreased physical capacity and recurring pneumonia of the right lung. Planar ^{99m}Tc-Technegas scintigraphy showed hypoplasia of the right lung (30% versus 70%; upper row). A subsequent ^{99m}Tc-MAA scan revealed a complete lack of perfusion (from vasa publica) in the right lung (lower row). In angiographic CT the pulmonary veins could not be detected. Angiography showed an outflow of the contrast medium from the right to the left pulmonary artery. V′/Q′ scintigraphy helped to identify noninvasively congenital abnormality of the pulmonary vessels.

assessed. Regional lung function (*V′/Q′*) can be evaluated in children with bronchiectasis as well as CF. Beyond which delayed mucociliary clearance can been seen in both diseases; however, this is still an experimental indication. Effects of foreign body aspiration (*e.g.* air trapping) can be demonstrated using *V′/Q′* scanning. In paediatric oncology with respect to thoracic masses, ^{18}F-FDG-PET is used specifically in children with lymphoma for staging, treatment response assessment and planning of radiation therapy. In inflammatory diseases, evidence provided in the literature so far suggests that ^{18}F-FDG-PET can be useful for the detection of active infective foci in children with chronic granulomatous disease and monitoring of disease activity in children with CF.

Patient preparation

There is no specific preparation that is necessary for children before *V′/Q′* scanning. However, mucus secretions should be removed with mucolytics and chest physiotherapy to facilitate ventilation scanning. Patients must avoid moving during acquisition. In children who are old

enough this might be achieved by careful explanation of the procedure together with the parents. Neonates and infants are conveniently studied when they have fallen asleep after feeding. Medicinal sedation should be the exception. If unavoidable, at $\geqslant$7 months of age the benzodiazepine midazolam can be given intravenously at a dose of 0.1 mg·kg^{-1}. Nevertheless this has to be agreed upon with the referring physician and the risk of hypoventilation has to be taken into account.

Radiopharmaceuticals

Nowadays, ventilation studies are most frequently performed using ^{99m}Tc-Technegas. This is a pseudo-gas produced using a dedicated generator containing a graphite crucible filled with ^{99m}Tc pertechnetate in a chamber, which is heated to a high temperature. Thereby an ultrafine aerosol of solid graphite particles with a 5–30 nm diameter is produced which, when inhaled, shows a static alveolar deposition. Due to the much simpler logistics, Technegas has largely replaced the use of inert gases such as xenon-133 (^{133}Xe) or krypton-81m. Nevertheless, ^{133}Xe allows sequential data acquisitions and thereby identification of air trapping as a hallmark of regional obstructive airway disease. However, ^{133}Xe application to the lungs requires a bag-box spirometer system, which is rarely available. With respect to producing aerosols of larger particles for mucociliary clearance a nebuliser is required. For perfusion studies ^{99m}Tc-MAA (macroaggregated albumin) is injected intravenously. It embolises a small proportion of (pre)capillary vessels in the lung. Since the number of these vessels is lower in children compared to adults the number of injected particles has to be decreased. The radiation exposure induced by lung scintigraphy is generally relatively low. For example, in a 5-year-old child weighing 20 kg, adapted application of ~10 MBq ^{99m}Tc-Technegas for ventilation scintigraphy would result in an effective dose of 0.47 mSv. In addition, the application of 46 MBq ^{99m}Tc-MAA for perfusion imaging would add 1.56 mSv. Together both scans would cause 2.03 mSv, which is below the natural annual radiation exposure in Germany.

Imaging equipment/acquisition

Lung scintigraphy is normally acquired with a dual-head large-field gamma camera from standard projection angles (anterior, oblique, lateral, *etc.*). The use of single-photon emission computed tomography (SPECT) offers the advantage of avoiding super-imposition and thereby creating the possibility of finer (sub-segmental) assessment. However, SPECT requires more patient co-operation or anaesthesia. Furthermore, SPECT/CT allows correlation of functional and morphological findings, which can provide unique diagnostic information, but specifically in children the additional radiation exposure has to be balanced against it. Regarding paediatric oncology, ^{18}F-FDG-PET/CT can be performed using specific CT-parameters for children to reduce radiation exposure (ultralow-dose CT) or, in the case when a diagnostic CT investigation is required, this can be performed in one session with PET obviating the inconvenience of two single examinations.

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Interventional radiology

Efthymia Alexopoulou, Argyro Mazioti and Dimitrios Filippiadis

The improvement of anaesthesiology techniques, imaging guidance and instrumentation has contributed to the evolution of several image-guided, minimally invasive, percutaneous diagnostic and therapeutic techniques, thus dramatically changing the role of interventional radiology in the treatment of paediatric patients.

Key points

- Proper and adequate training of the operator along with extensive local sterility measures and anaesthesiology control are prerequisites for safe and effectively performed interventional radiology.
- In cases where determining a lesion's nature will alter a patient's management and benefits outweigh risks, a percutaneous biopsy is indicated; core biopsy is preferred over fine-needle aspiration.
- Image-guided percutaneous drainage is a safe and efficacious technique for the treatment of pleural effusions, abscesses and empyemas; in the case of complex effusion, abscess or empyema drainage can be combined to fibrinolytic therapy.
- Tumour localisation or thermoablation can be performed in selected cases of paediatric patients.
- Transcatheter embolisation seems to be a first-line therapy for the treatment of pulmonary AVM or major haemoptysis in patients with CF.

Proper and adequate training of an interventional radiologist in paediatric patients along with strict local sterility measures are prerequisites. Prophylactic antibiotics are recommended in some of the techniques, but are not needed in most of the chest interventions. Although local anaesthesia would be fine for the majority of the procedures, deep sedation or general anaesthesia is required in order to ensure maximum cooperation and a safe environment for technique performance. Occasionally, in older children or young adults, local anaesthesia might be sufficient in certain techniques; however, this is not recommended.

Parents, and older children, should be informed about the invasive procedure, as well as the benefits and potential risks of the technique. Written consent from parents is required before beginning any procedure. Pre-procedural planning includes evaluation of the patient's medical record (including laboratory and imaging studies), control of renal function (in relation to intravascularly administered contrast), cardiac function and coagulation profile. Separate anaesthesiology evaluation should be performed as well. Post-procedural follow-up includes patient monitoring, control for any delayed complications and evaluation of the overall clinical condition of the patient. As the patient is admitted for medical therapy, most of these interventional radiology techniques are not performed on an outpatient basis.

Image-guided percutaneous biopsy

Percutaneous biopsy in paediatric patients is most commonly performed for diagnosis of a focal lesion rather than for evaluation of diffuse parenchymal disease. Especially in the immunosuppressed paediatric population, lung biopsy can be performed in cases where invasive pulmonary aspergillosis cannot be diagnosed with imaging studies alone. Core biopsy is preferred over fine-needle aspiration. Absolute indication for biopsy is the case where the management of a child will be altered according to the lesion's nature and characterisation. Furthermore, benefits should outweigh the risks. Contraindications of image-guided percutaneous biopsy in the chest include non-correctable coagulopathy, lack of safe trajectory and other comorbidities which might, for example, prohibit safe anaesthesia. Alternatives to percutaneous biopsy include bronchoalveolar lavage or transbronchial biopsy.

Percutaneous biopsy is performed under local sterility measures and anaesthesiology control (generally intubation is required in order to control breathing). Whenever a lesion is in contact with the pleural surface, ultrasound can serve as a guiding modality of choice; advantages for this include the lack of ionising radiation, low cost and wide availability. In cases where a lesion is surrounded by lung parenchyma, CT is the guiding modality of choice. The shortest trajectory that avoids fissures and blood vessels is chosen (fig. 1). Biopsy can be performed with direct or coaxial technique. Once the needle is at the lesion's periphery the biopsy system (semi-automatic or automatic depending upon operator's choice) is fired, thus obtaining the sample within the trocar.

Success rates of image-guided percutaneous biopsy in children are ~85%, whilst complications include pneumothorax (10–15%, usually not clinically significant) and mild haemoptysis. Erect chest radiography is performed 2 h post-biopsy for evaluation of delayed pneumothorax (figs 1–3).

Tumour localisation

The technique of localisation can be used in cases of a small lung nodule under the pleural surface, which will not be felt during thoracoscopic surgery. Localisation can be performed by means of image-guided percutaneous introduction of a hooked wire or needle and intralesional injection of methylene blue dye.

Tumour ablation

Image-guided percutaneous thermoablation in the lung is most commonly performed in secondary lesions that do not respond to radiotherapy (metastatic lesions from osteosarcoma, Ewing's sarcoma and hepatoblastoma). In most of the described series in the literature, radiofrequency ablation seems to be the most popular, as opposed to the other ablative techniques. Concerning paediatric ablation, all sessions are performed under general aesthesia and for the first 24 h a patient-controlled analgesia is administered. Ablation protocols in the lung are shorter when compared to procedures in the liver due to a lower vasculature. Complications include pneumothorax, haemorrhage and air embolism.

Image-guided percutaneous drainage

Occasionally, childhood pneumonias are complicated by pleural effusions, abscesses and empyemas which require drainage. Image-guided drainage of such collections is governed by high success (74–99%) with a suggested threshold of 95%, and low complication rates (1–10%) with a suggested threshold of 2–20%. Diagnosis of such collections is performed with chest radiographs, ultrasound or CT.

Indications for drainage include fluid sampling, the presence of large or complex collection (with pus or septae), and any collection (of fluid or pus) with symptoms warranting drainage. Whenever culture and laboratory testing is required a sample is obtained by needle aspiration. Sedation or general aesthesia is a prerequisite. Ultrasound is preferred as a guiding modality due to the lack of ionising

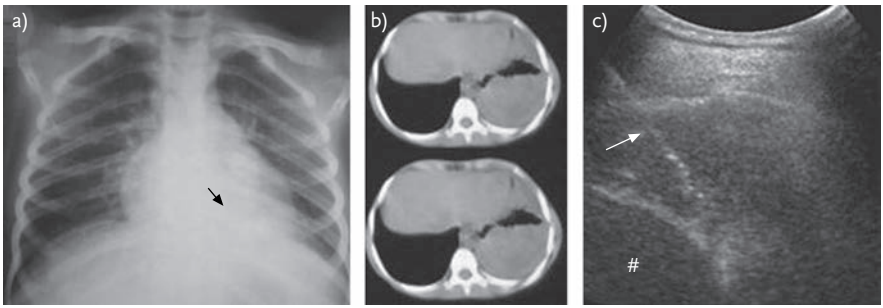

Figure 1. A 7-year-old girl with Louis–Barr syndrome, fever and cough. a) Initial chest radiograph and b) subsequent CT scan revealed left lower lobe consolidation (black arrow, a). Consolidation was not resolved after persistent appropriate treatment (antibiotics) and bronchoalveolar lavage was negative for common bacteria, mycobacteria and fungi. An additional PCR test was negative for Cryptococcus aspergillus, Candida *and* Pneumocystis carinii*, whereas cytology was negative for malignancy. c) The child was referred to our department for lung biopsy, which was performed under ultrasound guidance. The white arrow indicates the needle inside the lesion. Histology proved lymphoproliferative syndrome. #: the spleen.*

radiation, low cost and wide availability. Under extended local sterility measures, a tube (6–14 F in diameter) is introduced, usually at the level of the midaxillary line using a direct or seldinger technique, and then connected to a water seal. Output monitoring and catheter flushing (3–10 mL of sterile 0.9% saline solution every 8–12 h) are performed in order to keep the tube patent. It must always be remembered that the catheter should be placed at the superior rib margin in the pleural space in order to avoid intercostal vessels located at the lower margin of the rib.

The technique for draining abscess or empyema is similar; however, the need for CT guidance is higher in these indications. In any case, passage of the tube through lung parenchyma or fissures must be avoided (fig. 2).

In case of complex effusions, drainage of abscesses and empyemas can be combined to fibrinolytic therapy with tissue plasminogen activator (usual dose is 0.1 $mg \cdot kg^{-1}$, maximum 3 mg injected). Injection is performed through the tube which then remains closed for 1 h and then suction is resumed. Fibrinolytic therapy is performed with three doses injected every 12 h.

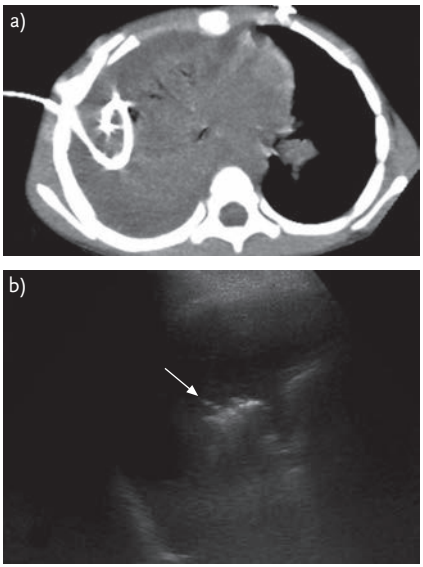

Figure 2. a) A 5-year-old boy with necrotic pneumonia and complicated right pleural effusion. A 10F pigtail catheter was placed under CT guidance for drainage and adjuvant fibrinolytic therapy. A 10-mm multiplanar reconstruction CT image in the axial plane displays the position of the catheter. b) A 10-year-old boy with necrotic pneumonia and right pleural effusion. An 8F pigtail catheter was placed under ultrasound guidance for drainage. The arrow indicates the catheter inside the effusion.

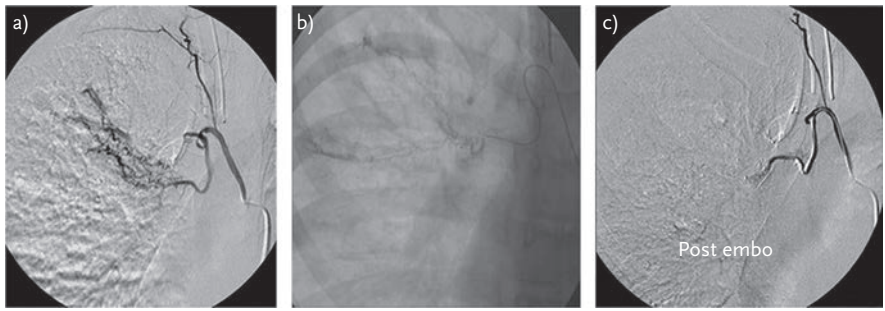

Figure 3. A teenager with CF and massive haemoptysis. a) Angiography after selective right bronchial artery catheterisation shows hyperaemia with dilated and tortuous vessels at the right upper lobe. b) Superselective catheterisation with a microcatheter was performed and subsequent embolisation with polyvinyl alcohol particles followed. c) Final post-embolisation (post embo) angiography revealed complete vessel obstruction.

Drainage complications include septic shock, bacteraemia, bleeding, superinfection, bowel or pleural transgression, bronchopleural fistula and complications associated with sedation or general anaesthesia.

Transcatheter embolisation

Transcatheter embolisation is mainly indicated for treatment of pulmonary arteriovenous malformations (AVM) or in cases of major haemoptysis. Embolic materials include coils, particles, gel foam and detachable balloons, as well as others depending upon pathological substrate, vessel size/location and material availability.

Scarce data are found in the literature concerning pulmonary AVM in children and no data are found for the same pathological entity in infants. There is a clear association between pulmonary AVM and hereditary haemorrhagic telangiectasia. Transcatheter embolotherapy seems to be an attractive alternative for these patients. Since this technique is governed by a 15% reperfusion rate of the AVM it should be reserved for symptomatic children. However, pulmonary AVMs are often embolised when they are $\geqslant$3 mm due to the risk of paradoxical embolisation and stroke. Symptoms include exercise intolerance, cyanosis or clubbing, neurological or haemorrhagic complications (which mainly occur in cyanotic patients).

The majority of pulmonary AVMs are simple, multiple and located on lower lobes of the lungs. Complications of transcatheter embolisation include pleurisy, transient angina, severe perioral pain or leg pain, brachial plexus injury or deployment complications.

Due to the decreased incidence of TB and bronchiectasis, CF has become the major cause of haemoptysis in childhood. Minor bleeding in the form of blood streaking is more common whilst major haemoptysis occurs in ~1% of children with CF. The term major haemoptysis implies the presence of acute bleeding (>240 mL·day^{-1}) or recurrent bleeding of small volumes (>100 mL·day^{-1} over several days or weeks). Pathophysiology of haemoptysis in CF includes erosion of enlarged thin-walled tortuous neovasculature of the bronchovascular net, which are located in bronchiectatic areas secondary to chronic infection. Cases of minor bleeding are usually self-limited. However, cases of major haemoptysis can be self-limited or require treatment, either conservative (bed rest, intravenous antibiotics, blood transfusion, vitamin K administration, temporarily postpone positive pressure chest physiotherapy) or transcatheter embolisation of bronchial arteries (fig. 3). It is noteworthy that both therapeutic arms are governed by similar success and recurrence rates.

Complications of transcatheter bronchial artery embolisation include post-embolic syndrome (fever, thoracic pain and potential dysphagia), iatrogenic ischaemic necrosis of other organs and, very rare but severe, cases of spinal cord ischaemia.

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Aerosol therapy

Hettie M. Janssens

Aerosol therapy has gained importance in the treatment of paediatric respiratory disorders over the last few decades. It is now the mainstay of asthma management in children (GINA, 2012) and is increasingly important for the treatment of other respiratory disorders, such as CF (Heijerman *et al.*, 2009) and broncho-pulmonary dysplasia (Tin *et al.*, 2008). Other indications are impaired mucociliary clearance such as in primary ciliary dyskinesia (PCD), neuromuscular diseases, tracheobronchomalacia and non-CF bronchiectasis (Boogaard *et al.*, 2007), croup (Rittichier, 2004), and atelectasis (Hendriks *et al.*, 2005). Aerosol therapy is considerably more complex than oral therapy, as drugs must be delivered to an organ that has mechanisms to exclude foreign material.

Key points

- To match the correct aerosol delivery device to a patient, a clinician should be informed about the disease, drug, deposition and device characteristics, and the ability or disability of the patient to perform an inhalation manoeuvre.
- A pMDI/VHC with an attached facemask is the first choice in asthma maintenance treatment in young children.
- DPIs are convenient for older children, who can perform a fast, deep inhalation.
- New (smart) nebulisers are promising but monitoring of safety and efficacy is important.
- Correct inhalation technique and adherence are mandatory for successful aerosol therapy.

As a rule of thumb, one needs to consider the "five Ds" for prescribing optimal aerosol therapy:

- disease,
- drug,
- deposition,
- device,
- disability of the patient.

One needs to be informed about the pathophysiology and the severity of the lung *disease*, the pharmacological aspects of the various *drugs*, and how the disease, drug, device and patients characteristics will influence the *deposition* of the aerosol into the lungs. This information and the technical qualities of the aerosol delivery devices are needed to be able to match the *device* to the patient. Last but not least, the abilities and *disabilities* of the child and parents should be known in order to use the device correctly. Available inhaled drugs include steroids, bronchodilators, mucolytics, inhaled antibiotics, prostaglandins, antiproteases, analgesia, anticarcinoid therapy, proteins and surfactant. Many more inhaled therapies are in development. For the treatment and choice of drugs of the different diseases, please see the sections relating to those diseases elsewhere in this *Handbook*.

This section will discuss some basic principles of aerosol technology and the

different delivery devices with information on choosing the right device. For detailed background information on all available aerosol delivery devices, please refer to the recently published European Respiratory Society (ERS)/International Society of Aerosols in Medicine (ISAM) Task Force consensus statement on inhaled therapies (Laube *et al.*, 2011).

Basic aerosol technology

An aerosol is best described as a cloud of fine particles that are small enough to remain suspended in the air for a considerable length of time. The probability of inhaled particles being deposited in the respiratory tract and their distribution pattern depends on: the particle characteristics, such as size, density and shape; the anatomy of the respiratory tract; and the breathing pattern. Particles are deposited by three mechanisms:

- impaction,
- sedimentation,
- diffusion.

Large particles and/or particles with high velocity tend to be deposited by impaction in the upper and central airways at airway bifurcations. Smaller particles have a higher probability of reaching the peripheral airways where they are deposited by sedimentation under the influence of gravitational forces. The smallest particles can make it all the way to the alveoli. The most important deposition mechanism of these particles is by diffusion through Brownian movements of the molecules.

The size distribution of aerosol particles is usually described as the mass median aerodynamic diameter (MMAD), which refers to the droplet diameter above and below which 50% of the mass of the drug is contained. The geometric standard deviation (GSD) is a measure of the distribution in size of the aerosol particles. Aerosol particles between 1 and 5 µm are thought to have a high probability of being deposited in bronchi and, therefore, are often referred to as respirable particles. Large particles have a higher probability of being deposited in the upper airways.

Smaller particles have a higher probability of being deposited in the smaller airways and alveoli, or being exhaled. It is important to realize that this 1–5 µm range is mostly derived from studies with healthy adult subjects. In the case of severe airway obstruction, like in CF, the deposition pattern is inhomogeneous and will move from the periphery of the lung to more central airways. Little is known about particle size deposition relation for young children. However, it is likely that the respirable fraction is in the smaller particle range. It has been shown in models and deposition studies that smaller particles more effectively bypass the upper airways and reach the periphery of the lungs, even in young children or in CF patients with airflow obstruction (Schuepp *et al.*, 2005; Janssens *et al.*, 2003; Laube BL *et al.*, 1998; Roller *et al.*, 2007).

Most aerosol delivery devices used for the treatment of children are suboptimal, as they were primarily designed for adults and, therefore, do not take into account the special characteristics needed for children.

Aerosol delivery devices: match the device to the patient

The current methods to deliver therapeutic aerosols can be classified in four categories:

- nebulisers;
- pressurised metered-dose inhalers (pMDIs), which can be used with a press-and-breathe technique, as a breath-actuated device, or in combination with a spacer or valved holding chamber (VHC);
- dry-powder inhalers (DPIs);
- soft-mist inhalers.

The choice of device for children depends on the availability of the specific drug and the ability of the child to perform an inhalation manoeuvre (fig. 1). In addition, not all devices are available in worldwide (Laube *et al.*, 2011). Firstly, it should be known for which device the intended drug is available. Secondly, one needs to determine whether the patient can perform an inhalation manoeuvre and whether they can achieve an inspiratory flow of around 30–60 $L \cdot min^{-1}$ reproducibly. The latter is necessary for

performing the right technique to use a DPI. Most DPIs give the best particle size and dose with a flow of 60 L·min^{-1}. Particle size increases and dose decreases with lower inspiratory flows (Ross *et al.*, 1996). Young children and dyspnoeic patients are often not able to achieve an inspiratory flow of 60 L·min^{-1} (Amirav *et al.*, 2005). For a breath-actuated pMDI, an inspiratory flow of 30 L·min^{-1} is required. For children under the age of 7–8 years, it is generally recommended to use a pMDI in combination with a VHC and to use an additional face mask if the child cannot breath consciously through the mouth (usually below 3–4 years). In addition, it is not recommended to use the pMDI directly in the mouth for children of all ages because the press-and-breath technique requires careful hand–mouth coordination, which is often not correctly performed. This leads to inefficient deposition with high oro-pharyngeal and low lung deposition. For young children, a pMDI/VHC with a face mask is now the mainstay of asthma home treatment. Nebulisers are used when a child refuses to use a VHC, the medication is not available in other forms, large doses need to be given or aerosol inhalation needs to be combined with oxygen suppletion.

Nebulisers convert a liquid medication into a mist for inhalation and can deliver a wide range of drug formulations. The traditional view of nebulisers is that they are expensive and bulky as well as inconvenient to handle and maintain. Therefore, they are relegated to third place in the market. However, perhaps as a direct consequence of a lack of pharmaceutical vested interest, nebulisers remain poorly researched and understood by many clinicians.

The use of nebulisers should be restricted to delivering drugs that are only available as liquids or that cannot be delivered by a pMDI with a VHC or autohaler, or DPI. Examples of such drugs are recombinant human deoxyribonuclease (rhDNase), tobramycin inhalation solution (TSI), colomycin and hypertonic saline. Drugs such as rhDNase or TSI are registered for delivery by well-defined nebulizer–compressor combinations.

A child should be switched from a mask to a mouthpiece as soon as they are old enough to inhale through the mouth voluntarily, as it will increase the efficiency of aerosol delivery (Chua *et al.*, 1994). An optimal seal between the face and mask is important to maximise the efficiency of aerosol delivery

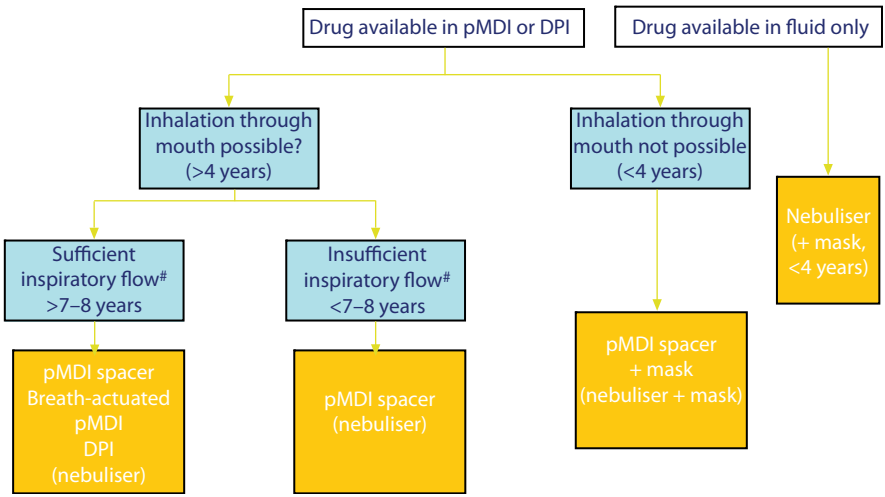

Figure 1. How to choose the right aerosol delivery device for a child. #: sufficient inspiratory flow depends on the intended inhaler; it is usually >30 L·min^{-1} but for some inhalers (DPIs) is ⩾60 L·min^{-1}.

(Everard *et al.*, 1992). Bronchodilators and inhaled steroids can be delivered faster, more efficiently and more safely by pMDI/VHC, breath-actuated pMDI or DPI. Even in acute asthma attacks, delivery of bronchodilators by pMDI/VHC is equally as effective as nebulisers (Cates *et al.*, 2006). If a child is very distressed during administration of aerosols by pMDI/VHC, a nebuliser can be a more acceptable alternative.

There are different types of nebulisers, which differ in the way the aerosol is generated. The differences in the delivered aerosol between currently available nebuliser systems are significant. There are the jet, ultrasonic and vibrating-mesh nebulisers, with or without smart nebuliser technology. Advancement in nebuliser and inhalation technology has developed modern smart nebulisers that are more effective than other devices. Nebulised drug delivery is possibly the most confused area of clinical practice, largely as a result of there being little or no regulatory control. In the European guidelines for nebulisers (Boe *et al.*, 2001), it is recommended that an inhaled drug is registered for use with a specified nebuliser. So, a pharmaceutical company should have tested the drug with a certain nebuliser in order to have recommendations for its use and guarantees for efficacy when used properly. This is, however, still not obligatory when a new nebuliser is introduced to the market. Using an alternative system can have an unpredictable effect both in terms of efficacy and toxicity, especially for potentially toxic drugs like inhaled antibiotics. If there is a good reason to choose another device than the recommended, the efficacy and toxicity should be closely monitored. New nebuliser technology offers greater convenience and portability and a significant increase in aerosol delivery. On one hand, this new, more efficient technology offers obvious benefit to patients. On the other hand, adoption of this new and improved nebuliser technology without due consideration of the consequences of increased dosing presents potential risk.

The *jet nebulisers* are the oldest, and most well-known and widely used nebulisers. The advantages of using a nebuliser over using a pMDI/VHC or DPI are that oxygen can be given during inhalation and that high doses can be administered over a prolonged time. Furthermore, only tidal breathing is required so nebulisers can be used in patients of all ages and disease severities. The disadvantaged are numerous. For the home setting, the equipment is expensive, cumbersome and noisy, and needs a power supply. The administration time can be as long as 20–30 min several times a day. This is not beneficial for patient compliance. Furthermore, it requires regular cleaning, with a high risk of contamination if the cleaning instructions are not followed correctly (Vassal *et al.*, 2000). Jet nebulisers use an electric compressor or compressed gas source (oxygen or air) to create the aerosol. There are numerous technical factors that can affect aerosol output and particle size distribution of a jet nebuliser. These may result in highly variable doses and poor reproducibility of particle size. These technical factors include the fill volume, the operational flow, the viscosity, concentration and temperature of the solution or suspension, the nebuliser design, and breathing pattern (O'Callaghan, 1997). It is important that the correct operational flow or compressor is used while nebulising. This is mentioned in the user's instructions. Usually, a flow of 6–8 $L \cdot min^{-1}$ is the optimal operational flow. A lower flow leads to larger particles and prolonged nebulisation time. The fill volume determines the concentration, particle size and nebulised dose. For each nebuliser and drug, there is a recommended fill volume. If a smaller volume is used, there might be less drug delivered, largely because there is a residual volume of 1–1.5 mL that remains in the nebuliser. There are different types of jet nebulisers. The most widely used unvented nebulisers, with continuous output of aerosol, are inefficient, as there is loss of aerosol during exhalation or when a patient is not breathing through the nebuliser. More efficient systems have been developed, such as open-vent and breath-enhanced nebulisers with in- and exhalation valves. The latest technology uses breath-actuated systems, which only deliver during

inspiration, either by using a mechanism that opens when an inspiratory flow threshold is reached, or electronically by following the patient's breathing pattern and giving a precise dose during inhalation (Laube *et al.*, 2011; Geller, 2008). The use of breath-actuated systems results in improved lung deposition, dose reproducibility and reduced loss by exhalation. Breath-actuated devices are suitable for children from 4 years of age.

Ultrasonic nebulisers use a piezoelectric crystal to convert fluid into a fine mist. The output of ultrasonic nebulisers is faster than that of jet nebulisers, which is useful for administration of large volumes. However, ultrasonic nebulisers are not suitable for nebulising suspensions, such as steroids, and viscous fluids, such as antibiotics. Furthermore, the fluid may become too warm in the ultrasonic nebuliser because the crystal produces heat by vibrating in high speed. This may inactivate certain drugs, like rhDNase. Ultrasonic nebulisers are not widely used because they are expensive and produce relatively large particles compared with jet nebulisers (Laube *et al.*, 2011).

The recently introduced *mesh nebulisers* use either a vibrating or fixed membrane with a piezoelectric element with microscopic holes to generate an aerosol. Vibrating-mesh devices have a number of advantages over other nebuliser systems. They are very efficient and quiet, and are generally portable, as they operate as effectively when using batteries as mains electricity. Lung deposition is substantially increased, varying between 30% and 80%, depending on the device. However, they also are significantly more expensive than other types of nebulisers, and require a significant amount of maintenance and cleaning after each use to prevent build-up of deposit and blockage of the apertures (especially when suspensions are aerosolised), and to prevent colonisation by pathogens (Geller, 2008; Rottier *et al.*, 2009). They are most widely used for the treatment of patients with CF.

There are breath-enhanced mesh nebulisers and those with dosimetric aerosol delivery, the so-called *smart nebulisers*. In smart nebulisers, the breathing pattern is controlled (slow and deep) and aerosol is delivered only during the first 50% of inspiration: the deeper the inhalation, the shorter the nebulising time (Nikander *et al.*, 2010). Almost no drug is lost during exhalation. Smart nebulisers can achieve a lung deposition of 60–80% (Bakker *et al.*, 2011), compared with 5–15% with the traditional jet nebulisers (Laube *et al.*, 2011). Furthermore, more peripheral lung deposition can be achieved, which may result in improvement in peripheral airway obstruction, as in CF (Bakker *et al.*, 2011). Another advantage is that adherence is logged electronically and the data can be downloaded afterwards (Dhand, 2010). This can be a useful tool to get insight into the adherence to aerosol therapy and discuss this with the patient, in order to improve the efficacy of the treatment.

Although they have many advantages, vibrating mesh and smart nebulisers have still not been extensively tested in children and there is little clinical information available. Lung deposition is improved but dose recommendations are lacking or based on *in vitro* or adult data. There might be indications that, especially in young children, higher lung deposition of aerosols can lead to toxic side-effects (Guy *et al.*, 2010). Therefore, clinicians should be cautious when using these new devices, especially in children. There are many good arguments to use one of the new-generation nebulisers but efficacy and toxicity should be carefully monitored, especially when using potentially toxic drugs, such as inhaled antibiotics.

pMDI, pMDI/VHC and breath-actuated pMDI Almost all drugs available for aerosol therapy of asthma are available in pMDIs. In a pMDI, the drug is present in a solution or suspension with propellants and surfactants. In the case of a suspension, the pMDI should be shaken before use to mix the drug with the propellant. When the pMDI is fired, an accurately metered dose is released at a high velocity. The mass of drug and its aerosol characteristics are largely independent of the inspiratory effort made by the patient.

Inhalation from a pMDI should be precisely timed with a press-and-breath manoeuvre.

Most patients are not able to coordinate actuation of the pMDI with the breathing manoeuvre, causing high oropharyngeal and low lung deposition. This coordination problem can be resolved by using a breath-actuated pMDI (Newman *et al.*, 1991) or a pMDI/VHC. Breath-actuated pMDIs automatically release the drug when a patient is inhaling. A patient should be able to perform a maximal exhalation followed with a slow inhalation with a breath hold. Lung deposition is improved using a breath-actuated pMDI but oropharyngeal deposition is still high. VHCs are used to facilitate inhalation from a pMDI with normal tidal breathing and decrease the oropharyngeal deposition. The use of a VHC is recommended for all patients in principle, especially using inhaled corticosteroids, but particularly for those who have difficulties with the press-and-breath technique with the pMDI, such as children. For children with asthma below the age of 7 years, the pMDI/VHC is the system of first choice. A VHC with a mouthpiece should be used whenever possible. In children below the age of 3–4 years, a face mask should be added to the VHC. In children younger than 2 years, it can be very difficult to obtain a proper seal between the face and mask (Amirav *et al.*, 1999; Janssens *et al.*, 2000). Even a small leak of 0.2 cm will dramatically reduce the output of the pMDI/VHC–mask combination (Esposito-Festen *et al.*, 2004). Each VHC comes with its own face mask. There are substantial differences in the efficiency of achieving a good face–mask seal with the different designs (Amirav *et al.*, 2001; Esposito-Festen *et al.*, 2005). After the face mask is positioned on the face, one puff of the pMDI needs to be fired into the VHC. As soon as the aerosol cloud is released from the pMDI, aerosol particles start to sediment onto the VHC wall as a result of gravitational forces. This effect is stronger when a plastic VHC is used, due to electrostatic charge. Therefore, any delay between the moment the dose is fired and the moment of effective inhalation will reduce the inhaled dose substantially (Wildhaber *et al.*, 1996). However when a plastic VHC is coated with detergent, electrostatic charge is minimised and lung deposition will increase substantially (Pierart *et al.*, 1999; Wildhaber *et al.*, 2000). Anti-static VHCs have been developed to overcome this problem (Laube *et al.*, 2011). In a model study, it was shown that when electrostatic charge is minimised, the deposition in the "lung" is dependent on the pMDI, and relatively independent of the VHC, used (Janssens *et al.*, 2004). The differences in aerosol deposition of the different pMDIs were explained by the particle size of the aerosol cloud. In general, it was shown that the smaller the particles, the higher the dose delivered to the lungs, and the lower the oropharyngeal deposition. In particular, a hydrofluoroalkane (HFA)–beclomethasone pMDI with a high proportion of extra-fine particles (MMAD 1.1 μm) resulted in a considerably higher lung dose (Janssens *et al.*, 2003). These *in vitro* data were confirmed by an *in vivo* lung deposition study with the same breath-actuated pMDI in children aged ⩾5 years (Devadason *et al.*, 2003). The higher lung deposition translates to a reduction by half of the effective dose in inhaled steroids if extra-fine particles are used (GINA, 2012; Busse *et al.*, 1999) but randomised controlled trials failed to show a superior clinical effect (Boluyt *et al.*, 2012). Even when an anti-static VHC and a pMDI with small particles is used, cooperation remains the most important determinant for the efficiency of dose delivery (Janssens *et al.*, 2000). Furthermore, if there is a suboptimal face–mask seal, the increase in dose obtained by minimising the electrostatic charge of a VHC by detergent coating is almost completely lost (Smaldone *et al.*, 2005). Parents of young children should be carefully instructed about the importance of an optimal mask seal, good administration technique and good cooperation during the administration procedure.

DPI Most anti-asthma drugs are available as DPIs. DPIs are small, portable, handheld devices. There are numerous different devices available, each with its own directions for use. Older children and adults prefer DPIs because they are "easy" to use in daily life, which may help adherence. In a DPI, the drug is present in single or multiple dosing chamber. DPIs are formulated with their drug particles either attached to a carrier or as agglomerates in the form of pellets.

To facilitate deposition in the lungs, drug particles are de-agglomerated during inhalation. Airflow through a DPI combines with its internal resistance to create turbulent energy inside the DPI. This internal energy is required to de-agglomerate the particles and aerosolise the dose. The turbulent energy created during inhalation is the product of the patient's inspiratory flow multiplied by the DPIs resistance (Laube *et al.*, 2011). Thus, for a set energy, a DPI with a high resistance will require a lower inspiratory flow than a DPI with a lower resistance. The mass of drug and the MMAD and GSD of the released aerosol cloud depends on the inspiratory flow of the patient. When there is insufficient inspiratory flow through the DPI ($<60\ L \cdot min^{-1}$ for most DPIs), the mass of drug that is released is reduced and the MMAD is increased. Sufficiently high and reproducible inspiratory flows through a DPI can be obtained in asthmatic children aged $\geqslant 7$ years (Amirav *et al.*, 2005). Clearly, such devices can only be used when a patient is able to generate sufficient flow for optimal drug dispersion. Careful inhalation instructions are important for correct use and effective aerosol delivery of DPIs. Mistakes in dose preparation, no maximal exhalation before inhalation, insufficient inspiratory effort and storage in a humid environment can lead to decreased lung deposition or even none at all (Laube *et al.*, 2011). The recommended inhalation manoeuvre for a DPI is to inhale as quickly and deeply as possible for optimal de-agglomeration of the particles. Consequently, this causes high impaction of particles in the oropharynx, which may increase local side-effects. The high inspiratory flow also causes the aerosol to be deposited mainly in the larger airways rather than the periphery. This may vary between different DPIs depending on particle size and internal resistance.

Recently, DPIs were introduced for inhaled tobramycin (Konstan *et al.*, 2011) and colistimethate (Schuster *et al.*, 2012). Tobramycin inhalation powder uses a new spray drying technique (Geller *et al.*, 2011). This results in hollow porous particles that behave like small particles because a lower density decreases the aerodynamic diameter. For this DPI, a slow, deep inhalation manoeuvre is needed. The colistimethate is a micronised dry powder in a low-resistance inhaler. For this DPI, a fast, deep inhalation is required.

In recent years, many different types of DPI have been introduced. They differ in the inhalator resistance and particle size. The newest technology uses feedback mechanisms and dose counters to check compliance and stimulate good inhalation. The clinician needs to be informed on which drugs are available in the different devices. In addition, most of the new DPIs are not well studied in children.

Soft-mist inhalers Currently, there is only one commercially available soft-mist inhaler. This inhaler is available for the delivery of fenoterol 50 µg/ipratropium bromide, and tiotropium bromide. The soft-mist inhaler atomises the drug solution using mechanical energy imparted by a spring. When the spring is released, the solution is forced through an extremely fine nozzle system. This produces a fine mist that is slow moving, giving the patient time to inhale after a press-and breath, leading to lower deposition in the mouth and throat, and relatively high lung deposition (~39%) (Laube *et al.*, 2011). Soft mist-inhalers have not been tested in children.

Inhalation instructions and adherence

For optimal effect of aerosol therapy, correct use of the aerosol delivery device is crucial. Any mistake during the inhalation procedure can influence the delivered dose substantially. It is known that inhalation instruction needs to be repeated several times before the inhalation is performed correctly (Kamps *et al.*, 2000). For detailed inhalation instructions for each device, please see the ERS/ISAM Task Force consensus statement on inhalation therapy (Laube *et al.*, 2011).

If the correct device is chosen for the patient and inhalation instructions have been given, the patient still needs to use the device daily at home. It is known that adherence to inhalation therapy is generally low, which

can lead to more severe disease and hospital admissions (Murphy *et al.*, 2012). In a good partnership with patients, parents and the doctor, the treatment needs to be discussed and explained.

Conclusion

There are many different types of aerosol delivery devices. In the last few years, many new devices have been introduced. Aerosol delivery devices can be divided in four groups: nebulisers (jet, ultrasonic, mesh and smart); pMDIs (combined with a VHC or breath actuated); DPIs; and soft-mist inhalers. The prescribing physician needs detailed knowledge about:

- aerosol and deposition characteristics of the various aerosol delivery systems;
- availability of drugs in the different devices;
- advantages and disadvantages of the devices;
- the pathophysiology of the lung disease;
- the skills of the patient in various age groups.

Only when this knowledge is available can the appropriate delivery device for the patient be selected. In addition, optimal aerosol therapy is only possible with repeated inhalation instructions and well-informed patients and parents, which will encourage adherence.

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Epidemiology

Steve Turner

The child's respiratory system is constantly exposed to infective agents and acute lower respiratory tract infections are normal in children. The global burden of acute respiratory infections in children is huge and the World Health Organization (WHO) estimates that approximately one-third of all deaths in children are due to acute respiratory infections. In contrast, chronic respiratory infection (arbitrarily defined here as symptoms lasting for more than 4 weeks) is never normal and is usually associated with bacterial infection. Bacteria causing chronic infection are usually part of the normal upper airway flora and what is not well understood is what transforms them from commensal to pathogenic. This section will describe the epidemiology and microbiology of acute and chronic lung infection. For the purpose of this section, croup, epiglottitis and tracheitis are considered airway infections and are not covered, and neither are TB nor infections associated with CF (refer to relevant sections in the *Handbook*). Infectivity, diagnosis, investigation, management and pharmacology are covered elsewhere.

Key points

- Acute lung infections have a very high incidence in children.
- Chronic lung infections (*i.e.* lasting more than 4 weeks) are also common in children.
- Sex, age, geography and vaccinations are important determinants of lung infection incidence.
- The incidence of many infections changes over time and this reflects changes in pathogen and/or host.

Acute infections

Bronchiolitis

Definition. Bronchiolitis is a clinical diagnosis based on history and examination, which has been defined by a Delphi consensus in the UK as "a seasonal viral illness characterised by fever, nasal discharge and dry, wheezy cough. On examination there are fine inspiratory crackles and/or high pitched expiratory wheeze".

Infective agents. Approximately 75% of cases are associated with respiratory syncytial virus (RSV) infection and the remainder are associated with other viruses, including parainfluenza virus type 3, human metapneumovirus and adenovirus. Infection with more than one virus is increasingly recognised with the advent of more sensitive PCR testing.

Incidence. Approximately 20% of all infants develop bronchiolitis and 3% of all infants in Europe are admitted to hospital with bronchiolitis. The median age of admitted infants is 2–3 months, the age range is not normally distributed and very young infants are much more commonly admitted than older infants. Figure 1 demonstrates the seasonality of RSV infections. In many European countries there is evidence of alternating years of higher and lower incidence. An RSV vaccine is not widely available at present but may be introduced in the near future, and this is likely to change the epidemiology of bronchiolitis.

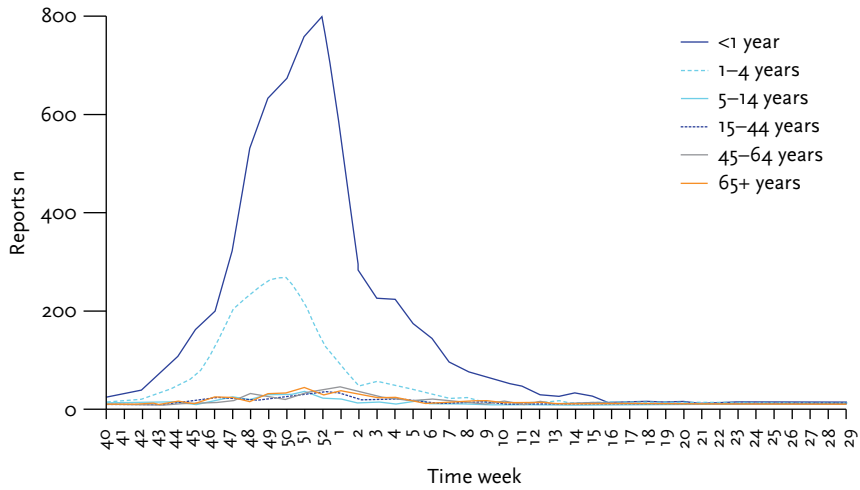

Figure 1. Laboratory reports of respiratory syncytial virus by week of specimen and age in 2009–2010. Reproduced from Salisbury et al. *(2013) with permission from the publisher.*

Risk factors. Young age, male sex, exposure to tobacco smoke and reduced lung function prior to onset of symptoms are associated with increased risk for bronchiolitis. More serious features of bronchiolitis are associated with prematurity (with or without bronchopulmonary dysplasia), haemodynamically significant heart disease and infection with RSV (compared with other viruses).

Prognosis. Approximately 20% of infants with bronchiolitis have respiratory symptoms for more than 1 month during convalescence. An association with increased risk for later asthma symptoms has been described but this relationship is not straightforward. The association is seen more clearly in those who were hospitalised for bronchiolitis rather than cared for in the community. The association usually becomes weaker as the children become older. One explanation for these observations is that a common airway abnormality or genetic predisposition may lead an individual to develop bronchiolitis in infancy and asthma in later childhood. Observations that infants with RSV bronchiolitis are less likely to develop asthma compared to those with non-RSV bronchiolitis suggest that RSV does not cause asthma.

Pneumonia

Definition. There are a number of definitions of pneumonia but no single gold standard definition. Pneumonia is a clinical diagnosis which is defined by the WHO as the presence of cough, fever and tachypnoea. Community-acquired pneumonia (CAP) is defined as "the presence of signs and symptoms of pneumonia in a previously healthy child due to an infection which has been acquired outside hospital". Crackles may be heard with a stethoscope in up to two-thirds of cases. A chest radiograph is not required for the diagnosis of uncomplicated pneumonia. Among infants, there is some overlap between bronchiolitis and pneumonia in clinical presentation. A broader term "acute lower respiratory tract infection" includes pneumonia and for the purpose of this chapter is considered synonymous.

There are a number of classifications of pneumonia. Different infective agents may be associated with different classifications so there is clinical merit in distinguishing between categories. Typical CAP is by far the most common presentation.

Table 1. Infective agents commonly associated with acute and chronic respiratory infection in children

	Bronchiolitis	Pneumonia	Empyema	Chronic bronchitis
Respiratory viruses				
Respiratory syncytial virus	++++	++	–	
Parainfluenza	++	++	–	
Influenza	+	++	–	
Human metapneumovirus	++	++	–	
Bacteria				
Streptococcus pneumoniae	–	+++	+++	++
Haemophilus influenzae	–	++	+	++
Streptococcus pyogenes	–	++	+	–
Moraxella catarrhalis	–	++	–	++
Mycoplasma pneumoniae	–	++	+	–
Staphylococcus aureus	–	+	+	–

+++: very common pathogen; ++: moderately common pathogen; +: not an uncommon pathogen; –: not thought to be a pathogen.

- *Typical/atypical*. Atypical pneumonia is characterised by respiratory distress and hypoxia, sometimes associated with headache, vomiting or diarrhoea, with essentially normal findings on auscultation but marked diffuse chest radiograph changes.
- *CAP/hospital-acquired/tracheostomy- or ventilator-associated pneumonia*. CAP is defined as the signs and symptoms of pneumonia in a previously healthy child. Hospital-acquired pneumonia infection is defined (in adults) as pneumonia that is acquired after at least 48 h of admission to hospital and is not incubating at the time of admission. Tracheostomy or ventilator-associated pneumonia are self-descriptive.
- *Radiological*. Chest radiographs (if taken) show patchy pneumonic changes in approximately 60% of cases, lobar consolidation in approximately 20% and perihilar changes in a further 20%.

Infective agents. The challenge in obtaining a sample of lower airway secretions in a small and often unwell child means that until recently an infective agent was not identified in most cases of pneumonia. Recent introduction of PCR testing now means that infective agents can be identified in up to 85% of cases. Pneumonia can be caused by a number of bacteria and viruses (table 1) and approximately one-third of hospitalised children have both viral and bacterial infections identified. Viral identification is more common in younger children and is present in 80% of infants and 60% of 1–2 year-olds. Wheezing and conjunctivitis are more commonly associated with viral pneumonia compared to bacterial pneumonia. Typical pneumonias are usually caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*, whilst the most common agents causing atypical pneumonia in children are *Mycoplasma pneumoniae* and respiratory viruses. *Chlamydophila pneumoniae* may also cause atypical pneumonia but *Legionella pneumophila* is rarely seen in immune-competent children. Children with influenza infection are at increased risk for *Staphylococcus aureus* co-infection including pneumonia. Hospital-acquired and tracheostomy-/ventilator-associated pneumonias are often associated with methicillin resistant *S. aureus* and *Pseudomonas* species.

Incidence. Age and geography are major determinants of the annual incidence of pneumonia in children. In Western

countries, the annual incidence ranges from approximately 600 cases per 100 000 in the neonatal period to 10 cases per 100 000 in 10–14 year-olds. In contrast, the WHO cites a median annual incidence for developing countries of 0.28 episodes per child-year (fig. 2). Widespread introduction of pneumococcal vaccination reduced the incidence of pneumonia by approximately one-third.

Risk factors. Pneumonia is a seasonal disease with peak presentations occurring at the same time as bronchiolitis, *i.e.* December and January in the Northern hemisphere. Boys are at increased risk for pneumonia compared to girls. Abnormal lung function in early infancy and exposure to tobacco smoke are associated with higher risk of later radiologically confirmed pneumonia. The risk for pneumonia is reduced in cases who consult with their primary care physician early in the illness and in those who have the pneumococcal vaccine.

Prognosis. Complete resolution is the usual outcome for childhood pneumonia although a small proportion (<1%) of children develop bronchiectasis.

Empyema thoracis

Definition. Empyema is thought to complicate 1% of childhood bacterial pneumonias and can be defined as a parapneumonic effusion, *i.e.* a collection of fluid within the pleural cavity. There is a continuum of parapneumonic effusion from a reactive (exudative) effusion to purulent effusion (empyema) to organised effusion (rind). Diagnosis requires imaging with ultrasound plus pleural aspirate. Clinically, the child will present with a prolonged pneumonic illness where the fever fails to settle and pleuritic pain develops. There is often an acquired scoliosis towards the affected side. Bilateral empyema is very uncommon. Rarely, an empyema may be associated with no preceding febrile illness and a lack of elevated inflammatory markers and this should raise suspicion of underlying malignancy. In these cases a CT scan with contrast of the chest and mediastinum should be taken and reviewed before considering drainage and/or anaesthetics.

Infective agents. The same infective agents associated with bacterial pneumonia are implicated in empyema causation (table 1).

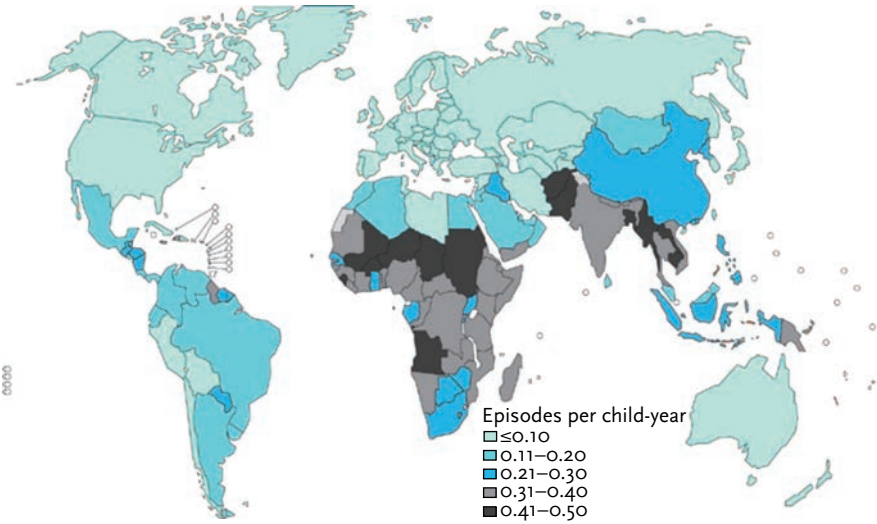

Figure 2. Incidence of childhood clinical pneumonia at the country level. Reproduced from the World Health Organization (2008) with permission from the publisher.

Bacteria are identified in pleural fluid and/or blood culture in approximately five times as many cases when PCR is used compared to standard bacterial culture, but even with PCR no infective agent is identified in at least 25% of cases. Where bacteria are identified, *S. pneumoniae* is present in 50–70% of cases and a recent study from Australia reported that 97% of *S. pneumoniae* were non-vaccine related serotypes; this demonstrates the efficacy of pneumococcal vaccination but also the ability for "new" serotypes to fill the void left by vaccination.

Incidence. This is currently approximately three cases per 100 000. Figure 3 demonstrates how incidence increased in Scotland, UK, during the early 2000s.

Risk factors. The mean age of children presenting with empyema is 4–5 years which is unexpected given the higher burden of pneumonia among infants compared to older children; a lower threshold for treatment with antibiotics in younger children may partly explain this apparent inconsistency. There is evidence that the prevalence in 1–4 year-olds is increasing.

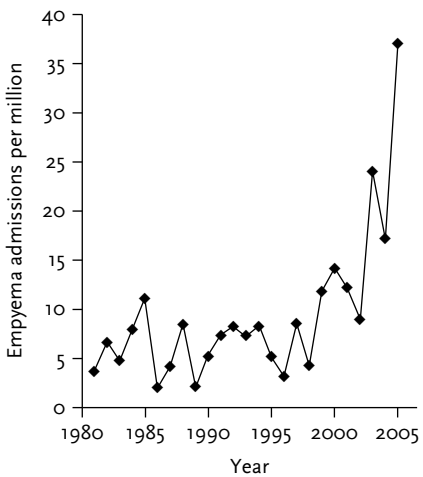

Figure 3. Empyema admissions per million per year in Scottish children between January 1981 and December 2005. Reproduced from Roxburgh (2008) with permission from the publisher.

Boys account for 70% of cases. Prior treatment with antibiotics and pneumococcal vaccination are associated with a reduced risk for empyema.

Prognosis. Empyema is a serious and potentially life-threatening infection but most children survive the initial illness and their long-term prognosis is usually excellent. Chest radiograph changes may persist for at least 12 months and there is a risk of bronchiectasis.

Chronic infections

Chronic bronchitis

Definition. This condition is not described in many text books and is not universally accepted as a diagnosis at present, but can be defined as a productive (*i.e.* wet) cough which lasts for more than 3 weeks or 1 month in an otherwise well child. An alternative term is protracted bacterial bronchitis, which includes an additional caveat that the symptoms should respond to a 10–14 day course of treatment with antibiotics. Chronic bronchitis is often associated with coarse, loud "rattly" respiratory sounds that can be wrongly interpreted as wheeze and the child is wrongly diagnosed with asthma. The reluctance in parts of the clinical community for accepting chronic bronchitis as an entity is the potential for misdiagnosis in serious conditions, such as foreign body aspiration, CF, immune deficiency and pertussis. It is possible that bacterial bronchitis and non-CF bronchiectasis are at opposite ends of the same disease spectrum.

Infective agents. Bacteria are identified in approximately 70% of cases where prolonged productive cough is reported and bronchoscopy is performed; *H. influenzae* is present in 30–40% of cases, *S. pneumoniae* in 20–25% and *M. catarrhalis* in 15–10%. Respiratory viruses are likely to be important in some cases but their role is not currently understood.

Incidence. Different definitions of chronic bronchitis (or cough) have been used in epidemiological studies making the incidence difficult to estimate. The incidence of chronic bronchitis is highest in children

aged 1–2 years. As many as 20% of preschool children may have a cough which lasts for more than 1 month.

Risk factors. Assuming that other alternative diagnoses for chronic cough are excluded, the main risk factor is young age. There is no evidence of an immune deficiency but absence of evidence is not the same as evidence of absence.

Prognosis. This is uncertain but is probably very good for most cases. There is a possibility that recurrent infection leads to progressive airway damage (a vicious cycle hypothesis) and, in some cases, to bronchiectasis.

Pertussis

Definition. Pertussis (or whooping cough) is characterised by paroxysms of coughing which can last for up to 4 months. There are three stages to the infection:

- the initial catarrhal phase lasts for 1 week and is characterised by runny nose and nonspecific cough;
- the subsequent paroxysmal phase lasts for 1 month and is characterised by paroxysmal cough and often also an inspiratory whoop and vomit at the end of paroxysms;
- the convalescent phase lasts for up to 3 months and is characterised by paroxysms of shorter and less frequent duration.

The catarrhal and early paroxysmal phases are when the individual is highly infectious. Inspiratory whoop and post-tussive vomiting are not necessarily specific for pertussis. In one community study of children aged less than 3 years, these symptoms were present in 50% and 70%, respectively, of cases of pertussis and 25% and 40%, respectively, of cases with chronic cough but not pertussis. In older children with pertussis who had been vaccinated, less than 15% of cases had whoop or vomiting and generally, those children who have been vaccinated and have pertussis have a less severe illness.

Infective agent. *Bordetella pertussis* usually causes pertussis but *B. parapertussis* and RSV can cause a pertussis-like illness.

Incidence. There are approximately 200 million cases of pertussis each year and there are peaks (epidemics) every 4 years. As in all respiratory infections, incidence is age-dependent; a survey of cases across Europe reported an overall incidence of 10 cases per 100 000 children but this was 100 cases per 100 000 among infants and one case per 100 000 among older teenagers.

Risk factors. The major risk factor for pertussis is not being vaccinated (*i.e.* very young infants and older children who have not been vaccinated). Prior vaccination does not protect all individuals against pertussis but is associated with less severe symptoms if these develop.

Prognosis. Pertussis remains a serious condition on a world-wide scale and is associated with 200 000 deaths, predominantly in infants. Once paroxysms fully resolve most children have made a complete recovery although some may develop bronchiectasis.

Conclusion

Acute lung infections are extremely common in children and chronic infections are also common. The epidemiology of acute and chronic infections is a dynamic field where incidence changes over time due to variation in both pathogen and host.

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Microbiology testing and interpretation

Elpis Hatziagorou, Emmanuel Roilides and John Tsanakas

Respiratory tract infections constitute a major health problem, with significant cost and mortality worldwide. These infections are mainly caused by viruses, bacteria, mycobacteria and fungi.

Viral infections

The majority of childhood lower respiratory illnesses are caused by viral agents. Technological developments in molecular biology show that known respiratory viruses are more prevalent than previously thought across the childhood age range.

- Rhinoviruses or "common cold" viruses are the most prevalent, usually causing mild disease. Although the severity of upper respiratory tract symptoms after rhinoviral infection does not differ between patients with asthma and normal subjects, both the duration and the severity of lower respiratory tract symptoms are more pronounced in patients with asthma.
- Respiratory syncytial virus (RSV) follows a well-characterised epidemiologic pattern, with annual outbreaks occurring between October and May in temperature climates. At least half of the infant population becomes infected during their first RSV epidemic and almost all children have been infected by 2 years of age.
- Three type of influenza virus have been identified; they are designated A, B and C.
- Parainfluenza virus (PIV)1 and PIV2 are generally associated with laryngotracheobronchitis (croup), URT illness and pharyngitis, whereas PIV3 is a major cause of infant bronchiolitis and is associated with the development of pneumonia in susceptible subjects.
- Adenoviruses may cause pneumonia, bronchiolitis or conjunctivitis.
- Human coronaviruses may cause milder lower respiratory tract symptoms than other viruses.
- Human metapneumovirus (MPV) causes symptoms ranging from URT disease to severe bronchiolitis and pneumonia. MPV is an important cause of RSV-like illness.
- Human bocavirus accounts for 1–3% of lower respiratory tract infection (LRTI) in infants.
- Viruses may be copathogens and this creates difficulties in the case of positive results. More recent studies using nucleic acid technologies have identified multiple viruses in up to 27% of hospitalised children with LRTI. The presence of more than one virus may result in more severe or prolonged infection.

Key points

- Rapid antigen detection and molecular tests are the methods of choice for the identification of viral infections.
- Blood culture is positive in <10% of paediatric patients with bacterial LRTIs.
- IGRAs are the method of choice for discrimination between *M. tuberculosis*, *M. bovis* and nontuberculous mycobacteria.
- BAL GM is a reliable test for the diagnosis of invasive aspergillosis.

It is difficult to determine the optimal method for virus detection. Although cell culture remains the gold standard, it is time-consuming and thus it has been replaced by antigen-detecting methods and molecular techniques. Their commercial availability, ease of performance and rapidity have made antigen-based methods increasingly popular. They can be performed within 15 min to a few hours. Antigens of the common respiratory viruses can be detected by direct immunofluorescence or by commercially available enzyme immunoassays. The sensitivities of these tests vary from 50% to 90%. Serological methods attempt to detect viruses in the host by assessing the presence of specific antibodies in blood, sputum and urine samples. Identification of the pathogen responsible for a recent infection may be achieved through detection of specific IgM in serum 1 week after symptoms begin, or a four-fold or greater increase in IgG. However, PCR has been widely used during the last decade and its clinical use is steadily increasing. PCR methods allow specific amplification of defined DNA sequences to a level at which they can subsequently be detected and these tests can be applied to any virus for which part of the genome sequence is known. Recent developments of this method include semiquantitation of results with the use of specialised equipment and primers specific for additional viral and bacterial species, allowing for the detection of as many as 19 different microorganisms in a clinical sample. PCR may give quantitative, as well as semiquantitative, results. In clinical practice, we may use any of these tests, according to their feasibility in the particular laboratory.

Bacterial infections

Specimens for bacteriological culture should be collected as soon as possible after the onset of disease and before the initiation of antimicrobial therapy.

Upper respiratory tract infections Pharyngitis includes tonsillitis, tonsillopharyngitis and nasopharyngitis. *Streptococcus pyogenes* causes 15–30% of acute pharyngitis in children. Identification can be with either culture or a rapid antigen detection test, after a throat swab. Retropharyngeal, parapharyngeal and peritonsillar abscesses have similar microbiology; most are polymicrobial infections. In acute otitis media, there is acute inflammation with 5% viral, 75% bacterial and, 20% mixed bacterial and viral aetiology. The most common organism is *Streptococcus pneumoniae*. The most common causes of sinusitis are *S. pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. These organisms, along with *Staphylococcus aureus* and *S. pyogenes*, account for >90% of sinusitis in children. Since the introduction of vaccines that protect against *H. influenzae* type b infection, epiglottitis has become a rare disease. Other causative organisms include nontypable *H. influenzae*, *Haemophilus parainfluenzae*, *S. aureus* and *S. pneumoniae*. *S. aureus* is the most common bacterium causing tracheitis. A significant proportion of infections are polymicrobial.

Fresh pus, fluid or tissue from the sinuses (obtained by washing, aspiration, biopsy, scraping or debridement), and pharyngeal swabs from the tonsils and/or the posterior pharynx are the main upper respiratory tract biological specimens.

Microscopy following Gram staining is useful for the examination of paranasal sinus smears (which are normally sterile), pharyngeal smears or material from the oral cavity for the detection of polymorphonuclear neutrophils (PMNs) and some microbes (*e.g.* corynebacteria (diphtheroids)), and nasopharyngeal smears for *Bordetella pertussis*. Following the isolation of the pathogen, serologic typing and antibiotic susceptibility testing are usually performed.

Lower respiratory tract infections are the third most important cause of mortality globally and are responsible for >4 million deaths annually. The aetiology of pneumonia varies based on patient age, vaccination status, immunological status and the clinical setting in which the causative agent was acquired. Determining the aetiology of pneumonia is difficult and the choice of

antimicrobial therapy is often empirical. In the neonate, the most common causes of bacterial pneumonia are group B β-haemolytic streptococci (GBS) and Gram-negative enteric bacilli, such as *Escherichia coli* and *Klebsiella pneumoniae*. *S. pneumoniae* is the most common bacterial aetiology of community-acquired pneumonia in all age groups, including children. *H. influenzae* type b was an important cause in the pre-vaccination era but is now rare. *S. aureus* pneumonia is also infrequent but may progress rapidly. In hospital-acquired pneumonia, Gram-negative organisms, such as *K. pneumoniae*, *Pseudomonas* and *Serratia*, and Gram-positive organisms, such as *S. aureus*, occur most frequently.

- There are >100 pathogens that may infect the lower respiratory tract and produce secondary bacteraemia. However, blood cultures are positive in only <10% of paediatric respiratory tract infections.
- Urine specimens may be used for the detection of antigens from *S. pneumoniae* and *Legionella*.
- Candidate lower respiratory tract specimens for processing include sputum (noninvasive), bronchoalveolar lavage (BAL) (invasive) and pleural fluid (*via* thoracentesis) (invasive).

Macroscopic and microscopic examination of a lower respiratory tract specimen (*i.e.* sputum or BAL fluid) gives valuable information. The appearance, colour, consistency (*e.g.* purulent, mucoid, serous or bloody), quantity, odour and presence of visible formations in lower respiratory tract specimens should all be considered. Direct examination of the specimen with Gram staining along with compatible symptomatology is sensitive in only 10% of cases but has a specificity of 70–80%. As it is an easy, cheap and fast method that provides information within 1 h, microscopy allows proper diagnosis and treatment of LRTI.

Culture for the identification of the responsible organism and susceptibility testing are useful in the case of resistance to initial antibiotic treatment, immunocompromised cases or CF.

Recovery of $<10^4$ bacteria per millilitre of BAL is most likely to represent contamination, while $>10^5$ bacteria per millilitre is indicative of active infection.

Antigen detection in blood and urine has a limited role in the diagnosis of bacterial pneumonia. The reported sensitivity for the detection of group A streptococci is 60–95% but can be as low as 31%. Urine detection of the polysaccharide antigen C, which is present in all pneumococcal serotypes, is performed with the use of an immunochromatographic method (Binax, Portland, ME, USA) and has high sensitivity among children with documented invasive pneumococcal infection. However, the capability of this method to discriminate between true pneumococcal disease and rhinopharyngeal carriage is questionable and is not recommended in the recent guidelines for diagnosis of community-acquired pneumonia.

Serological methods are also used for the diagnosis of pathogens responsible for atypical pneumonias but are rarely used in clinical practice for the diagnosis of bacterial pneumonia. A four-fold rise in titre or a titre greater than 1:32 in convalescent serum is diagnostic (sensitivity 80–95% and 60%, respectively). ELISA for IgM detection may diagnose infection using only one sample if this is collected after the 10th day of illness.

Nucleic acid persists in specimens after the initiation of treatment, and may be detected in smaller and noninvasive specimens. PCR using blood or pleural fluid specimens is mainly applied for the detection of *S. pneumoniae* and *H. influenzae*, with the sensitivity and specificity of the method depending on the specimen. Detection of bacterial antigens in pleural fluid is potentially useful in the diagnosis of empyema.

A variety of nonspecific laboratory evaluations have been used to support the diagnosis of bacterial pneumonia; these include an increased serum concentration of C-reactive protein, an increased erythrocyte

sedimentation rate and an increased blood leukocyte count with a predominance of polymorphonuclear leukocytes. However, all these techniques suffer from poor sensitivity and positive predictive values.

The diagnosis of empyema is strongly supported by the presence of thick pus with bacteria demonstrable by Gram staining, a pH <7.3 or a glucose concentration $<60\ mg \cdot dL^{-1}$. The average white blood count in empyema fluid is 19 000 cells per cubic millimetre. These findings may be variably present and must be interpreted in their clinical context.

Mycobacterial infections

TB is the most prevalent chronic infection in the world, with two-thirds of the global population infected. Most infection is asymptomatic (latent TB infection (LTBI)). In adults and older children, reactivation of LTBI causes active pulmonary TB disease in ~10% of individuals. A variety of specimens can be collected, including sputum, induced sputum, gastric aspirate, BAL, transbronchial biopsy, urine, blood, cerebrospinal fluid, tissue and other body fluids. Gastric aspirates are frequently obtained, as children cannot easily produce sputum. *Mycobacterium tuberculosis* may be recovered from gastric aspirates in almost 40% of children with radiographic evidence of significant pulmonary TB. The culture yields are as high as 70% in infants with TB.

Tuberculin skin test The tuberculin skin test (TST) remains the most widely employed test for the diagnosis of TB and LTBI in children. The sensitivity and specificity of the TST are significantly affected by a number of factors. The tuberculin reaction should be read 48–72 h following injection. A number of factors have been associated with false-positive tuberculin reactions and decreased TST specificity. The TST has the lowest sensitivity in younger children. There is no reliable method of distinguishing bacille Calmette–Guérin (BCG)-induced TST cross-reactivity from TST reactivity secondary to mycobacterial infection; interferon (IFN)-γ release assays (IGRAs) have the ability to make this distinction (see later). In general, the TST should be interpreted in the same way for patients who have or have not received a BCG vaccination; however, this will lead to some children with false-positive TST results being treated.

IFN-γ release assays The identification of genes in the *M. tuberculosis* genome that are absent from those of the *Mycobacterium bovis* BCG vaccine and most nontuberculous mycobacteria has supported the development of more specific and sensitive tests for detection of *M. tuberculosis*. IGRAs are designed to measure the host immune response to *M. tuberculosis* rather than the presence of the organism itself. In persons with *M. tuberculosis* infection, sensitised memory/effector T-cells produce IFN-γ in response to *M. tuberculosis* antigens, which is the biological basis for IGRAs. Available data suggest that the TST and IGRAs have similar accuracy for the detection of *M. tuberculosis* infection or the diagnosis of active TB in children. Use of *M. tuberculosis*-specific antigens leads to greater specificity ($>90\%$), which decreases the probability of false-positive responses, particularly in young, BCG-vaccinated children. Although the direct cost of IGRAs is greater than that of the TST, IGRAs may be cost effective in cases where there is difficulty in interpreting a TST or where the clinical index of suspicion is high but the TST is negative.

Tests for the detection of *M. tuberculosis* infection, such as IGRAs and the TST, are most helpful as adjunctive tests to confirm disease in a patient with a high probability of active disease. The likelihood that a positive TST represents true infection (positive predictive value) increases as the prevalence of infection with *M. tuberculosis* increases in that population. The same is true for IGRAs. Interpretation of the TST reaction is based on risk of infection.

Staining and microscopic examination of sputum or BAL fluid Acid-fast staining using the Ziehl–Neelsen technique and microscopic examination are the easiest, quickest and least expensive diagnostic procedures. There must be 5000–10 000 bacilli present per millilitre of specimen to

allow detection of the bacteria in stained smears, resulting in low sensitivity rates in children.

Culture for mycobacteria, identification and susceptibility testing Culture is the most important laboratory test for the diagnosis and management of TB. Mycobacterial culture from gastric aspirates has provided a more useful method of diagnosis in children with suspected pulmonary TB. The role of bronchoscopy in evaluating children with pulmonary TB is controversial. Cultures from BAL fluid in children with suspected pulmonary TB has a low yield and does not significantly aid bacteriological confirmation. In three studies evaluating the role of bronchoscopy, only 13–62% of cultures in children with pulmonary TB were positive. Bronchoscopy can be useful to define anatomy, bronchial obstruction or clarify the diagnosis but it cannot be recommended solely to collect culture specimens in children. In high-risk groups, such as those patients with immunodeficiency, where a positive diagnosis is needed and TSTs are often falsely negative, bronchoscopy can be useful.

Detection of mycobacterial nucleic acid Direct detection of the DNA of *M. tuberculosis* in clinical samples has been performed using nucleic acid amplification, most often by PCR. When compared with the clinical diagnosis of pulmonary TB in children, the sensitivity of PCR for sputum or gastric aspirates has varied from 25% to 83% and the specificity from 80% to 100%. A negative PCR never eliminates TB as a diagnostic possibility, nor does a positive result completely confirm it. The major use for PCR in children may be when the diagnosis of TB is not readily established on clinical and epidemiological grounds, and perhaps for children with HIV infection for whom a greater variety of causes of pulmonary disease must be considered.

The gold standard for diagnosis of childhood tuberculosis is a triad of:

- abnormal chest radiograph and/or clinical findings consistent with TB;
- a positive TST or IGRA result; and
- a history of contact with an infectious TB case within the past year.

Fungal infections

Filamentous fungi of the genus *Aspergillus* may cause transient asymptomatic colonisation, pulmonary hypersensitivity reactions, saprophytic colonisation of pathological airway structures, and life-threatening tissue invasive infections predominantly of the lung with or without dissemination in patients with congenital or acquired deficiencies in host defences. Most cases of human disease are caused by *Aspergillus fumigatus,* followed by *Aspergillus flavus* and, less commonly, *Aspergillus nidulans, Aspergillus niger* and *Aspergillus terreus*. Hypersensitivity reactions caused by *Aspergillus* spp. mainly include allergic bronchopulmonary aspergillosis (ABPA). Bronchopulmonary colonisation occurs in patients with asthma, bronchiectasis, CF and primary ciliary dyskinesia syndrome. Invasive pulmonary aspergillosis is the most frequent entity. In severely immunocompromised patients, a variety of fungi can cause invasive sinopulmonary disease, including the zygomycetes, *Fusarium* spp. and *Pseudallescheria boydii*.

Routine methods for rapid specific identification of *Aspergillus* spp. are generally not available. The current diagnostic markers for invasive aspergillosis include conventional and more recent methods under evaluation. Recently, more rapid and sensitive methods have been developed, for example, the detection of antigenic markers, such as galactomannan and β-1,3-D-glucan, and the detection of molecular markers of *Aspergillus* DNA by PCR.

Staining and microscopic examination of sputum or BAL fluid, and culture for fungi and identification Conventional methods of diagnosis include direct microscopy and histology, and culture of respiratory and various fluids and tissues. While microscopy and culture obtained from the clinically affected site remain the gold standard, technical problems in obtaining an appropriate specimen, the time of culture

and negative results all limit an efficient and rapid diagnosis; similarly, the diagnostic yield of histology is unsatisfactory, with an approximate sensitivity of 50%. Histological diagnosis requires invasive methods that are often difficult in children and are nonspecific for speciation. Although *Aspergillus* can colonise the respiratory tract, its isolation from sputum of BAL fluid in an immunocompromised patient with pneumonia is highly suggestive of invasive disease.

Given this background, detection of fungal cell wall antigens and DNA in blood and other tissues may enhance the diagnosis of invasive aspergillosis.

Galactomannan assay in serum and BAL fluid A serologic assay to detect galactomannan, a molecule found in the *Aspergillus* cell wall, is commercially available for diagnosing invasive disease but most data refer to adults. The galactomannan assay also has high diagnostic utility for analysis of BAL fluid of paediatric patients with suspected pulmonary aspergillosis. The presence of galactomannan in BAL fluid (BAL GM) is an alternative serological diagnostic marker, especially for invasive pulmonary aspergillosis, which constitutes the most common presentation of invasive aspergillosis. False-positive tests occur more commonly in children than adults and a negative test does not exclude the diagnosis. The reported sensitivity of BAL GM is in general higher than that in serum due to the increased fungal burden in the bronchi of patients with pulmonary invasive aspergillosis. However, the role of BAL GM in paediatric invasive aspergillosis has not been extensively evaluated. A recent retrospective study conducted by Desai *et al.* (2009) suggests that BAL GM is a valuable adjunctive diagnostic tool.

Detection of fungal nucleic acid PCR represents one of the most investigated rapid diagnostic methods with clinical utility for invasive aspergillosis. A recent meta-analysis of the use of PCR with blood, serum or plasma samples for the detection of invasive aspergillosis reported that the sensitivity and specificity for two consecutive positive samples were 0.75 (95% CI 0.54–0.88) and 0.87 (95% CI 0.78–0.93), respectively. A similar meta-analysis evaluating PCR with BAL fluid revealed a sensitivity of 0.91 (95% CI 0.79–0.96) and specificity of 0.92 (95% CI 0.87–0.96). For paediatric patients, data concerning DNA detection of *Aspergillus* spp. with different PCR techniques are lacking.

The galactomannan test can be used in children with caution. Molecular markers such as PCR present the same problems and difficulties as in adults. While progress has been achieved in terms of galactomannan and certain recommendations have been made, further research is needed for the validation of newer diagnostic procedures in paediatric patients.

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Immunisation against respiratory pathogens

Horst von Bernuth and Philippe Stock

Acute lower respiratory tract infection (ALRI) is still the leading cause of global child mortality. ALRI caused by *Streptococcus pneumoniae,* a Gram-positive bacterium, and respiratory syncytial virus (RSV), an enveloped single-stranded RNA paramyxovirus, and their prevention by vaccination will be addressed here.

Key points

- The natural course of RSV infection can be modified by passive immunisation with neutralising antibodies by monthly intramuscular administrations of Palivizumab, a humanised monoclonal IgG1 antibody directed against the F-protein of RSV.
- There is broad agreement that prematurely born children with chronic lung disease in infancy and children with haemodynamically relevant heart disease during the first 2 years of life may benefit from passive immunisation against RSV.
- Serious (in particular invasive) pneumococcal diseases can be avoided by active immunisation with either polysaccharide-protein conjugate vaccines during the first 2 years of life or with 23-valent pneumococcal polysaccharide vaccine after the first 2 years of life.
- Active immunisation against *S. pneumoniae* serotypes is highly recommended.

RSV infection

Epidemiology and risk factors RSV infects 99% of all children by the age of 2 years, with an estimate of 66 000–199 000 deaths being associated with RSV worldwide, 99% of these occurring in developing countries. Generally accepted independent risk factors for severe RSV infection requiring hospitalisation are 1) prematurity and 2) age <6 months at the start of RSV season (ranging from October to March or November to April). Other risk factors are: male sex, haemodynamically significant congenital heart defects, chronic lung disease (CLD) of prematurity (formerly called bronchopulmonary dysplasia), Down syndrome, presence of elder siblings/residential crowding and exposure to environmental tobacco smoke. Additional risk factors for RSV infection are malformations, neuromuscular disease, liver disease, chromosomal abnormalities, congenital immunodeficiencies and inborn errors of metabolism. For a comprehensive review of risk factors predisposing to RSV infection, see Sommer *et al.* (2011).

Immunisation The development of RSV vaccines to actively immunise the host has not yet led to satisfying results. In summary, either the immune responses were weak or short lasting, repetitive immunisation was required, or live attenuated vaccines even led to vaccine-primed disease enhancement, which is unacceptable for children at risk. However, the natural course of RSV infection can be modified by passive immunisation with neutralising antibodies by monthly intramuscular administrations of Palivizumab, a humanised monoclonal IgG_1 antibody directed against the F-protein of RSV.

Palivizumab was originally approved for the prophylactic treatment of infants born prematurely (before 35 weeks of gestation) and for the prophylactic treatment of children up to 2 years of age treated for CLD of prematurity <6 months before the anticipated RSV season. This recommendation was based on a double-blind, placebo-controlled, multicentre, multinational trial mainly conducted in northern America in which 10% of children with RSV infection born before the 35 weeks of gestation were hospitalised. Approval was later extended to children <2 years of age with pulmonary hypertension, relevant left–right or right–left shunting, and pulmonary venous congestion.

Given the high costs of passive immunisation with Palivizumab, and the fact that Palivizumab never proved to lower RSV-associated mortality but only protects a subpopulation of patients from rehospitalisation, passive immunisation against RSV remains a highly debated public health issue, as the costs of passive vaccination of large populations should be lower than the costs of rehospitalisation of patients with RSV infection. The number of patients needed to treat (NNT) to avoid rehospitalisation depends on the baseline rehospitalisation rate without RSV prophylaxis, a number that depends strongly on the proportion of children developing CLD. If the basal proportion of prematurely born children with CLD is lower, the rehospitalisation rate due to RSV is lower than published by the Impact trial in 1999 (mainly the USA and Canada) and the NNT will be higher than originally proposed in 1999 for a cohort comprising almost 50% prematurely born children with CLD. Notably, national guidelines for prophylaxis with Palivizumab differ substantially. This can be exemplified by comparing the Swiss and Austrian recommendations. Although it is rather unlikely that the Swiss and Austrian populations differ significantly in 1) ethnic or genetic background, 2) risk factors for severe RSV infections, or 3) rehospitalisation rates due to RSV infection, the Swiss recommendations are more restrictive than the Austrian guidelines. In Switzerland, Palivizumab is recommended only for infants younger than 12 months with severe CLD or with haemodynamically significant heart disease and additional risk factors. In contrast, the Austrian guidelines recommend the use of Palivizumab for all children 1) born prematurely below the age of 24 months with CLD, 2) born prematurely at <28 weeks plus 6 days of gestation below the age of 12 months, 3) born prematurely at 29–32 weeks plus 6 days of gestation and with certain risk factors, 4) born prematurely at 33–35 weeks plus 6 days of gestation below the age of 3 months at the beginning of the RSV season and with certain other risk factors, 5) with haemodynamically significant heart disease below the age of 24 months, 6) with diseases of the respiratory tract below 24 months (*e.g.* CF), 7) with "floppy infant syndrome" below the age of 24 months, 8) with inborn or acquired immunodeficiencies below the age of 24 months. Given the lack of evidence for the effectiveness of passive immunisation against RSV for many conditions, recent recommendations of the American Academy of Pediatrics (AAP) seek an optimal balance of benefit and cost for this intervention. In general, three major groups of infants that may benefit from Palivizumab are addressed. In infants and children younger than 24 months with CLD who receive medical therapy and infants born before 32 weeks of gestation, a maximum of five doses of Palivizumab (15 $mg \cdot kg^{-1} \cdot month^{-1}$ during the RSV season) is recommended for infants within these two groups. A third major group is defined as infants born at 32 to <35 weeks of gestation. The usefulness of Palivizumab in this group strongly depends on the presence of additional risk factors. If two of these risk factors are present, a maximum of three doses of Palivizumab should be administered. For details, see the AAP recommendations.

In summary, almost 15 years after approval of passive immunisation against RSV, recommendations are still mainly based on a single multinational, randomised, placebo-controlled trial for prematurely born children and on a single multinational, randomised, placebo-controlled trial for children with

congenital heart disease. According to medical as well as economic criteria, there is broad agreement that prematurely born children with CLD in infancy and children with haemodynamically relevant heart disease during the first 2 years of life may benefit from passive immunisation against RSV. Still, many guidelines recommend the use of Palivizumab for children born <28 weeks of gestation regardless of additional risk factors – an approach that is at least debated, if not highly controversial.

Conclusion Given the aforementioned unresolved public health issue on who will best benefit from passive "vaccination" against RSV, we consider the recommendations of the AAP as an acceptable compromise.

Pneumococcal pneumonia

Epidemiology and risk factors *S. pneumoniae* leads to substantial morbidity and mortality in children with an estimated 10 million deaths per year worldwide, particularly in developing countries. The most common form of the disease is bacteraemic pneumococcal pneumonia, which shows peaks of incidence below 2 years of age and above 65 years of age. In developed countries, *S. pneumoniae* in adults is a common cause of community-acquired pneumonia, while in children in developed countries, *S. pneumoniae* is a leading cause of invasive bacterial diseases (IPDs) (notably meningitis and sepsis). The annual overall European incidence of IPD in children aged <2 years is estimated to be 44 cases per 100 000 population. Children with an increased risk of pneumococcal diseases are those born prematurely, and those with sickle cell disease, cochlear implants and cerebrospinal fistulae, HIV infection, secondary loss of the spleen, or primary immunodeficiencies due to either a defect in opsonisation, phagocytosis of opsonised bacteria or in Toll-like receptor signalling. There are 40 serogroups and 91 serotypes of *S. pneumoniae*, and 20 of these account for >70% of IPD occurring in all age groups. The only natural reservoir of *S. pneumoniae* is the human nasopharynx, and colonisation of the nasopharynx is a prerequisite for both individual disease and infections of others. As pneumococcal resistance to antimicrobial agents is a growing problem in all age groups, active vaccination is the most promising strategy to prevent pneumococcal diseases worldwide.

Immunisation Current vaccines use bacterial capsular polysaccharides. These induce serotype-specific antibodies that activate and fix complement, and promote bacterial opsonisation and phagocytosis. The 23-valent pneumococcal polysaccharide vaccine (PPV23) is based on purified polysaccharide and was introduced in 1983. The heptavalent polysaccharide–protein conjugate vaccine (PCV7) is based on seven capsular polysaccharides covalently conjugated to a protein carrier and was introduced in 2000. Recently, two further PCVs were introduced, PCV10 and PCV13.

PPV23 elicits antibody responses in 60–80% of children older than 2 years after a single intramuscular injection. PPV23 is not sufficiently immunogenic in children <2 years of age: it does not prevent mucosal colonisation and does not elicit immunological memory. The clinical effectiveness of PPV23 in children between 6 and 24 months of age for the prevention of pneumococcal diseases is limited. PCVs, in contrast, are sufficiently immunogenic in children <2 years of age after three or four intramuscular injections. PCVs elicit immunological memory and prevent nasopharyngeal colonisation, thus promoting herd immunity. This has probably led to an even more substantial decrease in pneumococcal diseases in the elderly than in the vaccinees. Since the introduction of PCVs in 2000, vaccine efficacy has been shown to be 77–97% for the avoidance of IPD and 19–37% for the avoidance of pneumococcal pneumonia. PCVs also proved beneficial in HIV-infected children for both the prevention of IPD and pneumococcal pneumonia. Active vaccination against *S. pneumoniae* is beneficial not only from the individual, medical point of view but also from the socioeconomic point of view. The saved costs by reduced morbidity and mortality

outweigh the costs of vaccination, regardless of the epidemiological background and the price of the vaccine. The socioeconomic benefit will most likely be even higher if PCV13 is directly introduced, whereas the benefit may be less obvious if PCV13 replaces PCV7. The obvious current success of PCV7 has been shadowed by concerns about serotype replacement. Recent studies confirmed that serotypes not contained in PCV7 not only repopulate the niche in the human nasopharynx but may also cause pneumococcal diseases (*e.g.* serotype 19A). The challenge of serotype replacement has partly been met by the introduction of PCV10 and PCV13 vaccines comprising more serotypes. However, the approach to overcoming serotype replacement by introducing more and more serotypes in one vaccine is limited technically. Thus, it may become necessary to change the strategy by vaccinating against stable cell surface virulence protein(s), such as pneumolysin and pneumococcal surface protein A, which are shared by many pneumococcal serotypes.

Conclusion We strongly recommend active immunisation against *S. pneumoniae* serotypes with PCVs during the first 2 years of life as active immunisation will avoid a significant number of serious pneumococcal diseases.

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Upper respiratory tract infections

Rossa Brugha, Chinedu Nwokoro and Jonathan Grigg

The upper respiratory tract (URT) lies cranial to the thoracic inlet and comprises the nose (in continuity with the sinuses and the lacrimal sac) and nasopharynx, the mouth and oropharynx (in continuity with the middle ear *via* the Eustachian tube), and the larynx and laryngopharynx. The respiratory role of the URT is three-fold.

- To warm inspired air before it reaches the lungs.
- To trap and remove inhaled particles that may irritate the respiratory epithelium (dust, smoke or organic matter such as pollen).
- To perform innate and adaptive immune responses against inhaled pathogens.

The URT is also responsible for phonation and for preparing food and fluids for digestion. URT infections (URTIs) are the most common human malady (Johnston, 2005). For example, in the UK, one quarter of the population visit their doctor every year due to respiratory infections. URTIs make up 95% of these infections. Preschool children have six to eight URTIs per year. The vast majority of URTIs are self-limiting viral infections. Human rhinovirus is the most common causative organism (~40% of infections), and respiratory syncytial virus, influenza, parainfluenza and adenovirus are among the numerous (~200) viruses associated with infections throughout the URT (table 1).

Key points

- The majority of upper respiratory tract infections are viral in aetiology and self limiting.
- Consider epiglottitis or bacterial tracheitis in a child with stridor who looks unwell.
- Decisions regarding antibiotics for otitis media and tonsillitis are difficult and involve pros and cons for the patients and for society; these should be openly discussed when making treatment choices.

This chapter will outline clinical features and the management of common URTIs, alongside important rarer infections, rare complications of common infections, and important differential diagnoses.

Common cold or "viral rhinitis"

Common colds are self-limiting viral illnesses involving the nasal mucosa, and are experienced annually by the majority of individuals.

Clinical features Inflammation of the nasal epithelium (rhinitis) leads to a mucous or muco-purulent discharge (coryza). There may be associated sneezing, cough and/or fever. A "cold" is a diagnosis of exclusion: if there are symptoms associated with adjacent structures (such as sore throat or mid-facial sinus pain) then the diagnosis will be ascribed to inflammation at that site (tonsillitis/pharyngitis or rhinosinusitis) as a matter of convention.

Management Treatment is support (antipyretics) and reassurance, once relevant negatives have been excluded. A meta-analysis of the use of antibiotics for the treatment of common colds has been published by Arroll *et al.* (2005). It shows no

Table 1. Common viruses in upper respiratory tract infections

Rhinovirus
Respiratory syncytial virus
Influenza virus A and B
Metapneumovirus
Parainfluenza virus
Adenovirus
Coronavirus

benefit in comparison with placebo and an increase in adverse events when antibiotics were prescribed in children and adults for acute purulent rhinitis (relative risk 1.46, 95% CI 1.10–1.94).

Rhinosinusitis

"Rhinosinusitis" is the term encompassing infection and inflammation of the sinuses as the process involves the nasal passages both for route of infection and drainage. One in every 10 colds in children will go on to cause sinus inflammation. The infections are initially viral in aetiology, but the anatomy of the drainage means that bacteria may cause secondary infections in the sinuses. Acute rhinosinusitis should be considered when URTI symptoms have exceeded 7–10 days, and is defined as lasting up to 30 days by the Cochrane group.

Clinical features These are similar to the common cold (coryza, cough and fever), and in younger children (where the sinuses are still developing and the child may not communicate symptoms) sinusitis may be missed. The frontal sinuses can be demonstrated on plain radiographs in 20–30% of children by 6 years of age. Older children and young adults may experience facial "congestion" or "heaviness" alongside focal pains. The sinuses may be tender if gently percussed.

Management In acute rhinosinusitis in children there is no evidence for the use of nasal decongestants or saline irrigation. There is modest evidence for treatment with antibiotics (amoxicillin/clavulanic acid or an appropriate substitute if allergic), although most episodes are self-limiting and will resolve. Antibiotics should, therefore, be reserved for those children at risk of complications. In young adults intranasal corticosteroids may be of use as an adjunct to antibiotic therapy (Fokkens *et al*., 2012). Foul-smelling or bloody discharge should prompt consideration of a foreign body high in the nasal cavity.

Chronic rhinosinusitis is less common in children and management may require input from an Ear, Nose and Throat surgeon, as there may be an indication for adenoidectomy. A chronic sinus infection should lead the treating physician to consider an underlying diagnosis; gastro-oesophageal reflux, asthma, immunodeficiency, cystic fibrosis and primary ciliary dyskinesia are all associated with chronic rhinosinusitis in children. The presence of significant central nervous system symptoms should prompt consideration of a subdural empyema.

Acute otitis media

Acute otitis media (AOM) is extremely common in childhood, with a peak incidence between 6 and 15 months of age. Viral infections are commonest, although secondary bacterial infection may coexist or subsequently occur.

Clinical features Younger children will display nonspecific features of illness; fever, vomiting, minor irritability and poor feeding are all common, and young children with these symptoms should always have their ears examined. Older children may complain of dizziness and pain in the ear or pain when eating. Examination of the ear should demonstrate an inflamed erythematous bulging tympanic membrane. The tympanic membrane may rupture and there may be pus in the ear canal on examination. Lymph nodes draining the area may be inflamed.

Treatment should be to:

- give adequate analgesia and antipyretics,
- ensure parents administer sufficient doses of paracetamol and a nonsteroidal anti-inflammatory.

Acute otitis media is usually a self-limiting viral infection. Bacterial infection may rarely be followed by spread to the mastoid air cells with associated risk of intracranial infection and/or venous thrombosis. This risk has to be balanced against adverse consequences of antibiotic use both for the individual and the wider population. Other complications include middle ear effusions and hearing impairment.

A meta-analysis by Glasziou *et al.* (2004) of 10 trials using antibiotic *versus* placebo in AOM in children (using pain as an outcome measure) demonstrated no benefit at 24 hours, but some benefit at 2 and 7 days: however most children's symptoms (78%) are improved at this point. There was one case of mastoiditis in almost 3000 trial subjects (in a child treated with penicillin). The number needed to treat to prevent one child experiencing ear pain was 16. The number needed to harm due to antibiotic side-effects (vomiting, diarrhoea or rash) was 24. The authors conclude that antibiotics should be given to children with AOM who are <2 years old, and children with bilateral AOM or with AOM plus otorrhoea. Ventilation tubes (grommets) can be inserted into the tympanic membrane and one study from the early 1980s has demonstrated that they decrease the rate of subsequent episodes of AOM.

Otitis media with effusion

Otitis media with effusion or "glue ear" occurs when there is serous fluid in the middle ear without symptoms of acute infection. It occurs in association with Eustachian tube dysfunction, which may in turn be secondary to AOM. Over time this fluid can become tenacious. One in three affected children has culture positive effusions. Otitis media with effusion can lead to impaired hearing (conductive deafness) and antibiotics have been trialled to aid its resolution. A meta-analysis of 23 studies did not demonstrate any substantial improvement in hearing or need for grommets following antibiotic administration (van Zon *et al.*, 2012).

Chronic suppurative otitis media

Chronic suppurative otitis media is present when otitis media with effusion is associated with tympanic perforation and persistent (usually bacterial) discharge occurs. In children this may be a sign of underlying disease, such as immunodeficiency or primary ciliary dyskinesia.

Pharyngitis and tonsillitis

Inflammation of the pharynx is predominantly viral in aetiology and may coexist as a common pathology in many URTIs (such as a cold and a sore throat). Posterior pharyngeal wall inflammation is readily observed on depression of the tongue. Treatment is supportive with analgesia (oral syrups and topical local anaesthetic sprays) and antipyretics.

Acute tonsillitis Waldeyer's ring of lymphoid tissue includes the tonsils, adenoids and lymphoid aggregates in the pharynx, at the base of the tongue and in the pharyngeal walls. Tonsillitis is inflammation of the palatine tonsils, and is most common in children between the ages of 3 to 9 years, after which age tonsillar regression occurs. Tonsillitis may occur secondary to both viral and bacterial infections. The common bacterial pathogens include group A *Streptococcus*, *Staphylococcus aureus* and *Streptococcus pneumoniae*.

Clinical features: Younger children may have nonspecific features of fever, poor feeding, coryza, irritability and they may have a rash (either a viral exanthema, or a rash secondary to Streptococcal infection in scarlet fever). There may also be vomiting and diarrhoea. Older children and young adults may have similar symptoms plus localising throat pain, especially on eating or drinking. Local lymph nodes may be enlarged.

Complications of tonsillitis include the following.

- A peritonsillar abscess: a unilateral purulent collection in the peritonsillar fossa. Presents with pyrexia, ipsilateral otalgia (ear pain), odynophagia (pain on

swallowing) and often trismus (pain on opening the jaw). Examination shows a deviated uvula and swelling of the soft palate.
- A retropharyngeal abscess should be considered in children who present with fever, stiff neck, dysphagia and other symptoms related to inflammation or obstruction of the upper aerodigestive tract.
- Rheumatic fever and glomerulonephritis were previously associated with streptococcal tonsillitis but are now rare outside the developing world.

Treatment: Acute management options include analgesia, antipyretics and in some cases antibiotics. As with AOM conflict exists between the risks of antibiotic resistance and side-effects on the one hand, and acute and subacute post-infectious complications and morbidity on the other. Clinical scores have been developed for assessing the probability of Streptococcal infections. Of these, the Centor score is most widely used, although it was not developed in a paediatric setting. The McIsaac score (table 2) adjusts the Centor score for patient age.

β-lactam antibiotics are first-line drugs against bacteria that commonly cause tonsillitis. Amoxicillin may cause rashes in children who have sore throats due to Epstein–Barr virus (infectious mononucleosis and glandular fever).

Tonsillectomy Tonsillectomy prevents recurrent tonsillitis, but does not prevent recurrent sore throats as only the tonsillar or adeno-tonsillar lymphoid aggregates are removed. Tonsillectomy causes a sore throat for 5–7 days and exposes a child to the risk of anaesthetic and surgical complications (infection and haemorrhage) despite uncertainty over the likelihood of recurrence without surgery. A meta-analysis of tonsillectomy or adenotonsillectomy for recurrent or chronic tonsillitis in childhood found that severely affected children benefit from fewer episodes of sore throat in the first year following surgery (3.3 episodes *versus* 1.8 episodes plus one surgery-associated episode) (Burton *et al.*, 2009). In less severely affected children the review concluded that "surgery will mean having an average of two rather than three unpredictable episodes of any type of sore throat. The cost of this reduction is one inevitable and predictable episode of postoperative pain". Children and families should be invited to consider the relative risks and benefits of intervention in comparison to a "wait and see" approach when considering surgery for recurrent sore throats.

Diphtheria Diphtheria is a bacterial pharyngitis caused by *Cornyebacterium diphtheriae*. Mortality varies between 5% and 10%. Affected children will have a fever and sore throat; additionally there may be neck swelling and a characteristic posterior pharyngeal grey, adherent pseudomembrane that may progress to airway obstruction in which case urgent expert paediatric airway management is required. Diphtheria is prevented by mass immunisation; suggestive symptoms in an area of low immunisation should prompt consideration of diphtheria in the differential diagnosis. Russia, North Africa, the Middle East and East Asia all experienced diphtheria

Table 2. Centor score and McIsaac adjustment for assessing the likelihood of streptococcal infection in tonsillitis/pharyngitis

Centor score (1 point for each)	Guidance
Fever	Score 0–1: do not prescribe antibiotics
Absence of cough	Score 2: treat if the rapid antigen test is positive
Tonsillar exudates	Score 3: treat if the test is positive or treat empirically
Anterior cervical lymphadenopathy	Score 4: treat empirically
Aged <15 years (McIsaac adjustment)	

outbreaks in the 1990s. Treatment is isolation, airway management, antitoxin and systemic penicillins or erythromycin.

Laryngeal infections

Infection of the larynx causes characteristic changes in cough and phonation.

Croup (laryngotracheobronchitis) is a viral infection of the larynx and adjacent structures; the common causative organisms are rhinovirus, respiratory syncytial virus and parainfluenza 1 and 2.

Clinical features: The illness often begins with rhinitis as the upper airway is infected first. Distal progression irritates the larynx, resulting in a cough. With subsequent vocal cord oedema the cough becomes harsh or "barking" and inspiratory stridor will develop. Airway obstruction is progressive with limitation of airflow until the condition begins to resolve or anti-inflammatory measures are instigated. The onset of stridor usually occurs over 6–12 hours. Sudden onset of stridor should prompt consideration of an inhaled foreign body or anaphylaxis.

Treatment: Management should be aimed at maximising airflow through the larynx. Risk factors for significant hypoxia include diffusion limitation (*e.g.* chronic lung disease of prematurity) or pre-existing airway compromise (*e.g.* subglottal stenosis). It is imperative to keep the child as relaxed as possible as anxiety (*e.g.* from unwelcome or unwarranted interventions) may worsen airflow. Steroids reduce vocal cord oedema, facilitating respiration. They can be nebulised or delivered orally. More severely affected children may gain temporary benefit from nebulised epinephrine, with doses repeated as necessary due to the short half-life. Supplemental oxygen (which can be administered by a parent with the child on their lap) may be required and analgesia should be offered to all children. Decreasing the viscosity of inhaled gases results in improved large airway flow, and in severe cases a helium–oxygen mixture may be helpful.

Whooping cough (pertussis), caused by *Bordetella pertussis,* occurs in all countries and increased nine-fold in incidence in the USA between 1980 and 2010. The increase is thought to be multifactorial; but improved diagnosis (using PCR techniques) and a change to acellular vaccines (DTaP) are implicated (Cherry, 2012). Infants aged <2 months are most at risk from severe infection as there is little transplacental transfer of immunity. Recent anti-pertussis strategies include maternal vaccination with DTaP during pregnancy.

Clinical features: Children present with a coryzal, feverish illness which mimics a self-limiting URTI. At this stage the coryzal infant is highly infectious to non-immune close contacts. The classic, paroxysmal cough follows this stage and lasts for weeks or months; in China, whooping cough is known as "the hundred-day cough". The cough has a characteristic rise in pitch and may or may not be followed by a "whoop" or episodes of vomiting in younger infants. There may also be episodes of cyanosis, apnoea or bradycardia in infants. The cough may occasionally result in petechiae, subconjunctival haemorrhages, rib fractures and pneumothoraces.

Treatment: Accurate diagnosis with pernasal swab or PCR of nasopharyngeal aspirate is key; although cultures take up to 1 week and decline in sensitivity the longer the illness continues. Children requiring hospitalisation should be isolated and subject to barrier nursing. A macrolide antibiotic (conventionally 14 days of erythromycin) is first-line treatment, although shorter courses of newer macrolides may be considered (these may improve adherence). Supportive treatment including mechanical ventilation may be required.

Epiglottitis

Haemophilus influenzae type b (Hib) causes epiglottitis, a severe swelling of the epiglottis that leads to airway obstruction. Since the introduction of the conjugate Hib vaccine, the incidence of epiglottitis has fallen considerably.

Clinical features Features of infectious airway obstruction (fever, cough, stridor and recessions) occur rapidly (onset over hours) in a toxic-appearing child, without a clear viral prodrome. The child sits upright with the head held forwards to extend the neck and hold the larynx open. As airflow obstruction progresses, breathing becomes quieter and the child may become cyanosed with decreasing consciousness.

Treatment Suspected epiglottitis is an airway emergency and children should be managed in co-operation with anaesthetic and otolaryngology teams. Examination of the throat may precipitate acute obstruction (*via* distress causing laryngospasm) and should be avoided until measures are in place to secure a definitive airway at the point an intervention is required. The epiglottis typically appears swollen and ''cherry-red'' in appearance. There may be systemic features of sepsis and treatment includes fluid resuscitation and a third or fourth generation cephalosporin. Intravenous access should only be obtained once the airway is secure.

Bacterial tracheitis

As a result of the Hib vaccine and widespread use of steroids for croup, bacterial tracheitis is now the most common, although still rare, URTI cause of respiratory failure in children (Hopkins *et al*., 2006). Bacterial infection of the trachea with *S. aureus, S. pneumoniae* and *Streptococcus pyogenes* can result in erythema, oedema and purulent exudates in the trachea. There may be pseudomembrane formation. Viral tracheal infection may co-exist.

Clinical features Children present with fever, cough, hoarseness, stridor and recessions. Diagnosis is usually made at bronchoscopy where the differential includes severe croup or epiglottitis.

Treatment The majority of children require admission to intensive care, intubation and systemic antibiotic therapy. Aspiration of exudates and breakdown of membranes may be performed at bronchoscopy.

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Community-acquired pneumonia

Mark L. Everard, Vanessa Craven and Patricia Fenton

Pneumonia and lower respiratory tract infections

Pneumonia is defined as an inflammatory disorder of the lung characterised by consolidation due to presence of exudate in the alveolar spaces. There is, inevitably, associated inflammation in the surrounding interstitial tissues. In classic lobar pneumonia, watery exudates and pus filling the alveoli flow directly into adjacent zones, which extend to create a confluent and confined area of infection generally within the affected lobe; spread of infection predominantly occurs *via* the lumen of the airways (fig. 1). Invasive disease inevitably involves organisms penetrating into the interstitial tissues and, more importantly, adjacent capillaries leading to bacteraemia. Bronchopneumonia is characterised by inflammation primarily in the terminal and respiratory bronchioles with exudate spreading to surrounding peri-bronchoalveolae often resulting in a number of discreet foci. A wide range of organisms including viruses, bacteria, "atypical organisms" and fungi are capable of creating a pneumonic illness.

The limited response repertoire of the lungs ensures that many of the clinical features of pneumonia, such as fever, cough, respiratory distress and tachypnoea, are also features of other clinical entities, such as acute bronchiolitis, "wheezy bronchitis" and indeed viral exacerbations of asthma. Diagnosis remains largely clinical with most community-acquired pneumonia (CAP) guidelines recommending that chest radiographs are only undertaken in those with a more severe or atypical clinical course. This inevitably leads to over diagnosis of pneumonia and this reality is reflected in the use of the significantly less specific term "lower respiratory tract infection" (LRTI) in certain guidelines, which includes pneumonia and other clinical entities.

Key points

- Around 2 million children <5 years of age die from pneumonia each year.
- While *Streptococcus pneumoniae* is the "classic" organism it probably accounts for less than half of the cases of pneumonia.
- Many guidelines do not recommend the use of chest radiographs to make a diagnosis on pragmatic grounds but this is associated with over and under diagnosis.
- Most children can be treated with oral antibiotics unless they have severe and/or atypical disease or cannot tolerate oral therapy.

Importance of CAP

CAP usually refers to a pneumonia developing in a generally well individual who has acquired the organism outside of a healthcare setting.

Worldwide, CAP remains the biggest killer of children and, thus, is a major health issue. It has been estimated that approximately 2 million deaths per year in children <5 years of age are attributable to pneumonia, a fifth of all deaths in this age group. This is likely to be an underestimate as most deaths

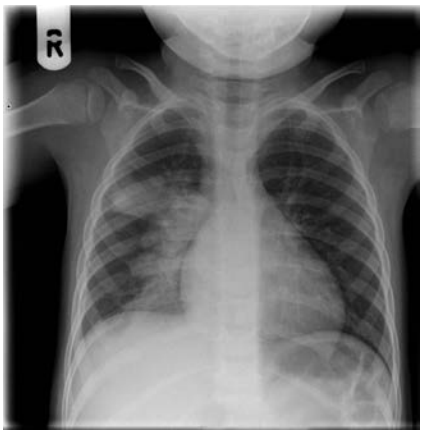

Figure 1. Lobar pneumonia.

probably occur without interaction with healthcare professionals. Epidemiological studies would indicate that the prevalence of CAP is significantly higher in developing countries, which would account, in part, for the higher mortality in these countries. However, the true incidence of pneumonia is difficult to define without confirmation of the diagnosis being confirmed by chest radiography with many LRTIs being labelled as ''pneumonia'' on clinical grounds. Studies assessing the accuracy of a clinical diagnosis of pneumonias when compared with chest radiographs have confirmed that there is significant over diagnosis, as well as under diagnosis.

UK and Scandinavian studies would suggest that incidence of chest radiograph-confirmed pneumonia is in the region of 15 cases per 10 000 children with high incidence in those aged 0–2 years (42 out of 10 000) and 0–5 years (33 out of 10 000). Higher incidences in excess of 100 per 10 000 have been suggested in European studies that did not include chest radiographs and/or did not exclude infants with acute bronchiolitis. Much higher levels are reported in the developing world, particularly sub-Saharan Africa and south-east Asia with estimates suggesting that 75% of the 150 million cases a year occur in just 15 countries. While figures may significantly over estimate the true incidence of pneumonia the catch all approach is based on the high levels of mortality seen in those with community-acquired bacterial pneumonia if not treated with antibiotics. Worldwide, under treatment is a much greater problem than over use of antibiotics for significant LRTIs.

Aetiology of CAP

Studies aimed at determining the causative organisms in children with CAP have been hampered by difficulties in obtaining samples from the site of infection in the distal lung as:

- young children rarely expectorate sputum,
- positive blood cultures resulting from invasive disease occur in a minority of bacterial infections,
- rapid antigen tests can be misleading due to false-positive results,
- sampling of the upper airways for viruses and bacteria may not be directly relevant to the organisms replicating in the alveoli.

It is believed that most episodes of pneumonia commence with colonisation of the mucosa of the nasopharynx with subsequent spread to the lower respiratory tract. Less commonly, a persistent bacterial bronchitis may precede an acute exacerbation with associated pneumonic changes.

A wide range of organisms including bacteria, viruses and so-called atypical organisms cause CAP. Mixed viral and bacterial infections are very common. *Streptococcus pneumoniae* is the most commonly identified bacteria and is frequently considered to be responsible for the classic pneumonic illness. However, studies have indicated that it accounts for less than half of all cases of paediatric CAP and indeed may account for as little as 5% of cases, although this will be influenced by definitions of disease and techniques available for diagnosis. The advent of conjugated vaccines has reduced the incidence of pneumonia although the magnitude of the impact varies depending

Table 1. Bacteria and CAP

Organism	Predisposing factors	Suggested first-line treatment	Comments
Streptococcus pneumoniae	Previously well	Amoxicillin (oral) Benzylpenicillin if *i.v.* therapy is required	13-valent vaccine in use in empyema? Add clindamycin to treatment
Streptococcus pyogenes	Chicken pox	Benzylpenicillin and clindamycin	Invasive group A *Streptococcus* is notifiable to the CCDC in the UK Contact tracing indicated
Mycoplasma pneumoniae	Outbreaks every 5–7 years	Clarithromycin	Often mild Organism has no cell wall so cannot be treated with penicillin
Staphylococcus aureus	Influenza A, PVL toxin	Linezolid, clindamycin and rifampicin	Health Protection Agency guidelines in UK Contact tracing indicated
Haemophilus influenzae	Immune defect if HiB isolated from vaccinated individual	Co-amoxiclav or cefotaxime/ceftriaxone	Rare

PVL: panton valentine leukocidin; HiB: *Haemophilus influenzae* type B; CCDC: consultant in communicable disease control.

of the definition of pneumonia used. Using a broad definition based on clinical criteria a study in the Gambia found that "clinical" pneumonia was reduced by 7%, increasing to 37% in patients with radiologically proven lobar pneumonia. Again this emphasises that clinically suspected pneumonia overestimates the true incidence of pneumonia and the fact that pneumococci are responsible for a minority of all pneumonias although it remains the target organism for empirical antimicrobial treatment in the hospitalised child with pneumonia. *S. pneumoniae* is the commonest bacteria found in analysis of parapneumonic effusion/empyema, although any organism, including viruses, may be associated with a parapneumonic effusion. Associated invasive disease, such as bacteraemia and meningitis, contributes to the poor outcome in untreated children. The current conjugated vaccines have targeted the serotypes most likely to cause invasive disease. While it is often remarked that most pneumonias in infants are viral and that an older child is more likely to have pneumoccocal disease or an atypical organism rather than a virus, it should be remembered that severe pneumococcal disease and invasive disease, in particular, is most common in infants and pre-school children.

Other bacteria that cause pneumonia include:

- *Haemophilus influenzae* type B (HiB) and nontypable species, although HiB is now very rare in developed countries and when it occurs in a vaccinated child it is an indication to look for an immune defect;
- group A streptococci, commonly associated with a history of recent chickenpox infection;
- *Staphylococcus aureus*, especially during influenza A epidemics or if the strain produces panton valentine leukocidin toxin.

In addition to these bacteria atypical organisms such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* may account for

20% of cases. Again they are classically considered to be causes of pneumonia in school-age children but are both capable of causing a severe pneumonia in younger children (table 1).

A wide range of respiratory viruses can cause pneumonia, particularly in infants and, to a lesser extent, pre-school children. As with any clinical syndrome from rhinitis through to bronchitis and bronchiolitis to pneumonia, any of the respiratory viruses may be responsible. In general they cause less severe illnesses than bacteria but remain an important cause of severe disease and indeed death. Viral LRTIs tend to affect the airways more diffusely than bacterial pneumonias and it is not uncommon for infants with clinical acute bronchiolitis characterised by widespread crackles to have evidence of collapse and/or consolidation on a chest radiograph. Moreover, with increasingly sensitive diagnostic techniques it is clear that many cases of bacterial pneumonia are preceded or accompanied by infection by one or more of these viruses.

In general, studies have found that the more severe illnesses are associated with bacterial infection but this is not necessarily the case and this is already changing with the widespread introduction of vaccines to *S. pneumoniae* and HiB. However, it should be remembered that the mortality of patients with viral LRTIs, such as acute bronchiolitis due to respiratory syncytial virus and other viruses in the absence of good supportive care and oxygen therapy, in particular, is very significant.

While it is widely stated that most pneumonias in very young children are viral this is also the peak age for severe bacterial infections and death due to organisms such as pneumococcus. Mixed viral and bacterial infections are very common.

Clinical assessment and diagnosis

When assessing a child who may have pneumonia it is important to make a diagnosis, assess the severity and consider comorbidities which may contribute to the development of the pneumonia or to the severity of the episode.

Diagnosis The World Health Organization's (WHO) recommendations are aimed at resource-poor countries and are based on simple clinical criteria. They suggest that pneumonia should be suspected in children with a cough and/or difficulty breathing with age-adjusted tachypnoea:

- >50 breaths·min^{-1} for infants aged 2–11 months of age,
- >40 breaths·min^{-1} for preschool children aged 1–5 years,
- >20 breaths·min^{-1} for children aged >5 years.

One study found that this approach had the highest sensitivity (74%) and specificity (67%) for radiographically defined pneumonia. Associated factors are used to determine severity with recession, grunting and nasal flaring being indicative of severe pneumonia while cyanosis, persistent vomiting, severe respiratory distress and confusion suggest a very severe illness. This pragmatic approach serves the needs of healthcare systems faced with a huge burden of disease and associated morbidity where clear, unambiguous direction in relationship to management is required in order to optimise outcomes. This approach has been incorporated into the WHO integrated management of childhood illness programme which has been proven to have had a significant impact on childhood mortality. It is widely recognised that the features above are not specific, with tachypnoea and fever being associated with many other conditions.

Interestingly, a very similar approach is observed in several developed countries as highlighted by the British Thoracic Society (BTS) guidelines which again advocate a clinical approach to diagnosis. The guidelines do not have clear recommendations regarding making a definitive diagnosis but state that "bacterial pneumonia should be considered in children when there is persistent or repetitive fever $>38.5^{\circ}$C together with chest recession and a raised respiratory rate". They make no

recommendation regarding the use of chest radiographs other than to state that they should not be a considered to be a routine investigation in children thought to have CAP. Once again this is likely to be associated with misdiagnosis; both false positive and false negative. It is known that chest radiograph changes lag behind the clinical picture and an early chest radiograph may miss a developing pneumonia. In contrast, other guidelines recommend the use of chest radiographs to make a definitive diagnosis and to assist with "antibiotic stewardship". Clinical judgement was shown to be associated with both over and under diagnosis in a recent Dutch study comparing general practitioner assessment with chest radiographs.

Cough is not a key feature and it is known that for classic bacterial lobar pneumonia cough may be infrequent until lysis occurs as there are few, if any, cough receptors in the distal lung. Of other symptoms that might be present the most predictive is wheeze which has a very strong negative predictive value. Conversely, the absence of wheeze in a known asthmatic with respiratory distress and fever may indicate bacterial pneumonia which generally does not cause an exacerbation of the asthma. Other auscultatory findings are considered to be unreliable but if localised crackles are present they increase the likelihood of a lobar consolidation and dullness to percussion is a good predictor of an associated effusion/empyema. Widespread crackles in an infant are consistent with a diagnosis of bronchiolitis rather than pneumonia. While tachypnoea is perhaps the most important symptom this is less specific and sensitive than noted above during the first few days of the pneumonia. It is likely that many children with pneumonia are treated inadvertently in primary care with antibiotics prescribed for conditions such as tonsillitis or ear infections.

Extrapulmonary symptoms are not uncommon. These may be nonspecific symptoms such as diarrhoea and vomiting, headaches and myalgia. Of note is that pneumonias may cause abdominal pain and should be considered in the differential of the acute abdomen even in the absence of coughing. Organisms such as *S. pneumoniae* and HiB may cause serious invasive disease such as septicaemia and meningitis with or without an obvious pulmonary focus.

Comorbidities While CAP is generally considered to be those pneumonias that develop in the community in previously well children, it is important to obtain a full history in order to try and determine whether there may be predisposing factors. These would include possible chronic aspiration associated with neuromuscular or other conditions and protracted bacterial bronchitis, both of which may be accompanied by a chronic cough, as well as a more acute episode such inhalation of a foreign body, influenza and recent chickenpox.

Severity Features reflecting the severity of the pneumonic illness have been outlined by the WHO as noted previously. These provide a guide to a step-wise approach to treatment, escalating from oral antibiotics to intravenous antibiotics in severe disease. In Europe, determination of apparent severity influences both the decision to admit to hospital and the route of administration of therapy. The BTS guidelines suggest that any of the following would indicate that admission to hospital is indicated:

- children with an oxygen saturation of $\leqslant$92% in air,
- apnoea or grunting,
- significant difficulty in breathing,
- poor feeding or dehydration,
- concerns regarding appropriate supervision.

Pulse oximetry is an important parameter influencing the use of oxygen therapy and, indeed, antibiotic therapy.

Investigations

Chest radiographs Current guidelines have concluded that for most cases of pneumonia a presumptive diagnosis can be made on the basis of clinical criteria outlined above

and that treatment can be initiated empirically. A definitive diagnosis would require a chest radiograph with changes consistent with consolidation, although it should be remembered that the chest radiograph changes may lag behind the clinical picture, both during the evolution of infection and the resolution. WHO and North American and European guidelines do not recommend the use of chest radiographs in the majority of cases for a number of reasons. These include the apparent inability to distinguish bacterial and viral infections on the basis of the chest radiograph appearances and studies which suggest that while in those with a clinical diagnosis obtaining a chest radiograph only leads to a change in management in a minority of case, this does not influence outcomes in the vast majority of cases. Furthermore, interobserver agreement regarding interpretation of chest radiograph changes is poor, even with clear guidance. There is certainly a consensus that they are not required in the vast majority of ambulatory patients treated in the community. The BTS guidelines suggest that a chest radiograph could be considered in those with fever $>39^{\circ}C$, children aged <5 years, and in those not responding rapidly and in whom complications, such as an effusion, may have developed.

Microbiology Making a positive identification of the causative organism(s) is clearly desirable as therapy could then be tailored more accurately. However, obtaining microbiological samples from the site of infections (the distal airways) is challenging, and invasive investigations such as bronchoscopy or lung aspirates are rarely indicated. Sputum cultures may be helpful if present but most young children do not expectorate sputum. Blood cultures are positive in a minority of patients, in part, because many clinical pneumonias are not due to bacteria and, in part, because bacteraemia is often not present or intermittently present. The likelihood of conventional microbiological approaches identifying bacteria in such samples is significantly reduced in the presence of prior antibiotic use.

Samples can be obtained from the nasopharynx and oropharynx and may reflect the cause of infection in the distal airways, but inevitably there are false positives and false negatives. This is particularly true for bacteria that are frequently present as transient ''commensals'' in the upper respiratory tract of infants and young children and, hence, bacterial culture of the upper airways is not recommended. Viral PCR may be helpful but a positive result does not exclude a bacterial pathogen and it is increasingly recognised that more than one organism may be involved. Paired serology is useful in epidemiological studies but contributes little to the clinical care and outcomes. The value of rapid antigen tests for pneumococcus is compromised by relatively low sensitivity and specificity especially in young children when false positives are common. A negative test in older children may be valuable.

For all these reasons it is widely recommended that no investigations are required in those ambulatory patients with suspected pneumonia treated in the community. In those admitted to hospital, blood cultures, viral PCR on nasopharyngeal aspirates or nasal swabs and paired serology for atypical organisms may all be of value. Where pleural fluid is obtained culture PCR for pneumococcus and other organisms and pneumococcal antigen detection should be undertaken.

Other investigations Evidence would suggest that acute-phase reactants are not helpful in distinguishing viral infection from bacterial infection and, hence, are not indicated in the management of uncomplicated pneumonia. Clinical experience, however, would suggest that they can contribute to the management of children who do not follow the expected clinical course.

Treatment

Treatment involves both supportive and therapeutic components. There is no question that children with hypoxia should be treated with supplemental oxygen although there is some debate as to whether a saturation of 90% or 92% is the appropriate

cut-off and altitude may need to be taken into account. Studies in Zambia and other countries have indicated the importance of oxygen therapy in reducing mortality. General supportive care including fluids, possibly restricted to 80% of maintenance, is indicated in those who are vomiting or unable to tolerate oral fluids. In the most severe cases intensive care may be required.

Specific treatment in the form of antibiotics should be given to all of those with a clinical diagnosis of pneumonia since there is no reliable means of distinguishing viral and bacterial infections. It is clear that this approach will result in many children with viral LRTIs being treated with antibiotics but the risk of mortality and adverse outcomes in untreated bacterial pneumonia is such that this is indicated. There is clear evidence that the oral route is appropriate for the vast majority of children with pneumonia. Intravenous therapy should generally be reserved for those with a severe illness or those not tolerating oral administration.

Amoxicillin is generally the antibiotic of choice as it is effective against the majority of bacterial pathogens. In older children where an atypical infection is suspected or there is poor response to therapy, a macrolide maybe used or added. Current recommendations are that co-amoxiclav is appropriate for influenza A-associated bacterial pneumonia. The optimal duration of treatment is unknown, with most courses consisting of 5–7 days of antibiotics. For streptococcal pneumonia in the presence of lysis and fever, shorter courses may be appropriate but evidence is lacking. Benzyl penicillin is generally appropriate for intravenous therapy although co-amoxiclav or a second- or third-generation cephalosporin may be used in severe disease.

Antibiotic resistance patterns vary from country to country and within countries. Hence the choice of antibiotics should be based on local guidelines developed as part of a multi-disciplinary approach involving microbiologists, those specialising in infectious diseases, pharmacists and paediatricians. In children with neurodisability or a history of recent intubation an anti-psuedomonal agent (such as piperacillin/tazobactam) is a good empiric choice.

Prevention

Vaccines against HiB and *S. pneumoniae* have had a significant impact in these specific diseases. While the HiB vaccine has largely eliminated this organism from the list of likely pathogens, the limited cover of conjugate pneumococcal vaccines means that the organism continues to cause pneumonia. Current vaccines cover up to 13 of the more than 80 serotypes and, hence, disease resulting from infection with other serotypes continues; this may, in part, be due to serotype replacement. The impact of the conjugate vaccines on the incidence of pneumonia depends upon the rigor of diagnosis ranging from a $<$15% reduction in those meeting the WHO definition of probable pneumonia to a $>$35% reduction in confirmed lobar pneumonia. One benefit of the widespread introduction of the conjugate vaccines is that they are effective against both antibiotic-susceptible and -resistant strains while the ''herd effect'' has led to an impact on the incidence in the elderly as well as the very young.

In the developing world, factors such as improved nutrition are associated with reduced morbidity and mortality.

Complications

The most common complication with CAP is development of pleural effusions and empyemas (fig. 2). Small uncomplicated effusions do not need draining. Ultrasound is a valuable modality in determining the size and distribution of the collection and its consistency. Current evidence suggests that in those developing an empyema, drainage with a small calibre catheter and intrapleural fibrinolytics is as effective as other approaches (fig. 3), although mini thoracotomy and video-assisted thoracic surgery (VATS) have their advocates. All of these approaches appear to shorten the duration of hospitalisation by a similar amount as compared with drainage and antibiotics alone. Some 10–15% of empyemas resolve relatively quickly with

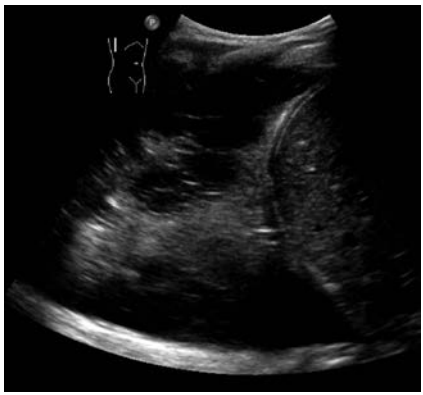

Figure 2. Ultrasound showing empyema with septations secondary to pneumonia.

antibiotic therapy alone and hence drainage on the basis of chest radiograph appearance alone is inappropriate. Whichever approach is used, outcomes are generally good. Up to 15% of patients treated with drainage and fibrinolytic therapy might subsequently require further intervention, such as VATS or decortication, although fever alone is not an indication of failed therapy.

Pneumatoceles are most commonly seen in those with *S. aureus* infection but may develop in pneumonia due to almost any of the common bacteria (fig 4). The vast majority regress spontaneously and surgical management is rarely required. Lung abscesses developing in the course of necrotising pneumonia are often associated with an empyema and are most commonly treated with a prolonged course of intravenous antibiotics, although radiological placement of a drain has been suggested as a way of more rapid resolution. Surgical resection should be avoided. Broncho-pleural fistulae may also develop in necrotising pneumonia. They are usually peripheral and usually resolve with continuous chest drainage.

Conclusion

CAP remains a major healthcare issue despite the development of vaccines directed against two of the major bacterial pathogens. A clinical diagnosis based on fever and

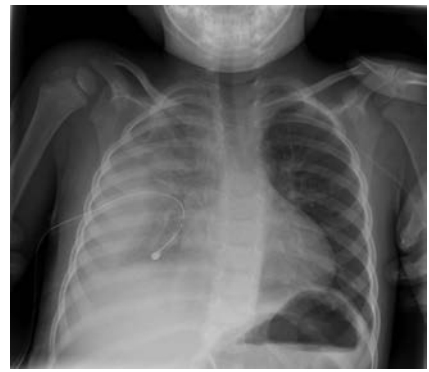

Figure 3. Empyema with a chest drain with urokinase.

tachypnoea is associated with improved clinical outcomes, particularly in the developing world, but inevitably results in large numbers of patients receiving antibiotics for non-bacterial infections. While the majority of pneumonias in infants and young children are viral this is also the peak age for serious life-threatening bacterial infections. Most pneumonias can be treated effectively with appropriate oral antibiotics, with intravenous antibiotics being reserved for those with severe infections or who are not tolerating oral therapy. Supportive care remains a vital aspect of care for those with severe infection.

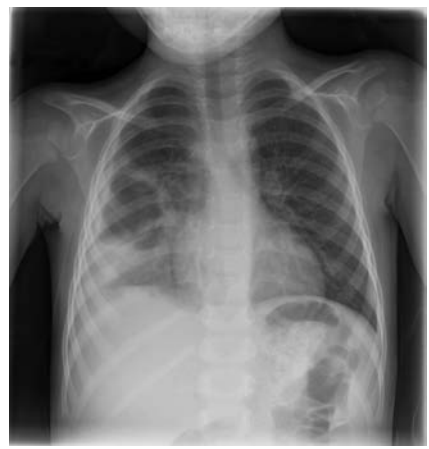

Figure 4. Pneumatocele developing during pneumonia.

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Hospital-acquired pneumonia

Vanessa Craven, Patricia Fenton and Mark L. Everard

Hospital-acquired infections, also known as nosocomial infections, are infections that are not present and that lack evidence of incubation at the time of admission to hospital. Pneumonia and other lower respiratory tract infections (LRTIs) account for a large proportion of these potentially serious complications of hospitalisation. Such infections can be transmitted to the patient from another source or may be due to an organism already carried by the patient. Interventions, such as endotrachel intubation or use of broad-spectrum antibiotics, may compromise host defences increasing the patient's predisposition to infection. Hospital-acquired pneumonia (HAP) is generally defined as one that presents with signs and symptoms that occur after, and not originating before, 48 h

Key points

- Hospital-acquired LRTIs are associated with significant mortality, morbidity and prolonged hospitalisation.
- Risk factors include intensive care, immunosuppression and admission of infants to paediatric wards containing patients with LRTIs.
- Organisms may be part of the patient's normal flora or maybe transmitted from another patient or healthcare provider.
- Following recommended infection, control policies significantly reduces rates of nosocomial infection.

(Foglia *et al.*, 2007). In the 2011 English Net Point Study, HAP in neonates and children was the second most common cause of nosocomial infection after clinical sepsis, accounting for 15.9% of cases and occurring most commonly in those aged <2 years old.

HAP poses greatest risk to those undergoing mechanical ventilation in which case it is termed ventilator-associated pneumonia (VAP). VAP is generally defined as development of a pneumonia >48 h after intubation. Many publications have addressed the issue of VAP although it should be remembered that most HAPs occur outside the intensive care unit (ICU). Attempting to define HAP and VAP has been challenging for those designing epidemiological and intervention studies. Variations in definition probably contribute to differing reports of incidence, with a recent UK paediatric ICU (PICU) review of ventilated patients reporting an incidence of 5.6%, accounting for 9.2 per 1000 ventilator days (Hunter, 2012), while US data indicates rates of 2.9 to 8.1 per 1000 ventilator days (Bingham *et al.*, 2009). Differing rates are likely to reflect variation in the case mix of different units.

HAP in neonatal ICUs (NICU) poses an even greater challenge as it is difficult to distinguish between hospital-acquired and vertically transmitted infections. This uncertainty is compounded by usual NICU practices being early intervention in suspected sepsis, often prior to chest radiograph changes, a feature usually integral to the definition of VAP, in addition to endotracheal secretions that can often yield positive growth in which colonisers and pathogens are difficult to distinguish.

Hospital-acquired LRTIs are also relatively common amongst infants admitted to hospital in whom viral LRTIs acquired in hospital contribute to increased mortality, morbidity and duration of stay. Other at risk groups include patients with immunodeficiencies such as those undergoing chemotherapy, patients with neuromuscular disease and post-surgical patients.

There is an extensive literature demonstrating the effectiveness of careful preventative strategies in greatly reducing the rates of nosocomial infection in both the ICU and paediatric wards.

Risk factors

HAP can be thought of as endogenous, in which auto-infection occurs when one's own microbes breach the usual protective barriers and become pathogenic, or exogenous in which external factors lead to the acquiring of new pathogens that proceed to cause infection. Certain factors in the host lead to this becoming more or less likely to occur and it is these risk factors that form the basis for interventions to limit nosocomial pneumonias.

Paediatric intensive care Mechanical ventilation poses the biggest risk in this setting as it is generally used in those with the greatest illness severity and is an invasive intervention that circumvents the normal upper and lower pulmonary antimicrobial defences. In this group, nosocomial pneumonia is usually synonymous with VAP and this has been linked to a prolongation of mechanical ventilation, as well as an increase in mortality and morbidity (Bigham *et al*., 2009).

Patients can become colonised with new organisms during hospitalisation, in particular those who are severely unwell and thus require PICU admission. These newly colonising organisms tend to differ between institutions and the rate of their establishment increases with acidosis, intubation, hypotension, broad-spectrum antibiotic use and those at risk of clinical or sub-clinical aspiration (Elward *et al*., 2003).

However, of all the adverse factors in this setting, it appears that intubation poses the greatest risk to the establishment of HAP. By providing a continuous foreign object extending through the upper airway into the trachea, the endotracheal tube permits organisms from the upper airway to reach the trachea more easily. Current evidence suggests that oral tubes have a lower rate of infective complication than nasal tubes. Endotracheal tubes also impair mucocillary transport while trauma from the endotracheal tube and suctioning may also impair host defences. Tracheostomies have an even greater effect (Bigham *et al*., 2009) and in this population, nosocomial infection rates are greater still. Neuromuscular blockade in all groups has a negative impact on rates of pneumonia.

In addition to the use of endotracheal tubes, intensive care patients frequently have a nasogastric tube which is likely to facilitate reflux and lead to aspiration of gastric contents into an artificially patent airway. The risk of infection appears to be increased by the use of drugs, such as H_2 receptor antagonists, that are used to prevent gastric stress ulceration as they increase gastric pH which contributes to an increase in bacterial growth which may, in turn, contribute directly to the establishment of pneumonia in the presence of aspiration (Kollef *et al*., 2013). The risk-benefit of adding a H_2 receptor to agents such as sucralfate continues to be debated.

Neonatal intensive care In addition to the risks addressed in the PICU setting, in NICU the population has its own unique factors that predispose to nosocomial pneumonia. Low birth weight, poor nutrition, a greater permeability of skin and mucous membranes, and hypogammaglobulinaemia due to a restriction in the time available for the placental translocation of maternal IgG all contribute to a greater risk of infection. In the NICU, as in the PICU, the effect of hand hygiene, local equipment practices and ward design also all impact on infection rates.

Post-surgical patients The post-operative period, with the risk of ventilation and the impact of pain or sedation predispose to

nosocomial pneumonia, in particular thoracic and abdominal surgery in which coughing may be painful and adequate mucous clearance difficult.

Chronic disease Immunodeficiency (primary and secondary), CF, cardiac disease, low birth weight and malnutrition all contribute to increasing rates of nosocomial pneumonia. In addition, those with gastro-oesophageal reflux, swallowing difficulties, trachea-oesophageal fistulae and neurological disorders are at risk of aspiration and subsequent nosocomial pneumonia (Zar *et al*., 2002).

Hospital factors Nosocomial infection rates vary among institutions and the impact of staffing, ward design, local hygiene practices among staff and the management of equipment have been shown to have a significant effect on infection rates, including pneumonias. The impact of acquiring an organism, such as the respiratory syncytial virus (RSV), in hospital is frequently overlooked in discussions about HAP, but studies have reported that ICU patients who acquire the virus after admission may have a mortality rate approaching 25%, while acquisition during an admission to the paediatric ward for an unrelated problem is associated with substantial increases in the duration of stay and readmission rates, as well as significant morbidity.

Antibiotic usage Sensitivity results vary markedly between different healthcare establishments and even within the same hospital on different wards. Empiric guidelines are usually available but results should always be kept under review. Antimicrobial stewardship guidelines should be followed by all prescribers.

Aetiology

Viruses Viruses are responsible for the majority of nosocomial pneumonias, being highly contagious and having the ability to infect relatively well children in addition to those who are deemed high risk. The epidemiology of these nosocomial pneumonias reflect epidemic patterns and are, in the most part, attributable to RSV, influenza and parainfluenza viruses, with RSV, by virtue of its high infectivity, being most common. Other implicated viruses include cytomegalovirus (CMV), Epstein–Barr virus (EBV) and adenovirus, although they occur less often and tend to be of most importance in the immunocompromised (Hall).

Bacteria Gram-negative organisms including *Pseudomonas aeruginosa*, *Klebsiella* sp., *Enterobacter* sp. and nontypable *Haemophilus influenzae* are the most common Gram-negative isolates. *Streptococcus pneumoniae* and *Staphylococcus aureus* are the most common Gram-positive isolates (Bradley, 2010).

Antimicrobial resistance poses a great problem in exogenous bacterial HAP and will differ between institutions according to local resistance patterns. Although one of the rarer causes, methicillin-resistant *S. aureus* (MRSA) infections do cause a therapeutic challenge, and third-generation cephalosporin resistance and extended spectrum β-lactamase producing organisms can cause significant morbidity and mortality.

Fungi The immunocompromised are at highest risk of fungal lung infections, particularly if exposed to broad-spectrum antibiotics for suspected bacterial sepsis. Building work is quoted as a risk factor for the acquisition of *Aspergillus* species whilst endogenous *Candida* and *Aspergillus* are a particular risk to neutropenic patients. It is due to this risk that in those with neutropenic sepsis, anti-fungal agents tend to be used early in those not responding to first-line antibacterial agents. High-efficiency particulate air-filtered positive pressure air supply to single rooms is recommended for children in the period immediately after bone marrow transplant.

Pneumocystis jirovecii This organism, classified as a protozoan, is an opportunistic organism with a high mortality that should increase the suspicion of an underlying immunodeficiency. This, as well as infections with CMV, EBV and adenovirus in this vulnerable population, tend to reflect

Table 1. Antimicrobial treatment for HAP in children[#]

Clinical setting	Likely organisms	Appropriate "first guess" treatment	Comments
Post-operative, previously healthy	*Streptococcus pneumoniae* *Haemophilus influenzae* *Moraxella catarrhalis*	Co-amoxiclav[¶] OR cefuroxime	If genuine penicillin allergy discuss oral switch with microbiologist Maximise physiotherapy
Post-viral, *e.g.* deterioration in bronchiolitis	*Streptococcus pneumoniae* *Haemophilus influenzae* *Moraxella catarrhalis* *Staphylococcus aureus*	Co-amoxiclav[¶] OR cefuroxime	If genuine penicillin allergy discuss oral switch with microbiologist
Ventilator-acquired pneumonia	*Pseudomonas aeruginosa* *Staphylococcus aureus*	Piperacillin/tazobactam[¶] OR ceftazidime plus teicoplanin	Usually requires full *i.v.* course
Neutropenic/post-transplant/immune deficient	Wide variety of potential organisms; bacterial, fungal and viral Consider possibility of *Mycobacterium tuberculosis*	Follow local protocols Consider anti-fungal and anti-viral treatment in addition to antibacterial	Discuss with microbiology, infectious diseases, radiology and oncology May need invasive diagnostic tests

Be guided by local protocols and sensitivity patterns. [#]: consider *i.v.* to oral switch as soon as clinically appropriate; [¶]: these agents are penicillins and should be avoided in cases of genuine penicillin allergy.

endogenous rather than exogenous acquisition and can be life-threatening.

Mycobacterium *Mycobacterium tuberculosis* should not be overlooked in the search for aetiology in HAP. Although all children are highly susceptible to *M. tuberculosis,* the immunosuppressed child is at increased risk of nosocomial infection with possible spread from undiagnosed adults posing a threat in the ward setting.

Prevention

Prevention of hospital-acquired infection, including HAP, should be at the forefront of the clinician's approach to the care of patients. There is a substantial body of evidence that HAP is associated with increased morbidity, mortality and healthcare utilisation and a similar body of evidence that the implementation of programmes designed to prevent such infections can be very effective both in the ICU and in paediatric wards. Attention to detail is the key to implementing well-known infection control measures, including rigorous hand hygiene, the use of disposable aprons and gloves, and isolating infectious patients. Ensuring that healthcare workers are immunised against influenza and ensuring those with respiratory viral illnesses do not look after at-risk patients are also important aspects of preventing nosocomial infection. Care bundles, including the previously mentioned precautions, together with recommendations such as nursing ventilated patients with their head elevated where possible, minimising changes in ventilator circuits unless contaminated; using oral rather than nasal tubes, and avoiding re-intubation where possible, in addition to ongoing education of staff have been shown to have a significant impact in lowering rates of VAP (Brierley *et al*., 2012).

Not only does attention to detail significantly improve clinical outcomes for the patient, but it also reduces healthcare costs and leads to much lower use of broad-spectrum antibiotics.

Diagnosis and surveillance

As noted above, the diagnosis of HAP and indeed VAP can be problematic. Common to all definitions is deterioration in respiratory status more than 2 days after admission or intubation that does not appear to be attributable to infection apparent at the point of admission/intubation. New chest radiograph changes associated with fever and leukocytosis or leukopenia, together with clinical features such as increased cough or airway secretions on suctioning, strongly support the diagnosis though it is clear from *post mortem* and other studies that over and under diagnosis occurs, as is the case with community-acquired pneumonia. Hospital-acquired LRTIs, due to viruses such as rhinovirus or respiratory syncytial virus, are often not classified as HAP as they develop after discharge and if the patient is re-admitted are frequently assumed to be community acquired.

Diagnostic approaches include sampling the lower airways in those being ventilated with simple endotracheal aspirates, blind protected brushings, and blind and bronchoscopic lavage. Identifying the bacteria responsible requires more focused antibiotic prescribing and reduces the use of broad-spectrum antibiotics. None of the sampling techniques are ideal, in terms of sensitivity and specificity, with the sensitivity increasing with combinations of techniques. For non-ventilated patients, obtaining samples from the lower airway is rarely undertaken other than in immunosuppressed patients, although upper airways sampling for respiratory viruses can be very valuable.

Treatment

Ideally treatment should be tailored to the specific organism. As noted previously this is not possible for many patients with HAP and empirical treatment is frequently used based on likely organisms. The choice of antibiotics should be based on local guidelines developed as part of a multi-disciplinary approach involving microbiologists specialising in infectious diseases, pharmacists, intensivists and paediatricians. A suggested approach is outlined in table 1.

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Lung involvement in immunodeficiency disorders

Rifat Chaudry and Paul Aurora

Overview of clinical approach

- Immunocompromise may be suspected in children experiencing recurrent infections.
- Differential diagnosis of lung disease is dependent on the underlying primary diagnosis. For example, in children who are immunosuppressed due to chemotherapy for malignancy, the possibility of toxic lung damage from chemotherapeutic agents must also be considered.
- An appreciation of the types of organisms immunodeficient children are susceptible to and their presenting features is necessary.
- Detailed history taking and examination remain crucial in providing diagnostic clues.
- Radiology and bronchoscopy are extremely useful in diagnosis.

Key points

- Immunocompromise/ immunodeficiency can be broadly divided into congenital (primary immunodeficiency) or acquired (through immunosuppression or infection such as HIV).
- Preventative measures such as antibiotic prophylaxis along with swift diagnosis and treatment can effectively reduce lung morbidity.
- Long-term sequelae vary from mild restrictive or obstructive defects to end-stage respiratory failure.
- Open-lung biopsy may be useful and should be considered if other causes of lung damage (*e.g.* interstitial lung disease or toxic damage) are high on the differential diagnosis.
- Additional advice from infectious diseases, microbiology and immunology specialists can be helpful.

Immune defences in the lungs and points of compromise

Natural barriers and immunological defences exist in order to protect our lungs from infection. Primarily, these are:

- hair within the nasal passages;
- lymphatic tissue within the pharynx (adenoids and tonsils);
- mucociliary clearance of lower airway secretions; and
- an effective cough with swallow.

If these mechanical barriers are breached, then the risk of recurrent respiratory infection increases. Specific deficiencies in cellular defence pathways increase susceptibility to particular organisms. Although when screening for infection, a broad investigative approach should be used in order not to miss causal agents, an understanding of the different components of the immune response can help to focus a diagnosis (table 1).

Features, diagnosis and treatment of opportunistic infections

The most important pathogens causing disease in immunocompromised children are listed here. It should be noted that this list is certainly not exhaustive.

Table 1. Components of the immune response

Component	Mechanism of compromise	Examples	Increased susceptibility to
Neutrophils	Reduced numbers or function	CGD Children with leukaemia Children after cytotoxic therapy Pancytopenia, either primary or in response to infection (*e.g.* parvovirus infection in children with sickle cell disease) More rare genetic conditions	Bacteria *Staphylococcus aureus* *Pseudomonas aeruginosa* *Klebsiella* *Escherichia coli* *Haemophilus influenzae* *Nocardia* Fungi *Candida* *Aspergillus* Mucormycosis
Complement	Reduced production or dysfunction	Mannose-binding lectin deficiency Early classical pathway (C_2, C_4, C1qrs) deficiency Alternate pathway deficiency Late lytic deficiency	Bacteria *Streptococcus pneumoniae* *Neisseria meningitidis*
B-lymphocytes	Reduced production or dysfunction	Common variable immunodeficiency X-linked agammaglobulinaemia IgG subclass deficiency SCID Acute lymphoblastic leukaemia, chronic lymphoblastic leukaemia, and lymphomas pre- and post-treatment	Bacteria *Streptococcus pneumoniae* *Haemophilus influenzae*
T-lymphocytes	Reduced production or dysfunction	SCID After chemotherapy for malignancy or organ transplantation Lymphoma Secondary to use of chronic high-dose corticosteroids HIV/AIDS	Bacteria *Listeria* *Mycobacterium* including *M. tuberculosis* *Nocardia* *Legionella* Viruses VZV CMV HSV Fungi *Candida* *Aspergillus* *Cryptosporidium* *Pneumocystis jiroveci* Parasites *Toxoplasma gondii*

VZV: varicella zoster virus; HSV: herpes simplex virus.

Aspergillus *and* Candida are highly prevalent in our normal environment, in soil and as part of the skin flora, respectively. These organisms rarely cause disease in healthy individuals, but can do in the immunocompromised.

Diagnosis is made as follows.

- History and examination findings: high-risk patients include those with primary or secondary neutropenia, chronic granulomatous disease (CGD) or hyper-IgE syndrome, and those receiving high-dose broad-spectrum antibiotics. Chronic or high-dose corticosteroid use also increases risk. Pleuritic chest pain is characteristic of invasive disease in conjunction with cough, dyspnoea, hypoxaemia and haemoptysis.
- Chest radiography may reveal new infiltrates or round focal opacity; however, CT is extremely useful for diagnosis as there are several characteristic features, including cavitations, air crescents and halo signs, all suggestive of fungal parenchymal erosion.
- Contamination of the upper airway with fungus is common in children with mucositis so sputum samples may give false-positive results; therefore, bronchoscopy with bronchoalveolar lavage (BAL) is helpful in confirming the diagnosis. It should be noted that yield can be poor and false-negative results are common.
- Examine other organ systems for signs of infection. Oncomycosis is particularly common in immunodeficient individuals.
- Open-lung biopsy may be the only means of diagnosis, but be cautious as, in CGD in particular, the fungal load in the lung may be very low.

Several antifungal agents are available but those with broadest cover, greatest tissue penetrance and lowest toxicity are liposomal amphotericin (Ambisome; Gilead, Foster City, CA, USA) and caspofungin. Azoles, for example voriconazole, are commonly used for prophylaxis; however, they are less effective for treatment of *Candida* infection. Duration of treatment is titrated to response and must be discussed with specialist teams. Treatment is often commenced empirically, as confirmation of the diagnosis may be difficult without biopsy. If such a decision is taken, then a full treatment course should still be completed.

Cytomegalovirus (CMV) can be transmitted vertically from mother to fetus but also through infected blood products or organs post-transplantation. In children with normal immune function, CMV infection is often asymptomatic. In the immunocompromised host, there is a wide range of nonspecific presenting symptoms including fever, malaise, arthralgia, pyrexia and macular rash. Patients post-transplantation are at particular risk.

CMV pneumonitis presents with insidious increase in dyspnoea, nonproductive cough and evolving oxygen requirement. Fulminant respiratory failure requiring ventilator support due to CMV alone is rare; and, more commonly, results from dual pathology or multiple pulmonary infectious agents for example secondary bacterial pneumonia with or without septicaemia.

Diagnosis is made by:

- history and examination findings, and exclusion of other infections;
- typical chest radiography changes of bilateral diffuse infiltrates;
- CT showing patchy bilateral consolidation and nodular shadowing;
- detection of CMV antigen in peripheral blood mononuclear cells;
- possibly, the presence of giant cells in BAL;
- PCR from blood, urine and or BAL specimens; and
- transbronchial or open-lung biopsy specimens can be stained and cultured for CMV.

In children with established CMV pneumonitis, intravenous ganciclovir is the treatment of choice. If ganciclovir resistance is suspected or if there is no clinical response, then foscarnet or cidofovir can be used as alternatives.

Neutrophil suppression by treatment drugs increases susceptibility to fungal infections; therefore, fungal prophylaxis should be considered. Children receiving stem cell or solid-organ transplantation who are at high risk of CMV infection (*e.g.* a CMV-negative child receiving a CMV-positive graft) may benefit from ganciclovir prophylaxis.

Protocols vary between centres, and by clinical situation.

Pneumocystis jiroveci , formerly known as *Pneumocystis carinii*, was originally misclassified as a fungus but is now known to be a protozoan; although the nomenclature has changed, the term "*P. carinii* pneumonia" (PCP) is still used. It is highly prevalent in the environment and infection is caused by inhalation of airborne cysts. In immunocompromised children, manifestations of infection can be slow and subtle with increasing signs and symptoms over several weeks. Patients with T-cell deficiency are particularly at risk (*e.g.* post-transplantation, severe combined immunodeficiency (SCID) and HIV infection).

Diagnosis is made as follows.

- History and examination findings are intermittent fever, dry cough and dyspnoea with weight loss. Hypoxia is a classic feature of *P. jiroveci* pneumonitis along with tachypnoea. Poor adherence to or prescription failure of prophylactic co-trimoxazole should always raise PCP as a differential diagnosis.
- Chest radiography findings include increased bilateral interstitial and alveolar markings. HRCT may only add a picture of ground-glass opacification and therefore is not always necessary, given the increased radiation exposure.
- Bronchoscopy with BAL if often diagnostic: cytology reveals characteristic foamy macrophages and casts with low neutrophilia suggestive of minimal inflammation. Lung biopsy is rarely required unless there is treatment failure.

High-dose intravenous co-trimoxazole is recommended and the treatment course will depend on clinical response. Pentamidine is an alternative should co-trimoxazole fail. Concomitant use of pulsed high-dose corticosteroids can expedite recovery as seen in adults with HIV; however, they can cause deterioration if there is co-infection with CMV. Milder disease may respond to treatment with combined oral antimicrobials such as clindamycin with primaquine.

Tuberculosis All children in high-risk groups are susceptible to pulmonary TB infection and subsequent disease. Risk factors include: close domiciliary contacts with others who have open disease; travel to or from areas of high TB incidence; children <2 years with relatively naïve immune memory; and those infants of HIV-infected mothers or those with some congenital immunodeficiencies (particularly SCID, CGD and defects of innate immunity). Patients with these primary immunodeficiencies and infants with confirmed HIV should not be vaccinated with bacille Calmette–Guérin (BCG).

Diagnosis is made as follows.

- History and examination findings: suspected contact with index case, weight loss, chronic cough, lethargy, pyrexia, night sweats and peripheral lymphadenopathy. History of BCG vaccination and scar should be noted.
- Gastric aspirates, and Mantoux and QuantiFERON (Qiagen, Hilden, Germany) tests can all be used to focus the diagnosis. Use local age-appropriate guidelines.
- Bronchoscopy with BAL permits staining and culture for alcohol- and acid-fast bacilli.
- Complications include: endobronchial lesions causing airway obstruction, pleural effusion, miliary disease with haematogenous spread, spinal lesions and meningitis.
- Typical chest radiography changes are hilar lymphadenopathy, calcification of lymph nodes, consolidation, atelectasis, effusions and miliary shadows. All of the changes noted on chest radiography, including cavitations in reactivation or more advanced disease in adolescents, can be seen by HRCT.

Diagnostic and treatment guidelines will differ geographically depending on strains and population mix. Four oral drugs are conventionally used for uncomplicated TB treatment: rifampicin, isoniazid, pyrazinamide and ethambutol. Adherence can be problematic as treatment courses generally last for 6 months (all four drugs for

the first 2 months followed by rifampicin and isoniazid for the remaining 4 months). Support from specialist nursing teams in the community with regular outpatient follow-up is vital to ensure correct and complete eradication. A diagnosis of multidrug resistance to rifampicin and isoniazid (multidrug-resistant TB) requires specialist advice on treatment. Ethambutol can rarely cause reversible ocular toxicity; therefore, ophthalmology screening and titration of drug doses is recommended.

Differential diagnosis

This will depend upon primary diagnosis, but the following must be considered.

- Infiltration by disease process, as in lymphoma and leukaemia
- Radiation pneumonitis
- Drug-induced inflammation and fibrosis
- Adult respiratory distress syndrome
- Lymphoid interstitial pneumonitis in HIV infection
- Pulmonary embolism
- Alveolar haemorrhage
- Graft-*versus*-host disease
- Post-transplant lymphoproliferative disease
- Alveolar proteinosis
- Acute chest syndrome in sickle cell disease

Long-term sequelae and follow-up

Immunocompromised children are susceptible to chronic, progressive damage of the lung parenchyma and airways from both infectious and noninfectious factors. Physiological monitoring (*i.e.* spirometry), bronchodilator reversibility, transfer factor measurement and polysomnography can provide objective information about the clinical course and guide supportive management. Echocardiography to assess pulmonary hypertension and dual-energy X-ray absorptiometry (DEXA) scans for measurement of bone density in children who are malnourished or have been on long-term corticosteroids should also be considered.

Examples of long-term sequelae are:

- scoliosis, thoracic growth arrest and crush fractures of the vertebrae;
- restrictive lung function defects;
- obliterative bronchiolitis;
- pulmonary fibrosis and traction bronchiectasis;
- pulmonary hypertension;
- pulmonary veno-occlusive disease; and
- pulmonary infarcts after recurrent acute chest syndrome in sickle cell disease.

Conclusion

Paediatric pulmonologists should have a good understanding of the systemic and pulmonary manifestations of both infectious and noninfectious disease processes in the immunocompromised child. Consultation with specialist colleagues in related disciplines will permit a holistic and effective approach to each individual patient's needs.

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Non-CF bronchiectasis

Elif Dagli

In 1819, Laennec first described the finding of ectatic bronchi in pathological specimens. Since then, bronchiectasis has been a morphological term used to describe dilatation of the airways, supported by radiological and clinical evidence. Dilated airways are often manifested with a thickened wall, bacterial colonisation and destruction of the surrounding tissue due to excessive inflammation.

Epidemiology

Non-CF bronchiectasis (NCFB) is still an important cause of chronic suppurative lung disease in low-income countries and among disadvantaged populations of high-income countries. A decline in prevalence has been noted since the 1950s in high-income countries with improved sanitation, nutrition, vaccination and use of early antibiotics. However, the ability to recognise bronchiectasis improved with novel imaging techniques has renewed the interest in this clinical condition globally.

Key points

- The diagnosis of non-CF bronchiectasis may be delayed as chronic wet cough can be misdiagnosed as other respiratory diseases.
- HRCT scanning is necessary as chest radiography is not sensitive for detecting early disease.
- Prognosis has been related to the extent of disease and the type of bronchiectasis.
- Treatment is based on optimising airway clearance techniques and intermittent courses of antibiotics for pulmonary exacerbations.

Pathophysiology

Bronchiectasis is categorised into three main phenotypes according to the shape of the dilatation:

- tubular,
- varicose,
- cystic.

This classification describes the progression of the disease without providing information about aetiology. The aetiology of NCFB is variable, but the common pathophysiological mechanism contains infection, inflammation and tissue damage.

The airway excessive inflammatory response triggered by bacterial burden may result in an increased production of proinflammatory cytokines and uncontrolled activation of effector cells.

Aetiology

An underlying cause for bronchiectasis cannot be determined in all patients. Improvements in diagnostic techniques, and facilities for more subtle immunological abnormalities and primary ciliary dyskinesia have decreased the proportion of idiopathic patients. Nevertheless, the prevalence of idiopathic cases in different series ranges from 17% to 40% depending on the facilities.

The period between the first symptom and diagnosis is usually too long to prove

causality in most clinical series. Among the identified aetiologies, severe childhood infections (measles, pertussis, adenovirus and TB), primary ciliary dyskenesia, α_1-antitrypsin (AAT) deficiency, atypical CF, immune deficiencies and congenital anomalies have been recognised. Missed opportunities such as undertreated asthma and undiagnosed foreign body aspirations may commonly be reported. Aspiration and gastro-oesophageal reflux, collagen vascular disorders and other conditions, such as sarcoidosis, Young syndrome, Mounier-Kuhn syndrome, Ehler-Danlos syndrome, Marfan syndrome and yellow nail syndrome, are less frequently reported aetiologies.

In affluent countries, primary immunodeficiency remains the most common cause accounting for 20–39% of paediatric bronchiectasis (table 1), whereas in non-affluent countries bronchiectasis as a result of past infection is much more common.

Missed diagnosis CF may be an underlying cause. 20% of patients with NCFB had diagnosis of CF after a comprehensive analysis in a clinical series. All patients with apparent NCFB should have comprehensive analysis to detect cystic fibrosis transmenbrane conductance regulator (CFTR) mutations.

Table 1. Immunodeficiencies usually identified in patients with bronchiectasis

Agammaglobulinaemia
Common variable immunodeficiency
IgA deficiency
Selective antibody deficiency
Severe combined immunodeficiency
TAP deficiency
Ataxia telangiectasia
Hyper-IgE syndrome
Cartilage-hair hypoplasia
Chronic granulomatous disease

TAP: transporter associated with antigen presentation.

Symptoms

Cough is the primary presenting symptom followed by sputum production, dyspnoea and wheeze. The most common reason for referral was reported as recurrent chest infection. Recurrent otitis media, failure to thrive, gastro-oesophageal reflux, rhinitis from neonatal period, exercise intolerance and haemoptysis were among other reasons for admission to a special care centre.

The distribution of bronchiectasis within the lung fields was not found to be correlated with the underlying aetiology. However, in most series localisation was in the middle and lower lobes.

Microbiology

Sputum culture is standard in evaluating airway colonisation and infection in NCFB. If sputum cannot be produced spontaneously, sputum induction could be used as an alternative. The most common bacterial isolates are non-typeable *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Moraxella catarrhalis*. Colonisation with *P. aeruginosa* is associated with more severe bronchiectasis and a worse prognosis as demonstrated by physiological and radiographical studies.

Diagnosis

The possibility of bronchiectasis must be considered under the following clinical conditions:

- chronic moist or productive cough, lasting longer than 8 weeks,
- asthma unresponsive to treatment,
- incomplete resolution of pneumonia after treatment or recurrent pneumonia,
- persistent and unexplained lung crackles,
- respiratory symptoms in children with structural or functional disorders of the oesophagus and upper respiratory tract,
- haemoptysis.

Imaging

As chest radiograph findings and HRCT scans of the chest show poor agreement,

a normal chest radiograph cannot exclude bronchiectasis in a symptomatic child.

Before the development of HRCT scans, diagnosis was made by bronchograms using contrast material to map the airways. When CT appeared as a diagnostic tool it replaced bronchography as the "gold standard" for the diagnosis of bronchiectasis. At present, chest HRCT is the gold standard for diagnosis with a sensitivity of 97%. Most paediatric studies report bronchiectasis as a multilobar disease.

The Bhalla scoring system is generally used for evaluation of the severity of bronchiectasis by CT. Bronchiectasis is present when the internal luminal diameter is slightly greater than the adjacent blood vessel. Peribronchial thickening is present when the wall thickness is equal to or larger than the diameter of the adjacent vessel.

Evaluating the extent of mucus plugging, bronchiectasis, the presence of abscesses or sacculation, the generation of bronchial divisions, the presence of emphysema, collapse, and/or consolidation can be made during further assessment.

MRI is a new method used in the diagnosis of NCFB. Chest MRI was found to be equivalent to HRCT in determining the extent of lung disease in children with non-CF lung disease. The findings support the use of chest MRI as an alternative to HRCT in diagnostic pathways for paediatric chronic lung disorders.

A sweat test must be performed in all patients with bronchiectasis and repeated in the case of doubt. Immune function test, such as serum Ig, IgG subclasses, specific antibody levels to vaccinations, T- and B-cell lymphocyte subsets, a Mantoux test and HIV detection, tests for primary ciliary dyskinesia in the form of nasal brushing to examine cilial motility under light microscopy and ultrastructure under electron microscopy, tests for aspiration contrast study of swallowing, and oesophageal pH studies may be performed to investigate underlying aetiology.

Spirometry does not provide diagnostic information but may serve as a marker of progression; however, it is not sensitive at detecting early bronchiectatic structural lung damage.

A study that investigated clinical, radiological and laboratory features of children with NCFB reported a significant correlation between HRCT severity scores and symptoms, FEV_1, sputum interleukin (IL)-8 and tumour necrosis factor-α levels proving ongoing inflammation.

The pulmonary function of children with NCFB declines significantly over time, despite treatment. Aetiology has a significant impact on severity which may indicate an opportunity to target screening and treatments.

Treatment

There is no evidence-based consensus on the treatment of NCFB. Management recommendations are mostly based on evidence extrapolated from trials in CF in high-income countries.

There are some general therapeutic recommendations for NCFB patients as follows.

- Chest physiotherapy and exercise are essential for airway clearance.
- Annual influenza and 5-yearly pneumococcal vaccinations should be given.
- The use of inhaled steroids remains controversial, however, cessation of inhaled steroids with bronchial hyperreactivity was reported to increase bronchial hyperresponsiveness and decrease in neutrophil apoptosis.
- Prompt and effective antibiotic use is essential in acute infectious exacerbations, increase in wheeze, breathlessness and sputum purulence. Antibiotic therapy should be prescribed based on bacterial cultures and sensitivity.

There is no evidence for the use of carbocysteine, mannitol, leukotriene receptor antagonists, anti-inflammatory drugs and methylxanthines. However, some beneficial effects on lung function were

reported of long-term, oral, low-dose azithromycin use. Azithromycin also reduced bronchoalveolar lavage neutrophilia and interleukin-8 mRNA.

Children with NCFB will require inpatient treatment for the following:

- increased respiratory rate and increased work of breathing,
- circulatory or respiratory failure,
- fever (a body temperature >38°C),
- no oral intake,
- infection not controlled with oral antibiotics.

Surgery

Surgery is indicated in patients with mild bronchiectasis confined to resectable limits who are unresponsive to medical treatment, or in patients with severe tissue damage causing threat to the intact part of the lung. Surgery has been performed in fewer cases as the diagnosis is made earlier and the medical treatment improves.

There are few data about long-term results of medical and surgical treatment. Nevertheless, correctly chosen cases may benefit from surgery. A study on 19 cases of bilateral surgical resection, six cases of complete pneumonectomy, 165 cases of complete resection and 11 cases of incomplete resection, with mean age of 12.3 years, reported a perfect outcome in 73.3% of patients.

Lung transplantation

- Lung transplantation might only be an option in patients with advanced lung disease and declining lung function.
- Comorbidities of advanced bronchiectasis should be detected and treated before referral for transplantation, as the underlying disease may cause morbidity after surgery.
- Patients with CF and NCFB generally have a good outcome following lung transplantation.
- Management of infection is a key issue both pre- and post-lung transplantation.

Prognosis

Long-term consequences of childhood bronchiectasis have been recently documented. Many reports, regardless of analysis strategy, have shown that children with bronchiectasis have significant airway obstruction which deteriorates over time. In one study, FEV_1 was reported to have declined by a mean of 1.6% predicted per year.

Patients with NCFB may have complications of the disease which may contribute negatively to the prognosis.

NCFB patients have been found to have disturbed sleep associated with severity of disease. Night-time symptoms and hypoxaemia during sleep may affect sleep quality in children with bronchiectasis. Poor sleep quality may impair growth, learning and emotional development of children. Patients with bronchiectasis who snored had poorer sleep quality and patients with wheezing had a significantly higher rate of snoring.

Other long-term outcomes of childhood bronchiectasis include impaired left ventricular diastolic functions and osteopenia. Osteopenia is reported to be more common in children with NCFB compared to controls and the risk of osteoporosis and osteopenia increases with age.

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Pleural infection, necrotising pneumonia and lung abscess

Fernando M. de Benedictis, Chiara Azzari and Filippo Bernardi

Pleural infection, necrotising pneumonia and lung abscess are serious conditions in children and deserve a systematic, multidisciplinary approach.

Pleural infection

In children, the presence of pleural fluid collection is usually the consequence of underlying pneumonia. Pleural infection is a continuum, but classically it has been divided into three stages according to the evolution of the inflammatory process: exudative (simple parapneumonic effusion), fibropurulent (complicated parapneumonic effusion) and, eventually, overt pus in the pleural space (empyema). A simple parapneumonic effusion (PPE) is present in up to 40% of community-acquired pneumonia (CAP) and more than half of cases may complicate further. In our setting, the term of empyema is used generically to describe an advanced stage of PPE.

Key points

- The incidence of pleural empyema is increasing in many countries.
- The most common pathogens associated with empyema, necrotising pneumonia and lung abscess are *S. pneumoniae* and *S. aureus*.
- Chest CT is unnecessary for most cases of complicated pneumonia and should be considered in selected cases.
- Therapeutic choices should be evaluated individually and shared in a multidisciplinary team.
- Antibiotics remain the mainstay of treatment.
- Chest drain with fibrinolysis is the preferred primary therapy in empyema; VATS should be reserved for use in patients refractory to medical treatment.
- The long-term outcome for children with complicated pneumonia and no predisposing conditions is usually good.

Evidence suggests that the incidence of pleural empyema has increased in many countries over the past few years. The reasons for this dramatic increase are not known, but possibilities include changing bacterial resistance and virulence, introduction of the pneumococcal vaccination, adjustments to primary care antibiotic prescribing practices and referral patterns.

Diagnosis

Clinical features of empyema can closely resemble those of an uncomplicated pneumonia, but the possibility of a pleural complication should be considered especially in children who remain pyrexial or unwell 48 h after starting antibiotic therapy. Judicious use of appropriate investigations can clarify what is often a difficult clinical diagnosis.

Imaging studies may help to confirm the clinical suspicion and to better follow the evolution of the infectious process.

Chest radiographs are usually the first investigation to confirm the presence of PPE. Early signs include blunting of the

costophrenic angle and a rim of fluid ascending the lateral chest wall (meniscus sign) (fig. 1). Large effusions may appear as complete "white out" of the lung field, making it impossible to differentiate between pleural fluid and consolidated lung. Lateral chest radiographs are not necessary in most cases.

Chest ultrasound scans are critical in the diagnosis of PPE, especially as they do not involve radiation and sedation is not necessary. Although it cannot reliably establish the stage of pleural infection, it can differentiate pleural fluid from consolidated lung in children with complete white out of the lung field, estimate the size of the effusion, reveal fibrinous septations and assess loculation of fluid. It can also be used to guide chest drain insertion and assess treatment response.

Chest CT scans do not appear able to reliably distinguish the stage of pleural collection and predict the outcome of empyema. While unnecessary for most cases of paediatric empyema, CT scans should be considered when there is concern that infection is not the underlying cause (*i.e.* blood-stained pleural fluid or tumours) or when clinical improvement is not obtained with appropriate treatment (fig. 2). Many surgeons will require that a CT be performed before surgical intervention in order to delineate the anatomy further.

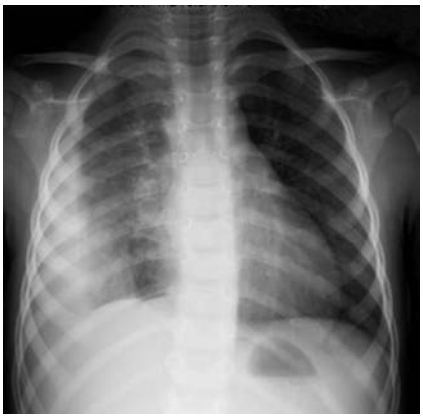

Figure 1. Pleural effusion: blunting of the right costophrenic angle and a rim of fluid ascending the lateral chest wall.

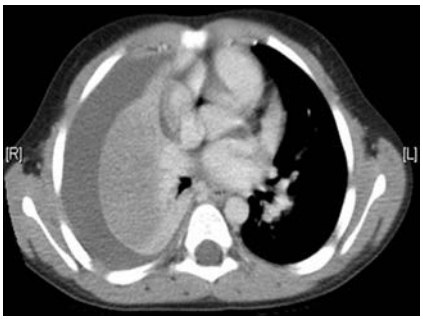

Figure 2. Empyema: consistent amount of infected fluid in the right pleural space and a totally collapsed right lung.

Laboratory

Blood Acute reactants such as white cell count, C-reactive protein, erythrocyte sedimentation rate and procalcitonin are unhelpful in distinguishing bacterial from viral pneumonia. However, an initial evaluation of acute reactants should be obtained to provide supportive evidence for an infective aetiology of PPE. Serial measurements can be helpful in monitoring the progress.

Blood cultures should be obtained despite the low isolation rate in PPE (10–22%), as they may be positive when pleural fluid culture proves sterile.

Real-time PCR analysis of blood and respiratory specimens has become more widely available over the past years, enabling rapid identification of potential pathogens. This molecular technique appears to add diagnostic value and should always be considered for specific pathogens, if available, especially when cultures are negative.

Sputum Any available sputum should be sent for culture, as microbiology isolation is likely to represent the infecting organism from the lower airways. However, the low quality of specimens often obtained from children, and the inability to distinguish colonisation from infection of the respiratory

tract limit the usefulness of this analysis, the results of which should always be interpreted with caution.

Pleural fluid Although frequently sterile due to prior administration of antibiotics, any pleural fluid that is available should undergo biochemical, cytological and microbiological analysis including Gram stain, acid-fast bacilli stain, culture and antibiotic sensitivity testing. Molecular analysis by PCR of pleural fluid more than doubled the detection of pathogens causing empyema.

Other analysis In children, the immunochromatographic membrane test (Binax Now) for rapid detection of pneumococcal C polysaccharide antigens in urine showed false-positive results which make this test unhelpful for diagnostic purposes. Mantoux testing and microbiology for *Mycobacterium tuberculosis* should be performed if there is a predominance of lymphocytes in the pleural fluid or risk factors for TB are present.

Management

Despite the fact that empyema has been recognised for over 2000 years, its management in childhood remains controversial, mainly because of the paucity of evidence-based studies at this age. This has led to treatment being determined by personal experience and local availability of different therapeutic options.

The goals of treatment are sterilisation of the pleural cavity and drainage of excessive pleural fluid, in order to allow re-expansion of the lung and restoration of normal pleural fluid circulation. Since management is harder in those with an advanced organised empyema, prompt recognition and treatment remains important. Preferably, children with PPE should be transferred to a tertiary paediatric respiratory unit, particularly if the effusion is large or the child is unwell. The therapeutic choices should be evaluated individually and shared in a multidisciplinary team.

Treatment

Antibiotics There is undoubtedly a role for antibiotic treatment alone in children with mild PPE and no respiratory compromise. Indeed, most small PPE will respond to antibiotics without the need for further intervention. Decisions on empirical antibiotic therapy should be based on pneumonia treatment guidelines and take into consideration whether the infection was community or hospital acquired, local antibiotic resistance patterns, and whether the child has any underlying medical problems (*i.e.* CF or immunodeficiency). The choice of antibiotics should be modified accordingly once the causative pathogens and sensitivities are known. If culture results are negative, the adjustment may depend on the response of clinical and radiography parameters.

Given evidence from epidemiological studies, it is imperative that initial antibiotics provide good *Streptococcus pneumoniae* cover pending culture results. If there is radiological evidence of pneumatocoeles, adequate staphylococcal cover is required. Anaerobic cover should be added if the child is at risk of aspiration. A second- or third-generation cephalosporin (cefuroxime, cefotaxime or ceftriaxone), or amoxicillin-clavulanate are often used empirically intravenously. In areas where there is a high prevalence of methicillin-resistant *S. aureus*, clindamycin or a glycopeptide can be used as additional first-line agent. In children with known allergy to penicillin, clindamycin should be considered as the first-line antibiotic treatment.

Intravenous antibiotic therapy is usually continued until there is definite evidence of clinical improvement and resolving fever, or at least until the chest drain is removed. While there is no evidence to guide the duration of treatment, oral antibiotics, such as amoxicillin-clavulanate or a second-generation cephalosporin, are generally continued for 2–3 weeks following discharge.

Routine diagnostic thoracentesis is not recommended in children, unless there is a suspicion of a noninfectious aetiology. Unlike adults, biochemical analyses of pleural fluid (pH, glucose levels, proteins or lactate dehydrogenase) has not been shown to be of any value in the practical

management of children with pleural effusions. In addition, obtaining a sample of pleural fluid is technically challenging in children, requires sedation and results in a significantly higher re-intervention rate when compared to insertion of a pigtail catheter as a primary procedure.

Chest drain alone Following the introduction of appropriate antibiotics, the decision to proceed to drainage should take into consideration a number of factors including clinical and laboratory response to antibiotic therapy at 48–72 h and evidence of enlarging effusion on repeated ultrasound.

Development of respiratory compromise is an indication for drainage. While chest drain insertion alone can be effective in children with empyema, the length of stay (LOS) in hospital is prolonged (20 *versus* 10.7 days) and there is a higher failure rate (23.6% *versus* 9.4%) compared to chest drain with intrapleural fibrinolytics.

Chest drain plus intrapleural fibrinolytic agent The aim of instilling a fibrinolytic agent in the pleural cavity is to break down fibrin strands in order to improve drainage and re-establish pleural circulation. Numerous case series and a few randomised controlled trials on the use of intrapleural fibrinolytic therapy in childhood empyema have been published to date. They have used different agents, dosage schedules and treatment protocols, and there was a great diversity in the stage at which treatment was started. Not surprisingly, outcomes varied greatly.

Urokinase is actually the preferred fibrinolytic agent for the treatment of empyema. The most widely used dosage regimen is 40 000 units of urokinase in 40 mL of normal saline, or 10 000 units in 10 mL of normal saline for children <1 year of age, which is administered twice daily for 3 days. After instillation, the chest drain is clamped for 4 h and the child is encouraged to mobilise. The drain is then left on a suction pressure of -20 cmH_2O until the next dose. There is some evidence to suggest a potential advantage for smaller catheters in reducing the time of drainage, time until the patient became afebrile, and LOS.

Surgery The role of surgery in the management of childhood empyema is controversial. While surgery was previously reserved for cases of failed medical therapy, the advent of less invasive techniques has led to an increasing interest in surgery's potential role in primary treatment.

Video-assisted thoracoscopic surgery (VATS) achieves debridement of fibrinous material, breakdown of loculations and drainage of pus from the pleural cavity under direct vision. The more controversial area is the role of VATS *versus* chest drainage with intrapleural fibrinolysis in the primary management of empyema. In a systematic review of 67 studies published over a period of >20 years, primary operative therapy was associated with a lower LOS, time of drainage, time of antibiotic therapy, re-intervention rate and mortality rate compared with nonoperative treatment. However, the majority of these studies did not include treatment with fibrinolytics in addition to chest drainage.

Two prospective randomised trials have compared primary VATS to chest drain with intrapleural fibrinolysis, either urokinase or tissue plasminogen activator, in children. No difference between treatment groups was found in the main outcomes, but VATS cost significantly more. Current evidence suggests that chest drain with fibrinolysis is the preferred primary therapy in empyema, and that VATS should be reserved for failure of medical management. In clinical practice, the choice of one of these options is often conditioned by local experience and tradition.

Open thoracotomy enables removal of the thickened pleural rind and irrigation of the pleural cavity. Potential drawbacks include a large scar and the risk of wound infection, persistent air leaks and bleeding. Mini-thoracotomy involves a similar procedure through a small incision.

A number of retrospective studies have compared VATS to open thoracotomy for rescue treatment demonstrating less post-operative pain, a better cosmetic result and, in some cases, a shorter LOS.

Open thoracotomy procedures should, therefore, only be reserved for late presenting empyema with significant pleural fibrous rind.

Prognosis The prognosis in children with empyema is usually very good. Unlike adults, empyema in childhood is associated with a low mortality (<0.5%) with the majority of children eventually making a complete recovery. Follow-up studies have shown that chest radiography returns to normal in almost all patients by 6 months and that lung function returns to normal or shows only minor abnormalities long-term.

Pneumatoceles are generally complications of a staphylococcal pneumonic process and may be associated with empyema. They are more common in infants and young children. They usually regress spontaneously with the improvement of the pneumonic process, but sometimes they require surgical intervention when they become taut or infected, or when they break in the pleural cavity, thus inducing pneumothorax or pyopneumothorax.

Necrotising pneumonia

Necrotising pneumonia is a severe complication of CAP and is characterised by liquefaction and cavitation of lung tissue. In the last few years, increasing cases of necrotising pneumonia in previously healthy children have been reported with special emphasis on laboratory, pathology, radiology and clinical aspects. This increased incidence is probably due to a combination of improved recognition of necrotising pneumonia as a specific entity and heightened detection resulting from the use of CT scans in the evaluation of children with complicated pneumonia. However, the observed increase of necrotising pneumonia parallels that of complicated PPE observed in several nations over the past years. The necrotic process can occur at any lobe of the lung, but involvement of lower lobes is more frequent. The affected extent may be patchy, segmental, lobar or even an entire lung.

The pathogenetic mechanisms of necrotising pneumonia are not clear, but it is commonly believed that tissue necrosis occurs as a result of inflammatory response due to toxins produced by the invasive pathogen or the associated vasculitis with thrombotic occlusion of alveolar capillaries. The process may rapidly progress to tissue destruction and intraparenchymal bullae, even in the presence of proper antibiotic therapy. At such stage, the process may further extend to the pleural space and create a bronchopleural fistula, especially when the necrotic segment is adjacent to the pleural surface. When multiple necrotic foci are involved, they may coalesce and a large cavity can result.

Clinical features Children with necrotising pneumonia usually present with symptoms of severe pneumonia, such as high fever, cough, and tachypnoea, lasting for several days. Necrotising pneumonia should be suspected when a patient with pneumonia develops progressive respiratory distress, haemoptysis or septic shock despite appropriate antibiotic treatment. Pleural effusion is often detectable at physical examination.

Imaging The diagnosis of necrotising pneumonia can be detected by chest radiography, but the presence of pleural effusion may obscure the underlying lung process. Chest radiography underestimates the degree of parenchymal destruction, therefore contrast-enhanced CT may be needed for a more definitive diagnosis when necrotising pneumonia is suspected. Radiographic criteria for necrotising pneumonia include the loss of the normal lung architecture and the presence of areas of decreased parenchymal enhancement, representing liquefaction, that are progressively replaced by multiple small air or fluid filled cavities. Transition from liquefaction to cavitation may progress rapidly within 48 h. Although CT offers the advantage of being able to identify parenchymal complications over chest radiography (fig. 3), clinical management is not changed in the majority of cases and routine use of CT is therefore not justified.

Abnormal laboratory findings of increased acute reactants, low haemoglobin level and hypoalbuminaemia are observed in many

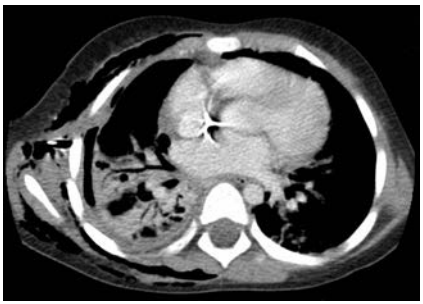

Figure 3. Necrotising pneumonia: multiple cavitary lesions and air bronchogram in the consolidated right upper lobe.

patients. The pleural fluid characteristics associated with necrotising pneumonia reflect those usually found in PPE.

Microbiology Like empyema, *S. pneumoniae* is the more frequent aetiological agent of necrotising pneumonia. *Mycoplasma pneumoniae* and *S. aureus* strains, often methicillin-resistant, producing cytotoxin Panton-Valentine leukocidin have been also involved in the genesis of necrotising pneumonia. Other bacteria less frequently reported include *S. pyogenes*, *S. viridans, Pseudomonas aeruginosa* and anaerobes. Almost 50% of the cases of necrotising pneumonia have no identified aetiological cause with common microbiological methods. However, new methods, such as PCR analysis, could potentially increase the diagnostic yield in necrotising pneumonia.

Treatment There is not a general agreement on the best therapeutic strategy for necrotising pneumonia, mainly because the frequent coexistence of empyema prevents uncoupling of the two conditions and the separate evaluation of their respective contribution to overall morbidity. Studies comparing the effect of different interventions (*i.e.* conservative *versus* surgical) on the evolution of necrotising pneumonia are unfortunately lacking, and there is an urgent need for these to be addressed. However, it should be borne in mind that, in children, parenchymal complications of pneumonia do not carry a particularly adverse prognosis and usually do not warrant specific intervention strategies beyond a prolonged course of antibiotics.

Antibiotics Unlike adults, exclusive treatment with high-dose antibiotics is frequently successful in children, with unexpected parenchymal conservation and lung re-expansion over time, even in cases of severe pulmonary involvement. As for empyema, the choice of initial antibiotics should be directed at broad coverage of commonly implicated pathogens and modified accordingly once the causative agent and sensitivities are known. Penicillins or cephalosporins may be administered initially, while clyndamycin or metronidazole can be added to cover possibly involved *S. aureus* or anaerobes.

A chest drain may be mandatory in cases of concomitant pleural effusion. Intrapleural fybrinolysis may potentially result in a risk in necrotising pneumonia, since the breakdown of the fibrinous seal in the pleura may favour the lack of air from necrotic peripheral areas of the lung.

Surgery VATS has been used successfully in children with necrotising pneumonia. It should be reserved for patients with associated empyema or to resolve bronchopleural fistulae that do not close with conservative treatment. Surgical resection of the lung should be reserved to particularly severe cases, bearing in mind potential complications of surgical intervention and the possible long-term impairment of pulmonary function.

Prognosis Long-term outcome for children with necrotising pneumonia is usually good. Follow-up chest radiography and, in a few cases, CT scan have shown almost complete normalisation of pulmonary parenchyma within months of hospitalisation. This pattern of improvement suggests that the lung damage caused by necrotising pneumonia in children is transient and that no or minimal functional sequelae are expected.

Lung abscess

A lung abscess is a thick walled cavity containing purulent material resulting from

suppuration and necrosis of the lung parenchyma. It is an uncommon paediatric condition, with a paucity of quality data in the literature.

Lung abscesses may be single or multiple and are classically divided into primary and secondary according with their appearance in previously well children or in those with predisposing comorbidities, such as significant neurocognitive disability, immunodeficiency, CF or congenital lung malformation (*i.e.* pulmonary sequestration). Lung abscesses may develop in any area of the lung, but are more frequent in the lower lobes.

A lung abscess may arise from the aspiration of infected fluid, aspiration of noninfected fluid which triggers a chemical reaction (*i.e.* gastric content), a primary bacterial infection of the lung, haematogenous spread of bacteria or spread of infection from a contiguous organ. The time course for progression from initial involvement to abscess formation is usually slow.

Clinical features Children may present for several days with a low grade cough and mild fever. Less commonly, chest pain, dyspnoea, sputum production and haemoptysis may be seen suddenly. The clinical history is important in revealing predisposing conditions, such as recurrent pulmonary aspiration of airway secretions, neurocognitive disability, immunodeficiency and proximal airway structural abnormalities. Physical examination may reveal normal chest auscultation or signs of consolidation.

Imaging Typically, the diagnosis of lung abscess is based on the chest radiograph, which will reveal a well circumscribed shadow containing an air–fluid level (fig. 4). Less frequently, multiple abscesses may be present. Distinction between parenchymal abnormalities and pleural collections is normally possible by ultrasound, but CT may be reserved for the occasional cases where there is unresolved doubt.

Microbiology More invasive procedures, aspiration and drainage, together with

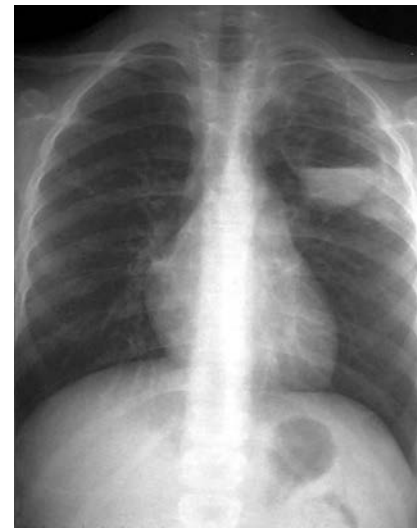

Figure 4. Lung abscess: well-circumscribed shadow containing an air–fluid level in the left upper lobe.

improved microbiological diagnostic techniques, such as PCR, have increased the yield of pathogens identified from abscess fluid samples. *S. aureus,* group B *Streptococci, Escherichia coli* and *Klebsiella pneumoniae* are the more common pathogens in primary abscesses and in young children. In older children, the likelihood of aspiration increases, and oral anaerobic bacteria (*Peptostreptococcus, Fusobacterium spp., etc.*) or mixed flora may be found. More rarely, fungi such as *Candida albicans* or *Aspergillus spp.* can cause lung abscess in children.

Treatment

Antibiotics Treatment with a course of systemic antibiotics will usually successfully treat a lung abscess. The choice and duration of antibiotic therapy will be guided by local experience, the type of abscess (primary or secondary), and the ability to isolate pathogenic organisms. At baseline therapy, antibiotics will cover *S. aureus*, streptococcal species and Gram-negative bacilli that are usually found in the upper respiratory tract. Treatment may include cephalosporins, vancomycin, clindamycin, aminoglycosides, quinolones and

carbapenems. In patients where anaerobic infection is suspected, metronidazole should be considered. Generally, a 2–3 week course of intravenous antibiotics is sufficient to induce clinical and radiological improvement of the lesion. Once the child has improved, the intravenous route may be replaced by oral antibiotics to complete a 4-week treatment course.

Interventional procedures and surgery Many centres will use ultrasound or a CT scan for interventional, image-guided aspiration and drainage of the abscess cavity with a percutaneously placed pigtail catheter for both diagnostic and therapeutic purposes. Thoracoscopic drainage of lung abscesses may be obtained concurrently with treatment of empyema. In children, the role of surgical therapy for lung abscess should be limited to a minority of patients who are refractory to medical treatment or who develop complications such as bronchopleural fistula.

Prognosis Complications of a lung abscess may include pneumothorax, bronchopleural fistula, lung compression and mediastinal shift with progressive respiratory compromise. The existence of underlying conditions will influence the prognosis. The long-term outcome of lung abscesses in immunocompetent children is favourable. Mortality rate is estimated about 5%, predominantly in children with predisposing conditions.

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Bacterial bronchitis with chronic wet cough

Petr Pohunek and Tamara Svobodová

Protracted bacterial bronchitis (PBB) is a clinical condition characterised by isolated wet cough lasting for >4 weeks with absence of pointers suggestive of an alternative specific cause of cough, which resolves fully following appropriate prolonged antibiotic treatment. It should be differentiated from bronchiectasis and chronic suppurative lung disease (CSLD), which presents with excessively prolonged moist cough with persistent purulent secretions.

Key points

- Bacterial bronchitis should be suspected in a child with protracted wet cough.
- Detailed differential diagnostic protocol aims to exclude other underlying causative factors.
- Treatment should target the most frequent pathogens.
- Protracted bacterial bronchitis can be a precursor of chronic suppurative lung disease and bronchiectasis, if left untreated.
- If detected early and adequately treated, prognosis of protracted bacterial bronchitis is good.

Epidemiology

The general epidemiology of PBB is not known. In a study of 108 children with chronic wet cough PBB was the final diagnosis in 39.8% of patients. In a recent study analysing 197 children with protracted wet coughing, bacterial cultures were positive in 91 (46%) children. More than half of the study patients (55%) were aged 0–3 years, 36% were aged 3–7 years and only 9% were >7 years of age.

Aetiology

Among the positive bacterial cultures the leading pathogen is usually nontypable *Haemophilus influenzae* (~50%), followed by *Streptococcus pneumoniae* and *Moraxella catarrhalis* (~20% each). *Staphylococcus aureus* is less common with a frequency of ~12%. Combinations of more than one pathogen at the same time have been described. A recent study that compared serotypes of *S. pneumoniae* in children with bacterial bronchitis from the UK with those from Greece found an important impact of vaccination. In children vaccinated with a pneumococcal vaccine they found a trend to serotype replacement with more frequent presence of serotypes not included in the vaccine. Infection by *Pseudomonas aeruginosa* or other more difficult pathogens does not occur in PBB. When these pathogens are found in a child with chronic cough, the search for underlying aetiology should be actively undertaken (*e.g.* CF, primary ciliary dyskinesia and immunodeficiency).

Risk factors

The main risk factors for developing PBB are as follows.

Impaired mucociliary clearance after viral respiratory infections Lack of convalescence after viral bronchitis may lead to impaired airway clearance (secondary disorders of ciliary epithelium and persistent

inflammation of airway mucosa) and facilitation of bacterial infection.

Airway malacia Tracheomalacia/bronchomalacia has been detected in children with PBB more frequently than in the general population. In one study evaluating children with PBB aged <60 months the authors found laryngomalacia or tracheomalacia in 74%. Another study found tracheomalacia in 30% of young children with PBB. How far the malacia is a causative factor or to what extent instability of the airways may be secondary to prolonged infection and protracted coughing remains to be speculated.

Immunodeficiency Disorders of humoral immunity can be associated with insufficient protection and may facilitate bacterial growth in the airways.

Environmental burden An important environmental risk for the development of PBB is environmental tobacco smoke (ETS). In many countries the frequency of smoking in families with children is as high as 40–50%. Local heating by burning wood or coal has been described as a significant risk factor for the paediatric airways.

Industrial pollution Industrial pollution has been found to be a risk factor for respiratory infections in children. The most important part of industrial emissions is particulate matter (PM). The concentration of PM may increase under local adverse climatic conditions. For respiratory health, particles with a 50% cut-off aerodynamic diameter of 10 μm (PM_{10}) or smaller play a major role as these particles are respirable and can easily reach the lower airways. A correlation of PM exposure with increased respiratory symptoms has been repeatedly documented.

Pathogenesis

PBB usually develops as a result of an insult that suppresses the local mechanism of the airway defence. There may be initial acute viral bronchitis followed by inappropriate regrowth of damaged cilia, healing of airway mucosa, and re-establishment of a proper mucosal barrier. With some risk factors this may start gradually and be based on continuous damage of the mucosa (*e.g.* recurrent aspiration, environmental triggers or gastro-oesophageal reflux) with no apparent initial acute event. Additionally, high presence of neutrophils with their enzymatic activity enhances the process. In various studies the fraction of neutrophils in differential count from bronchoalveolar lavage fluid (BALF) was as high as 90%. Uncontrolled bacterial infection, mucus retention and high proteolytic activity of the neutrophils can lead to CSLD, damage to the bronchial wall and gradual development of bronchiectasis. If diagnosed early, this can be interrupted by appropriate treatment and even the development of mild bronchiectasis can be reversed. Changes in the properties of some of the pathogens also contribute to chronicity. Microbes can regulate their gene expression based on the environment and signalling within the bacterial population and develop protective mechanisms that suppress host defence mechanisms. Biofilm formation by some pathogens (*e.g.* nontypable *H. influenzae* and *P. aeruginosa*) is well documented. Bacteria can also cleave Ig and, thus, suppress specific immune response.

Symptoms

The leading symptom of bacterial bronchitis is wet cough with or without sputum production. Generally, the wet sound of the coughing suggests an intrabronchial content of secretions of various quality and consistency. The ability to produce sputum is age and training dependent. Infants and very young children are generally not able to spit out sputum; however, this can be successfully trained by a physiotherapist as early as in the third year of life. Coughing is usually present both during the day and the night, which is often more pronounced in the mornings as secretions tend to accumulate during the night. Physical exercise can also exacerbate coughing. Wheezing is not a typical symptom. In bacterial bronchitis the patient may wheeze on occasion based on obstruction by mucus; this is usually only transient and

variable and changes after coughing. Recurrent wheeze may signal bronchial hyperresponsiveness and should raise suspicion of asthma.

Fever is generally absent in PBB. The infection is mostly limited to the bronchial tree and does not trigger general systemic inflammatory response. Fever and elevation of acute phase proteins may signal an acute exacerbation or more severe affection of lung parenchyma.

Diagnosis

The main task in early detection of PBB lies with a general practitioner (GP). Children with protracted wet cough should be noticed early in the general practice. An important initial task for the GP is to map and properly characterise the symptoms. Basic differential blood count, C-reactive protein and erythrocyte sedimentation rate belong to standard first-line investigations. GPs should also trace possible environmental risk, such as smoking, local heating or other local risk in the household.

Detailed investigation is needed, mainly in children with repeated episodes of PBB. In further investigation algorithm, a plain chest radiograph is mandatory. A sweat test excludes CF and assessment of clinical risks for primary ciliary dyskinesia helps to exclude this condition. Pulmonary function testing using basic forced expiration test, with recordings of flow–volume loop, is then performed. Forced expiration testing can even be performed with children as young as 3 years of age if properly trained. Reversibility testing should be performed using an inhaled rapid acting β_2-agonist.

Microbiological testing of sputum is a crucial step. If the child is able to properly expectorate, the sputum should be sent for cultures and microscopic evaluation. This should be done before any antibiotics are administered. If the child is already treated, the antibiotics should be stopped for at least 48 h. In a child not able to expectorate, deep suctioning from the pyriforms in the morning or after physiotherapy or the cough swab may help.

The most reliable method of microbiological sampling with high yield is bronchoscopy. It is not indicated in children with a single episode of PBB. Even in children with recurrent PBB it is usually not necessary if they expectorate sufficiently. Bronchoscopy may be considered in cases with inadequate expectoration or in those with other suspected underlying pathology. Flexible bronchoscopy is best performed with preserved spontaneous breathing. It allows visual assessment of airways anatomy, excluding aspirated foreign body. It also helps to assess the level of mucosal inflammation, observe stability of the airways during breathing and coughing and find possible tracheomalacia/bronchomalacia. Removing mucus plugs, providing appropriate bronchial toilette and direct sampling of mucus specimens are essential. In addition, a standardised bronchoalveolar lavage should be performed and a specimen of BALF sent for microbiology, differential cytology and staining for lipid-laden macrophages. Anaerobic and mycotic cultures should also be considered.

Additional examinations must include detailed ENT assessment to exclude focal infection in the upper airways area (adenoids and sinuses).

Immunological testing should mainly include testing of humoral immunity, including concentration of vaccination-specific antibodies and total serum IgE. Allergic sensitisation should be tested in context with symptoms and history either by skin prick tests or specific IgE antibodies.

When there is suspicion of a development of bronchiectasis, the diagnostic method of choice is HRCT. Current protocols are fast and use low-dose techniques. Therefore, they are considered safe and can even be used in young children.

Testing of older school children and adolescents for active smoking using cotinine in urine or carbon monoxide in exhaled breath can reveal another contributing factor.

Management and prognosis

Uncomplicated PBB is easily treated; however, untreated persistent bacterial infection and accompanying inflammation is associated with development of chronic suppurative lung disease and bronchiectasis. In most cases the treatment is based on expected or confirmed microbial aetiology and broad-spectrum antibiotics targeted against *Haemophillus* spp., *Pneumococcus* spp. or *Moraxella* spp. are used. As *Haemophillus* spp. and *M. catarrhalis* usually produce penicilinase, this should be respected in the selection of antibiotics. Generally, there is an agreement that uncomplicated PBB should resolve after a 2-week course of an appropriate antibiotic. This was also shown in a randomised controlled trial analysing a 2-week course of amoxycilline–clavulanate against placebo. Children in the active arm showed a significantly higher resolution rate (48%) than children in the placebo arm.

The benefit of antibiotics has also been shown in a systematic review that found the use of inhaled corticosteroids to be justified in limited situations. There are no consistent data available on the effect of physiotherapy in PBB. It is certainly reasonable to employ at least some basic techniques of airway clearance, especially in young children.

Even though the effect of antibiotic treatment is usually very good, a rather high frequency of relapse (up to 70%) has been described, with good effect when the antibiotic course is repeated. In a child with high frequency of recurrence, a prolonged course of antibiotics may be considered. If an underlying condition is found, it is critical to treat this pathology together with the treatment of infection.

Conclusion

PBB with chronic wet cough is a diagnosis that requires attention and should be suspected in children with protracted coughing. Appropriate diagnosis and early institution of proper management should lead to complete resolution and prevention of severe sequelae, such as chronic suppurative lung disease or bronchiectasis.

Acknowledgements

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Pulmonary TB, latent TB, and *in vivo* and *in vitro* tests

Zorica Zivković and James Paton

Burden of disease in children

TB in children has been called a "hidden epidemic". Poor ascertainment and reporting of cases in children have hindered accurate estimates of the global burden of TB in children, but in 2011 the World Health Organization (WHO) estimated there were 490 000 cases of TB in children aged <15 years with 64 000 deaths. Children are also susceptible to the dual epidemics of TB/HIV with HIV-infected children at 20 times greater risk of TB disease than HIV-uninfected children.

The reasons for underestimating TB in children include:

- children with TB are generally not infectious: at <10 years of age children develop pauci-bacillary types of TB and are usually not infectious compared to adults with caseating pulmonary TB;
- difficulties in confirming a case of childhood TB: because of the inability to produce sputum and the low concentration of organisms in children, <30% of paediatric cases will have bacteriological confirmation of TB;
- lack of awareness of multidrug-resistant (MDR)-TB in adults and, more especially, in children.

Key points

- TB remains a major, but often unrecognised, cause of disease and death in children.
- Children with TB are generally not infectious.
- TB in children generally reflects active disease in the adult population.
- Treating TB in children is not straightforward.

In Europe, overall TB rates in children have been declining, and were 4.2 per 100 000 in 2009 although there is wide variation in rates both within and between countries.

Natural history in children

The natural history and presentation of *Mycobacterium tuberculosis* infection in children is different from adults, being strongly influenced by age and immune status. Children aged <4 years have a greater risk of developing clinical and radiographic complications shortly after infection, but will rarely present with reactivation of disease in adulthood. Teenagers develop forms of the disease more typical of adults.

M. tuberculosis infects almost all children *via* inhalation by the respiratory tract, usually from an infectious adult in their close environment. A number of factors influence the likelihood of infection including:

- intensity and duration of exposure to the infectious case,
- ability of the infectious case to cough and generate an infectious aerosol,
- virulence of the organism,
- age,
- innate and acquired immune defences of the child exposed.

In the pulmonary alveoli, *M. tuberculosis* organisms are ingested by alveolar

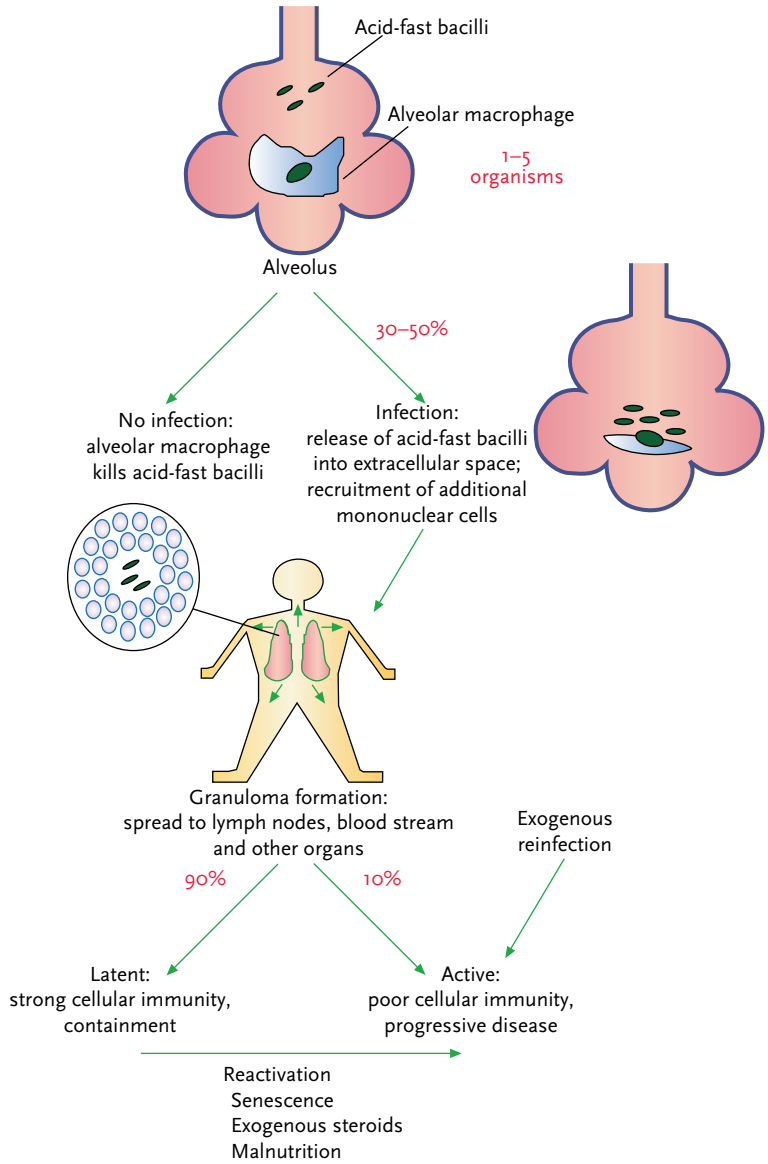

Figure 1. Outcomes following exposure to Mycobacterium tuberculosis. *The percentages in red are typical of outcomes in older children and adults. Reproduced from Manabe* et al. *(2000) with permission from the publisher.*

macrophages and may be killed without causing further problems (fig. 1).

The organisms that survive initiate a localised granulomatous inflammatory process in the mid to upper zones of the lung, the Gohn focus. In most cases, the centre of this focus undergoes caseous necrosis. *M. tuberculosis* bacilli, either free or within phagocytes, drain to the main regional, mediastinal lymph nodes (hilar, para-tracheal and sub-carinal), which also often caseate. Enlarged regional lymph nodes along with the Gohn focus and the local tuberculous lymphangitis constitute the primary complex. The enlarged regional lymph nodes can be seen in 50–70% of children on good quality plain radiographs.

From the regional lymph nodes, bacilli can enter the systemic circulation. Occult haematogenous spread can occur before the immune response contains the disease. The disseminated bacilli can then survive in target organs for long periods of time.

The immune response, marked by the development of a positive tuberculin skin test (TST), develops about 3–8 weeks after primary infection and it usually stops the multiplication of *M. tuberculosis*. The end of the asymptomatic incubation period and the development of an immune response may be marked by immune hypersensitivity reactions. These include nonspecific, self-limiting viral-like symptoms such as fever, or, more rarely, florid reactions such as erythema nodosum. In most cases the child will have no symptoms.

In the majority of children, the primary complex heals completely and the organisms are contained by the cell-mediated immune response within the tissues. In up to 50% of children, the regional lymph nodes calcify within 12–24 months indicating the disease is quiescent. But *M. tuberculosis* can persist in calcified lymph nodes and dormant organisms may reactivate to cause TB later in life.

Sometimes, following primary infection, a parenchymal lesion continues to enlarge and spread resulting in focal pneumonitis and pleural involvement (primary progressive TB).

Enlarged mediastinal lymph nodes do not usually cause problems but they can compress the airways producing ventilation disturbances and, occasionally, complete bronchial obstruction and distal atelectatic changes in the affected segment. If caseating lymph nodes liquefy, there may be local extension and distant haematogenous spread of *M. tuberculosis* organisms. If the lymph nodes are sub-carinal, infection can spread to adjacent structures such as the heart, causing pericarditis, or the oesophagus resulting in a tracheo-oesophageal fistula. Haematogenous spread seeds *M. tuberculosis* in others tissues and organs. Disseminated TB appears when multiple foci develop in the lungs or other organs.

The natural history of primary TB in children follows a typical time-course. In the vast majority, disease occurs within 2 years of primary exposure infection with the very young (0–4 year) and the immunocompromised being most at risk. Massive lympho-haematogenous dissemination leading to miliary or other disseminated disease is uncommon and occurs in 0.5–2% of cases usually between 3 and 39 months after lymph node involvement. Bone and joint TB develop later, usually a few years after infection.

Only a small proportion of children with TB develop post-primary TB, either due to reactivation or re-infection. Adult-type disease can follow recent primary infection in children aged >10 years, particularly girls around the age of menarche.

Age and risk of progression The risk of TB after infection in children varies with age (table 1). In children aged <2 years, the risk is as high as 50% with most disease occurring within 6 months of infection. With the onset of puberty, the risk rises again and there is a switch in disease phenotype to adult-type cavitary disease.

Sites of disease *Pulmonary TB* Most children with TB have pulmonary TB (fig. 2).

More than half of children with TB will have chest radiographic changes with no symptoms or clinical signs of disease and

Table 1. Age-specific risk of progress after primary infection in immunocompetent children

Age years	Risk of disease progression following exposure
<1	No disease: 50% Pulmonary disease (Ghon focus, lymph node or bronchial): 30–40% Tuberculous meningitis or miliary disease: 10–20%
1–2	No disease: 70–80% Pulmonary disease (Ghon focus, lymph node or bronchial): 10–20% Tuberculous meningitis or miliary disease: 2–5%
2–5	No disease: 95% Pulmonary disease (lymph node or bronchial): 5% Tuberculous meningitis or miliary disease: 0.5%
5–10	No disease: 98% Pulmonary disease (lymph node, bronchial effusion or adult type): 2% Tuberculous meningitis or miliary disease: <0.5%
>10	No disease: 80–90% Pulmonary disease: 10–20% Tuberculous meningitis or miliary disease: 0.5%

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are identified only through contact tracing. Infants have more intensive symptoms of TB, while school age children may have disease that is not clinically apparent. Adolescents develop adult-type TB and can present with parenchymal destruction and cavity formation. Such children will be sputum-smear positive and are able to transmit infection. Pleural effusions are rare in children aged <5 years and are most common in adolescent boys.

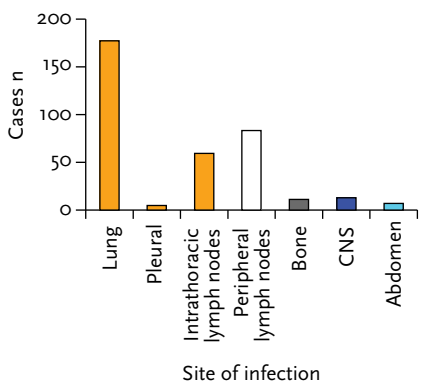

Figure 2. The different sites of infection in children with TB in the UK from 1988–1998. Orange bars signify pulmonary disease. CNS: central nervous system. Information from Balasegaram et al. *(2003).*

Extra-pulmonary TB in children develops by dissemination of *M. tuberculosis* through lymphatic and haematogenous spread with the development of foci in various organs.

Miliary TB characteristically occurs in immunocompromised and malnourished children with infants being the most vulnerable. Typical miliary changes on chest radiographs take 1–3 weeks to develop. The illness can progress rapidly and the prognosis is poor. TB meningitis is the most serious complication in childhood with a risk of significant long-term neurological seqeulae and death if diagnosis is delayed or treatment inadequate. Bone and joint TB is mainly mono-articular involving the spine, hip or knee.

Congenital TB: M. tuberculosis infection may be acquired before birth during intrauterine life, perinatally or post-natally. In a pregnant female with active TB, *M. tuberculosis* can be transmitted transplacentally from the blood stream of the mother to fetal blood. Once in the fetal circulation, the organisms spread by the umbilical veins to tissues and organs, mainly to the liver and spleen. Symptoms (failure to thrive, jaundice and hepatosplenomegaly) develop within a couple of weeks after birth.

A newborn infant may also acquire *M. tuberculosis* infection during delivery or soon after through the close contact with an infectious case, *e.g.* breast feeding mother. In this situation, nonspecific respiratory symptoms develop after 3–4 weeks. Chest radiography is not diagnostic and a TST may be negative.

Diagnosing TB

History and examination Children are usually evaluated for TB either after presenting with symptoms or signs suggestive of TB (passive case finding) or, most commonly, as a result of contact investigation or routine new entrant immigrant screening (active case finding). The clinical presentation is different between these two groups with children detected through active case finding often having either TB infection or TB disease in a very early phase.

History of contact Since children generally acquire TB following exposure to a sputum-positive case of pulmonary TB, a key piece of diagnostic information is a history of close contact with an infectious source case. The WHO defines close contact as living in the same household as or being in frequent contact with sputum smear-positive pulmonary TB cases. Cases of smear-negative TB that are sputum culture positive are also infectious but to a much lesser degree.

The infection risk from close household contact is greatest for infants and young children <5 years of age (table 1). Apart from age, other important risk factors for TB include HIV infection and severe malnutrition.

Symptoms and signs In children identified through active case finding who have radiographic changes of TB, more than half will have no symptoms or signs of disease.

For children with symptoms, well-defined symptoms of recent onset that are persistent and non-remitting are typical of TB. The frequency of the five most relevant symptoms from a community study in South Africa is shown in table 2. Both persistent cough and/or persistent fatigue of recent onset were highly sensitive and specific markers of TB. A persistent non-remitting cough in childhood was almost exclusively associated with TB (table 2). As a result, in this setting clinical follow-up was a useful diagnostic tool because a non-remitting cough persisting beyond 2–4 weeks was uncommon other than with TB, and no child whose symptoms spontaneously resolved was diagnosed with TB in the following 6 months.

There are no specific identifying physical signs that unequivocally establish that a child has TB. Some signs are highly suggestive of extrapulmonary TB (*e.g.* gibbus of recent onset and painless cervical adenopathy with fistula) while other signs require investigation to exclude extrapulmonary TB (*e.g.* pleural effusion, phlyctenular conjunctivitis and erythema nodosum).

Tests of adaptive immunity

For more than 100 years, the TST was the only test available to detect infection with *M. tuberculosis*. The test involves the intradermal injection of purified protein derivatives derived from *M. tuberculosis*. There are a number of TSTs available but the WHO recommends using the Mantoux test. Interpretation of the TST test depends on the clinical situation. In children identified by active case finding, or in those where TB is suspected clinically, induration of >5 mm in children who have not had a Bacillus Calmette–Guérin (BCG) vaccination or are at high risk, or induration of >10 mm (according to WHO or >15 mm in other countries) in all other children (whether they have had a BCG vaccination or not) should be considered to indicate infection.

Unfortunately, the TST has problems with both false-positive and false-negative results. This has led to the development of peripheral blood T-cell-based interferon (IFN)-γ assays. Two are commercially available:

- whole blood IFN-γ release assay (IGRA) (QuantiFERON Gold; Cellestis Ltd, Victoria, Australia);

Table 2. Persisting non-remitting symptoms in children aged <13 years in Cape Town, South Africa, presenting to the local community clinic with a cough >2 weeks duration

Symptom	No TB[#]	TB[¶]	Odds ratio
Cough	2 (1.6)	15 (93.8)	2010.0
Chest pain	0 (0)	4 (25)	NA
Weight loss	3 (2.6)	6 (37.5)	25.0
Fatigue	1 (0.8)	13 (81.3)	580.7
Fever	0 (0)	4 (25)	NA

Data are presented as n (%), unless otherwise stated. NA: not available. [#]: n=135; [¶]: n=16. Reproduced from the International Union Against Tuberculosis and Lung Disease; Copyright The Union (Marais *et al.*, 2005) with permission.

- an enzyme linked immunospot assay (T-SPOT.*TB*; Oxford Immunotec, Oxford, UK).

IGRAs measure IFN-γ production *ex vivo* by circulating T-lymphocytes when incubated in the presence of highly specific *M. tuberculosis* antigens (early secreted antigenic target (ESTA)-6 and culture filtrate protein (CFP)-10). IGRAs are more specific than the TST and can distinguish a positive TST due to BCG vaccination or to environmental atypical mycobacterial (NTM) infection from a positive TST test due to infection with *M. tuberculosis*. However, despite their greater specificity, IGRAs cannot differentiate between active and latent TB, and a negative IGRA test does not exclude TB.

Neither the TST nor the IGRA test can differentiate latent infection from active disease and neither test should be used for the diagnosis of active TB. The place of IGRA tests in children, particularly young children aged <5 years, is still being evaluated. The TST and IGRA tests may be complementary, improving the sensitivity and specificity of the assessment in specific clinical circumstances. At present, the WHO recommends that for children in low- and middle-income countries IGRA tests should not be used in place of the TST for the diagnosis of latent TB infection (LTBI).

Radiography and other imaging techniques

The majority of children with pulmonary TB will have chest radiography changes, typically hilar and mediastinal lymphadenopathy (figs 3 and 4). Extraluminal compression of the enlarged lymph nodes may cause partial luminal obstruction of the airway leading to radiographic signs of hyperinflation and ''air-trapping''. Caseous lymph node may ulcerate into the airway closing the lumen completely and causing distal atelectasis. Persistent pulmonary opacification, especially if there is no improvement with antibiotics, along with prominent hilar or subcarinal adenopathy is highly suggestive of TB.

A chest CT may be very useful in demonstrating early cavitation and bronchiectasis. However, while HRCT offers excellent visualisation of mediastinal lymph nodes, treatment algorithms for latent TB and pulmonary TB in children have been

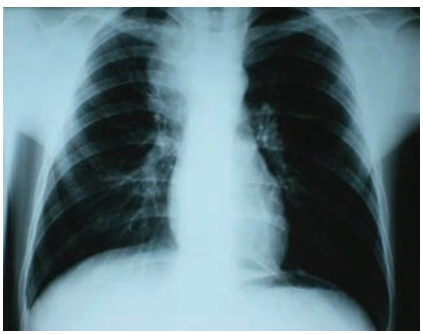

Figure 3. Right mediastinal lymphadenopathy in a child with TB.

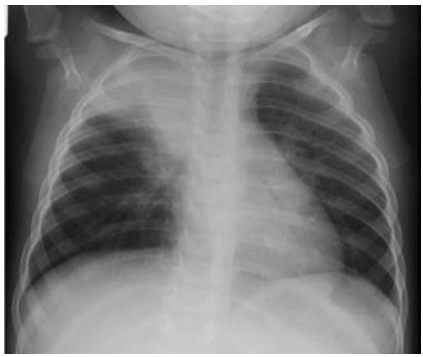

Figure 4. Right upper lobe atelectasis and hilar adenopathy in a child with TB.

based on plain radiographs. Accordingly, chest CT is usually reserved for more complex cases.

Bronchoscopy may be useful in children with areas of atelectasis where compression by lymph nodes or caseating material ulcerating through an airway can be visualised (fig. 5).

Ultrasound can identify and guide drainage of pleural, pericardial or abdominal effusions (fig. 6) and can help in guiding fine-needle aspiration of lymph nodes.

Microbiological confirmation

Children generally have pauci-bacillary disease, which makes microbiological

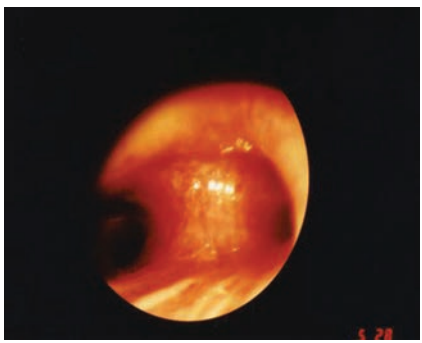

Figure 5. Extramural compression demonstrated on bronchoscopy with broadening of main carinal bifurcation due to subcarinal lymphadenopathy.

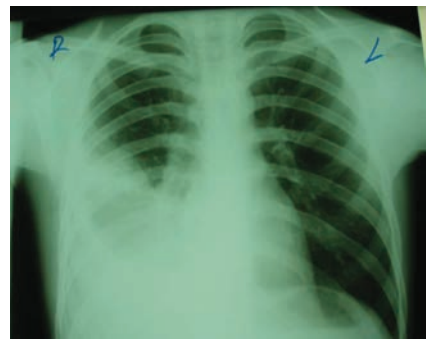

Figure 6. Chest radiograph from a 15-year-old boy with TB with right lower lobe atelectasis and pleural effusion.

diagnosis of TB more difficult than in adults. Microbiological confirmation is commonly not achieved, and in many cases is not even attempted. The European Centre for Disease Prevention and Control estimated between 2000 and 2009 that less than one in six children had their diagnosis confirmed by TB culture. Nevertheless, a positive culture for *M. tuberculosis* remains the gold standard for the diagnosis of TB. Microbiological confirmation is increasingly important because of the increase in drug-resistant TB. The WHO recommends that bacteriological confirmation should be sought wherever possible. Appropriate samples from suspected sites of involvement should be obtained for microscopy and culture and, if appropriate, histopathology. However, culture can take weeks and is consequently unavailable to inform clinical decisions at the start of treatment.

Collecting samples Sputum samples from spontaneous coughing may be obtainable in older children (>10 years). In younger children, particularly those <5 years, sputum is more difficult to obtain. Smaller amounts of sputum are produced and are swallowed rather than expectorated. Consequently, most children are sputum-smear negative even when optimised techniques are used. Bacteriological samples can be collected by three early morning gastric washings *via* nasogastric tube, following an overnight fast. More recently, sputum induction following

nebulisation with hypertonic saline (3–5%) has been shown to be safe and effective in children of all ages with bacterial yields as good, or better than, for gastric aspirate. One induced sputum specimen provides a similar microbiological yield to three gastric lavage specimens in children admitted to hospital with pulmonary TB. However, the technique requires training and equipment and staff need to follow effective infection control procedures appropriate for infectious aerosol exposure. At least two samples should be collected.

TB lymphadenitis is a common form of extrapulmonary TB. Fine-needle aspiration of accessible enlarged lymph glands has been shown to be useful with a high bacteriological yield. Aspiration of cerebrospinal fluid, pleural or other fluids may also provide material for microscopy and culture in appropriate situations.

Molecular testing Molecular testing techniques are being developed for TB. One system, the Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) has been endorsed by the WHO as an initial diagnostic test in people suspected of having drug-resistant or HIV-associated TB. This system combines integrated sample processing and a nucleic acid amplification test for the detection of *M. tuberculosis* and rifampicin resistance. The test can detect resistance to rifampicin with a high degree of sensitivity and specificity. Results are available much more quickly than culture results, often within 1 day of testing.

In one large South African study in children, when two induced sputum samples were used, the MTB/RIF tests were shown to detect three-quarters of culture confirmed cases of pulmonary TB with a very high specificity. The test had a lower sensitivity in smear negative cases with two tests detecting ~60% of cases. Thus a negative MTB/RIF test cannot rule out TB and has to be interpreted in the context of other clinical and radiological findings. MTB/RIF testing was more sensitive than smear microscopy detecting twice as many cases. It worked well with gastric lavage aspirate samples with an accuracy similar to testing induced sputum and was not affected by whether a child had HIV or not.

HIV testing In high prevalence areas where TB and HIV are likely to coexist, or in low prevalence areas where risk factors are identified for HIV, HIV counselling and testing is indicated.

Making the diagnosis: putting it altogether In children, because microbiological confirmation is commonly not available, the diagnosis of TB is often based on a careful assessment of the available evidence and a high index of suspicion. TB can mimic many common childhood diseases. However, a combination of clinical, radiological and laboratory findings along with a history of TB exposure and immunological evidence of *M. tuberculosis* allows an accurate diagnosis in most cases.

Treatment of TB

Management of active TB Because large studies in children are generally lacking, the principles of drug treatment and recommended drug regimens are the same as for adults. TB should never be treated with a single drug; a single drug should never be added to a failing regime because of the risk of developing drug resistance.

Although every effort should be made to attain a microbiological diagnosis, the threshold for starting treatment therapy empirically is lower for children, especially for young children where potentially life-threatening conditions such as TB meningitis or miliary TB can develop quickly. Fortunately, drug-related adverse events are rare in young children treated with first-line drugs and they are at low risk for acquiring or transmitting drug-resistant disease.

The goals of treatment are to cure the individual and prevent late complications, as well as to decrease transmission to others and prevent the development of drug resistance. Successful TB treatment requires more than just anti-TB chemotherapy medicines. Medications need be provided within an appropriate clinical and social framework if an effective cure is to be achieved.

Combination anti-tuberculous regimens
Combination regimens are used to treat active disease. The aim is to eliminate both actively replicating and dormant or near-dormant mycobacteria by using a combination of drugs with different anti-mycobacterial actions while minimising toxicity and preventing the emergence of drug-resistant organisms.

Bactericidal drugs are used to kill actively metabolising and replicating organisms. They bring about a rapid reduction in microbial load leading to clinical improvement, preventing disease progression and stopping transmission. Isoniazid (H) and rifampicin (R) are the most important first-line drugs with isonizaid having the most important bactericidal activity.

Sterilising drugs aim to eradicate organisms that are less metabolically active in order to prevent relapse. Rifampicin (R) and pyrazinamide (Z) are important first-line sterilising agents. Protection against the emergence of drug-resistant organism is achieved through the combination of effective bactericidal activity with effective sterilising activity and is strengthened by the addition of ethambutol (E).

Treatment regimens The drugs and treatment regimens for TB in children are the same as those used in adults. Recommended regimens are based on national programmes recommended for a particular country (if one exists), or by the WHO.

In Europe, the most frequent scenario is that the *M. tuberculosis* is sensitive to all first-line agents. Consequently, for new cases of pulmonary TB in children (smear positive or negative), the current WHO recommendations for Europe are treatment with the four first-line drugs (HRZE) for 2 months as an initial bactericidal regimen. After 2 months, treatment is continued with a prolonged sterilising regime of H and R for a further 4 months. In some less developed countries, the initial 2 months of treatment is given in hospital to ensure administration. In children, TB relapse or reactivation occurs rarely.

Recommended treatment regimens are listed in table 3.

Recommended drug doses The WHO has recently recommended revising the doses of the main first-line anti-TB drugs for HIV-uninfected children (table 4). At present, HIV-infected children should receive the same dosages of anti-TB therapy as HIV-uninfected children.

Treatment should be given daily. Thrice weekly regimens should only be considered during the continuation phase for children known to be HIV uninfected living in settings with well-established directly observed therapy (DOT) programmes.

Adherence Ensuring adherence to the long courses of treatment used for treating TB is a major problem. Poor adherence is an important factor in the emergence of resistance to TB therapy and in treatment failure. The WHO recommends that all children should receive TB drugs free of charge irrespective of whether the child is smear positive at diagnosis or not. Fixed-dose combinations of drugs should be used whenever possible. These simplify adherence and minimise the risk of developing drug resistance. However, this is often not possible in children because of a lack of suitable drug combinations. In addition, there is a lack of drug formulations suitable for children, *e.g.* liquids.

Children, parents and families should be educated about TB and the importance of completing treatment. Providing anti-TB medications directly to the patient and watching them take them is termed DOT and is recommended for all patients diagnosed with TB. As a minimum, all children and families should be assessed for the risk that adherence is likely to be poor and DOT should be used for those at high risk of non-adherence. A healthcare worker or a trained community worker can administer DOT. In some settings, children with severe disease, such as TB meningitis, or with severe side-effects may need prolonged hospitalisation during the first 2 months of treatment to ensure that treatment is successfully delivered.

Table 3. Treatment regimens for children with TB as recommended by the World Health Organization (WHO)

TB cases and diagnostic criteria	Anti-TB drug regimen	
	Intensive phase	Continuation phase
New smear-positive pulmonary TB	2 months HRZE	4 months HR
Smear-negative pulmonary TB with extensive parenchymal involvement	2 months HRZE	4 months HR
Extrapulmonary TB-peripheral adenitis	2 months HRZE	4 months HR
Tuberculous meningitis	2 months HRZE	10 months HR
TB osteoarthritis	2 months HRZE	10 months HR
MDR-TB	Individualised regimens	

H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol.

Side-effects Hepatotoxicity is the major drug-related adverse event, with case reports of hepatic failure even when recommended doses of anti-tuberculous therapies are used. However, extensive experience has demonstrated that the first-line drugs used in treating TB are well tolerated in children with a low risk of side-effects. Indeed, the drugs are better tolerated in children than adults perhaps because of the lower peak serum levels achieved in children when using the same dose per kg as adults.

Hepatotoxicity may be detected more frequently in children who are malnourished, immunocompromised, *e.g.* with HIV infection, or who present with extensive and serious TB disease. If signs of hepatotoxicity develop (vomiting, jaundice, liver tenderness and hepatomegaly) all drugs should be stopped and levels of hepatic enzymes monitored. Reintroduction of anti-TB therapy should not be tried until liver function is normal and should then proceed on a step-wise basis with one drug reintroduced at a time.

Ethambutol is now recommended for use in children of all ages including those aged <5 years. At the recommended doses and durations, a review of the evidence suggested that ethambutol is safe with a negligible risk of toxicity throughout childhood. Screening for visual related side-effects is not required.

Other drugs Corticosteroids may be used for the management of some specific cardio-respiratory complications of TB, *e.g.* airway obstruction and atelectasis secondary to TB mediastinal lymph gland enlargement, or pericardial TB. Corticosteroids have been used in advanced pulmonary disease with clinical and radiological benefits. They are recommended for all children with TB meningitis. Prednisolone (1–2 $mg \cdot kg^{-1}$ daily for 3–4 weeks and then tapered) has been the most commonly used drug. Rifampicin induces hepatic enzymes that catabolise corticosteroids and reduce effective bioavailability by ~50%.

Corticosteroids are also used in the management of the immune reconstitution syndrome (also known as paradoxical reaction). In this, a temporary deterioration occurs after the start of anti-tuberculous treatment due to restitution of the capacity to mount an inflammatory immune response. It may cause fever, increased lymph node size and tuberculomas. It can occur after the start of anti-TB treatment, *e.g.* commonly as the enlargement of the mediastinal lymph node on chest radiographs, after improved nutrition or following the initiation of antiretroviral therapy in children with HIV infection.

Table 4. Recommended doses for first-line anti-TB drugs for the treatment of TB in children aged >3 months

Drug	Daily dose (range) $mg \cdot kg^{-1}$
Isoniazid	10 (10–15), maximum 300 mg daily
Rifampicin	15 (10–20), maximum 600 mg daily
Pyrazinamide	35 (30–40)
Ethambutol	20 (15–25)

Management of drug-resistant TB in children

Rates of resistant TB are increasing. Drug resistance originates in adults with TB who have a high bacillary load and who receive inadequate anti-tuberculous therapy or are poorly compliant. Acquisition of resistance is rare in the pauci-bacillary disease that occurs in children.

Resistance to isoniazid and/or rifampicin is most important because these two drugs are the mainstay of current first line treatment. In MDR-TB, the organism is resistant to both rifampicin and isoniazid with or without resistance to other anti-TB drugs. Infection is usually the result of transmission of a strain of MDR-TB from an adult index case.

Treatment is often complex and specialist advice should be sought. There is uncertainty about activity and safety of the available second line drugs. Suitable formulations for children are often not available. If an isolate from the child is not available, the best guide to treatment is the susceptibility pattern of the adult source case. In general, at least four drugs certain to be effective (and to which the child is naïve), including an injectable and a fluorquinolone, are given on a daily basis using DOT for an extended initial period of 6 months followed by at least three of the most active and best tolerated drugs for a further period of 12–18 months.

Current recommendations are to avoid using primary chemoprophylaxis or treatment for latent TB in cases of close contact with a case of MDR-TB if the child is clinically well, and to observe for 2 years.

Children with TB who are co-infected with HIV

Children with TB should be screened for HIV. Similarly, children newly diagnosed for HIV should be screened for TB by history and chest radiograph. Drug interactions between HIV antiretroviral therapy and the similar side-effect profiles of the drugs involved in treating the two diseases make managing the two treatments challenging. Rifampicin, in particular, reduces the concentrations of many HIV drugs. For children with significant immunosuppression, treatment for HIV should be delayed for 2–8 weeks once anti-tuberculous treatment is started. For those with mild or no immunosuppression, treatment for HIV may be deferred until treatment of TB is completed.

Guidelines recommend that TB in HIV-infected children should be treated with a 6-month regimen as for uninfected children. The WHO recommends that rifampicin should be used for the entire duration of treatment. In children, intermittent regimens (twice or thrice weekly) should not be used in areas with high HIV prevalence for the treatment of pulmonary TB or TB lymphadenitis.

Immune recovery in children with HIV after initiation of antiretroviral therapy, nutritional rehabilitation or sometimes just beginning anti-TB therapy may unmask subclinical disease or induce a paradoxical temporary deterioration despite adequate therapy for TB, the so-called immune response inflammatory syndrome (IRIS). This can simulate worsening TB disease with fever and increased size of lymph nodes or tuberculomas. Treatment for TB should not

be interrupted. A course of steroids may be required for severe IRIS.

In adults with HIV-infection in endemic areas, the use of secondary isoniazid preventive therapy after completion of TB therapy significantly reduces the risk of recurrent TB. The WHO has therefore recommended 6–36 months isoniazid therapy in all patients with HIV infection including children living in high-prevalence areas of TB.

The WHO has recently published updated policy guidelines for the collaborative management of TB and HIV.

TB control and prevention

Preventive chemotherapy TB preventive therapy is important in two broad categories of children:

1. children who have been recently exposed to *M. tuberculosis*, *e.g.* following close contact with an infected case;
2. children at increased risk of progression of *M. tuberculosis* infection to TB because of age or other clinical conditions, such as HIV.

Controlled trials have focused on preventing progression from latent infection to active disease by providing a limited course of treatment (either in duration or number of drugs) to sterilise existing subclinical lesions and prevent future progression to TB disease (treatment of LTBI). Genuine primary prevention (primary chemoprophylaxis) is used to prevent primary infections from becoming established during/after a period of contact with an infectious case. Preventing recurrence of TB may be targeted by "secondary chemoprophylaxis" provided after successful completion of therapy.

Treatment of children recently infected
Treating recently infected children and preventing progression to active TB (treatment of LTBI) eliminates reservoirs of *M. tuberculosis* and prevents later reactivation disease. Such treatment is particularly important in young children because of the higher risks of disease progression.

For the last 20 years, WHO guidelines have recommended that all children aged <5 years (irrespective of BCG status) in close contact with an infectious (usually smear positive) case of TB receive 6–9 months isoniazid therapy. However, screening is frequently not provided in endemic areas. Treatment with isoniazid for 9 months has been established to reduce the risk in exposed children by >90% if adherence is good. A shorter 3-month course of rifampicin and isoniazid has been shown to be equally effective and may improve treatment compliance. Before treating latent TB it is important to exclude active TB by a chest radiograph and/or symptom review.

Unfortunately, the implementation of preventive strategies has been poor because parents are often reluctant to provide preventive treatment to a well child and because of the long duration of treatment required.

Treatment for TB exposed children with HIV
In HIV-infected children the value of post-TB exposure prophylaxis and the need for careful ongoing screening is clear. Isoniazid preventive therapy is indicated following every documented exposure to TB, particularly for the young and the immunosuppressed. The value of pre-exposure routine chemoprophylaxis in children with HIV remains uncertain.

BCG vaccination is a live attenuated vaccine derived from *Mycobacterium bovis* prepared as a freeze-dried powder for suspension prior to injection. It was first used in humans in 1921 and is one of the most widely used of all vaccines.

The BCG vaccination is given intradermally normally into the lateral aspect of the left upper arm at the level of the insertion of the deltoid muscle (the left arm is recommended by the WHO).

Vaccination soon after birth is recommended in high-prevalence countries. Low-prevalence countries use risk-based strategies targeting neonatal BCG vaccination to protect those children most at risk from exposure to TB. Targeted

approaches require careful ongoing audit to ensure that high proportions of those at-risk continue to be vaccinated.

Effectiveness in preventing progression to disease Studies of the effectiveness of BCG in protecting against TB have given widely varying results, ranging from no protection in some studies in India to 70–80% protection in UK school children. The reasons for the variation in efficacy in different regions of the world are not well understood.

BCG vaccination has been shown consistently to be 70–80% effective in preventing against TB meningitis and miliary TB, the more severe forms of disseminated disease that occur in young children. Recent studies combining IGRA and TST have suggested that BCG may also protect against TB infection reducing the risk of primary TB infection and the development of latent TB infection by up to 50%. However, BCG offers no consistent protection against adult-type TB with the most limited protection in geographical areas such as India where TB is most prevalent.

Levels of protection from the BCG fall with time with the best estimates of suggesting protection for around 10 years. BCG is not protective if given to those already infected and revaccination does not seem to offer substantial re-protection.

Side-effects BCG is the one of the most widely administered vaccines worldwide and only a small number of children (1–2%) develop an adverse effect. The most common complications are local abscesses, secondary bacterial infections and suppurative adenitis or keloid formation. Serious adverse effects are rare.

However, individuals with genetic defects in key immune genes or, more commonly, infants with clinically active HIV infection are highly susceptible to developing disseminated BCG disease. As a live vaccine BCG should not be used in children with HIV/AIDS or in children with congenital immune deficiencies.

New developments Intensive research is underway to develop more effective TB vaccines and has followed two basic approaches. The first aims at replacing BCG by either improved recombinant (r)BCG or by genetically attenuated *M. tuberculosis*. The second approach focuses on subunit vaccines, which may be used as booster vaccines on top of BCG-, recombinant BCG- or attenuated *M. tuberculosis*-priming vaccines. Around 12 candidate vaccines are currently in clinical testing.

Importance of well-functioning TB control programmes

Children are generally infected with TB by close contact with an infectious adult, therefore, early diagnosis and treatment of adult infectious cases is the best way to stop children from becoming infected. A well-functioning TB control system, which ensures the early diagnosis and treatment of infectious adults with TB, has a key role in preventing TB in children.

Within hospitals and clinics, the risk of infection to healthcare workers from paediatric patients with primary TB appears to be minimal, and most children with TB do not need isolation. However, it is important to remember that symptomatic parents or caregivers may have TB and pose an infection risk. Infection control efforts should, therefore, be focused on accompanying adults and adult visitors.

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Extrapulmonary TB and TB in the immunocompromised host

Toyin Togun, Uzor Egere and Beate Kampmann

Globally, an estimated 11% of the nearly 10 million new cases of active TB diagnosed annually occur in the paediatric population, but the true burden of TB in children remains underestimated.

Extrapulmonary TB is common in children and refers to the isolated occurrence of active TB at body sites other than the lung. The exact mechanisms that determine the clinical outcomes following infection in children are not completely understood, but include:

- age,
- nutritional status,
- underlying immunity,
- vaccination status,
- genetic susceptibility,
- microbial virulence.

Key points

- Young children are more likely to develop extrapulmonary manifestations of TB, associated with age-related impairment of cellular immune responses.
- Extrapulmonary TB can have very severe consequences and thorough investigations and prolonged therapy are required.
- Conditions of immunosuppression, in particular HIV, are more likely to lead to extrapulmonary severe manifestations. This is proportionate to the level of suppression of T-cell function.

The risk of disease progression and extrapulmonary dissemination is highest in the first 2 years of life, with risk of disease progression estimated at 40–50% in the absence of Bacille Calmette–Guérin (BCG) vaccination or prophylactic therapy. The majority of disease occurs within 2–12 months of initial infection with pulmonary TB accounting for 60–80% of all cases.

Extrapulmonary TB usually originates from lymphohaematogenous spread of TB bacilli from a primary pulmonary focus, contiguous spread from infected lymph nodes or direct inoculation of bacilli. Generally, superficial lymphadenopathy is the most common form followed by central nervous system (CNS) disease, pleural, miliary/disseminated and skeletal TB. Less common forms include abdominal, pericardial, renal and cutaneous TB.

The role of age-related immune responses in clinical manifestations of TB in children

It is well established that less mature or impaired immune responses contribute to the disseminated forms of TB seen in children and immunocompromised hosts.

A number of studies have reported an age-related functional impairment of both innate and adaptive immune responses in children. The current paradigm in TB immunology is the crucial importance of *Mycobacterium tuberculosis*-specific $CD4^+$ T-cells and the key cytokines such as interferon gamma (IFN)-γ produced in the protection against *M. tuberculosis*. However, *M. tuberculosis*-specific IFN-γ responses alone are not an absolute correlate of protection against the development of TB.

Following inhalation of *M. tuberculosis* in infected aerosols into the terminal alveoli, it is immediately engulfed by resident phagocytes including the alveolar macrophages and dendritic cells. Activated macrophages infected with *M. tuberculosis* induce the synthesis and secretion of chemokines and cytokines which recruit other inflammatory cells to the site of infection. The dendritic cells, which are the major antigen presenting cells in the lung, migrate to regional lymph nodes where they present processed *M. tuberculosis* antigens to naïve $CD4^+$ T-cells *via* major histocompatibility complex (MHC)-class II molecules. The antigen presentation by dendritic cells with the aid of co-stimulatory molecules such as CD80 and synthesis of polarising cytokine such as interleukin (IL)-12 promotes the priming, proliferation and differentiation of naïve $CD4^+$ T-cells into *M. tuberculosis*-specific CD4 T-cells with T-helper (Th)-type 1 effector function, which produces classical Th-1 cytokines including IFN-γ, tumour necrosis factor (TNF)-α and IL-2. IFN-γ produced by the *M. tuberculosis*-specific $CD4^+$ T-cells is critical for the optimal activation of infected macrophages to become microbicidal, promoting killing of the phagocytosed bacilli and thus protection against TB.

Specifically, it has been reported that the alveolar macrophages in children show diminished phagocytosis, cellular recruitment and microbial killing when compared with adults, which could promote delayed initiation of antigen-specific T-cell responses and disease progression. Further studies are needed to define the role and importance of CD8 T-cells in immune responses to TB in children.

These immunological differences described above could largely be a reflection of immaturity of the immune response and explain the high rate of progressive TB seen in young children.

Apart from the intrinsic deficiencies in cell-mediated immune responses in children, there are other primary and acquired causes of immune suppression which could further increase the risk of TB disease progression in children.

Genetic susceptibility to TB

Mendelian susceptibility to mycobacterial diseases (MSMD) Additional evidence of the importance of cell-mediated immune response and Th-1 IFN-γ response in the protection against *M. tuberculosis* infection has come from genetic studies reporting an increased risk of progressive disease in specific genetic defects affecting the IL-12/IFN-γ pathway.

MSMD is a familial inherited disorder associated particularly with an increased susceptibility to severe disseminated mycobacterial diseases that often manifest in childhood. Affected children have a diminished ability to induce activation and upregulation of the killing mechanism of *M. tuberculosis*-infected macrophages because of a number of specific mutations in the genes encoding major components of the IL-12/IL-23 IFN-γ axis of the Th-1 cytokine pathway. A number of mutations have been identified in the autosomal genes including *IFNGR1* (encoding IFN-gR1), *IFNGR2* (encoding IFN-gR2), *STAT-1* (encoding signal transducer and activator of transcription-1), *IL12P40* (encoding IL-12p40 subunit), *IL12RB1* (encoding IL-12Rbeta1 chain), *TYK2* (encoding tyrosine kinase 2) and *NEMO* (encoding nuclear factor-κB-essential modulator).

Acquired susceptibility to TB

HIV infection The most compelling evidence for the crucial role of $CD4^+$ T-cells in protection against human mycobacterial infection is the increased risk of infection, reactivation and progression to TB disease in individuals with HIV co-infection. A number of studies have reported a higher risk of TB and poorer survival among HIV-infected children when compared with HIV-negative children with TB, while the reported risk of disseminated BCG disease (called BCG-osis) in HIV-infected children has prompted the World Health Organization (WHO) to recommend avoiding BCG vaccination in newborns with known HIV-positive status.

Although the attributable effect of the HIV epidemic on the burden of TB in children is less well defined than in adults, the HIV epidemic has resulted in a shift of TB disease burden to younger adults resulting in an increased exposure of both HIV-infected and -uninfected children at a very young age. While HIV is known to be a strong risk factor for TB, this risk is further increased in HIV-infected children by younger age and underlying immune status as defined by the CD4 count and viral loads. The incidence of TB has been reported to be four times higher in children with a CD4 count <15% and 30 times higher in children with viral load >5 $\log_{10}$ copies per mL when compared with other children.

The diagnostic difficulties in childhood TB are further compounded in HIV/TB co-infection, as the clinical presentations in both diseases are similar and radiological features are nonspecific. The tuberculin skin test (TST), which is the most widely used immunological test supporting the diagnosis of TB, is frequently false negative because of HIV-associated "anergy" in delayed-type hypersensitivity to purified protein derivatives. Thus, diagnosis of TB in children, especially in resource-limited settings, relies on practical algorithms, which lack standard symptoms definitions and adequate validations, with HIV co-infection aggravating these shortcomings.

Transplant-related immune suppression Impairment of immune control of *M. tuberculosis* can also result from the immunosuppression, either due to disease and/or treatment in solid organ transplant and/or haematopoietic stem cell transplant (HSCT). Lung transplantation has the highest risk of such donor-derived transmission and of post-transplant TB. As such, the incidence of TB and its associated mortality is higher in transplant recipients than in the general population and the incidence is directly proportional to endemicity of *M. tuberculosis* infection in the general population. These risks are further heightened or amplified in paediatric transplant recipients due to compounded immunosuppression. Therefore, efficient pre-transplant risk assessment and screening of both the transplant recipient and the donor/donor organ is an important part of the management of recipients which will allow for preventive intervention in the pre- and/or post-transplant period.

Helminth infestation, nutritional deficiencies and vitamin D Several studies have suggested that helminth infection could downmodulate the protective immune response against *M. tuberculosis* thereby facilitating progression to active TB disease. Heavy helminth infection in humans has been shown to be associated with a generalised state of immune hyporesponsiveness, probably facilitated through immunoregulatory pathways involved in mycobacterial control.

The association between malnutrition and risk of TB is largely derived from observational studies in humans, experimental studies in animal models and *in vitro* studies. However, it is still unclear whether malnutrition facilitates TB or TB leads to malnutrition. Similarly the effect of different forms and degrees of malnutrition and the population attributable risk due to malnutrition in communities where both TB and malnutrition are endemic remain to be defined.

Vitamin D deficiency is associated with TB among children and immigrants in low-endemic settings, as well as in people in TB-endemic settings regardless of HIV status. A seasonal variation in the notified cases of TB related to exposure to UV light and vitamin D deficiency has also been reported from several populations. Vitamin D, through its active metabolite 1-alpha-25-dihydroxy-vitamin-D, contributes to the host immune protection against TB through "non-classical" mechanisms including upregulation and activation of antimicrobial peptides such as cathelicidins, promoting IFN-γ induced activation of *M. tuberculosis*-infected macrophages as well as the maturation and activation of dendritic cells.

Clinical manifestations of extra-pulmonary TB

Lymph node TB Superficial tuberculous lymphadenitis involves mainly cervical lymph nodes and is the most common form of extrapulmonary TB in children from TB-endemic areas. Environmental factors and other mycobacteria can also cause cervical lymphadenitis depending on their prevalence in a given setting.

Clinical features Lymphadenitis presents 6–12 months after initial TB infection as non-tender, non-erythematous solid masses 2–4 cm in size. They may become matted together and develop a chronic discharging sinus. Constitutional symptoms such as fever, fatigue and failure to thrive are observed in >50% of the children. Anterior cervical lymph nodes are more commonly involved; posterior cervical, supraclavicular and submandibular nodes are less involved. Infants are rarely affected.

Diagnosis Fine-needle aspiration for acid-fast bacilli, cytology and culture are usually adequate for accurate diagnosis. Lymph node biopsy confirms diagnosis and excludes other causes of lymphadenopathy such as malignancy. Histology shows the typical features of necrosis and epitheloid granulomata.

CNS TB constitutes around 13% of all cases of extrapulmonary TB in children and complicates the clinical course of TB in 0.5–2% of cases. Tuberculous meningitis (TBM) is the most common form (~95% of cases); tuberculomas and abscesses are less common. The spinal cord is rarely involved. CNS TB develops 3–6 months after primary infection, usually in children <2 years of age. TBM is a devastating illness. It may develop acutely or more commonly evolve slower than other forms of bacterial meningitis. Serious neurological sequelae develop in almost 50% of cases and overall mortality is ~13%. TBM is very rare in low-TB prevalence countries. Seeding of TB bacilli in the CNS leads to formation of small subpial and subependymal foci in the brain and spinal cord referred to as Rich foci. Rupture of Rich foci and release of bacteria into the subarachnoid space causes meningitis. In some individuals, Rich foci enlarge to form tuberculomas.

Clinical features TBM can manifest in progressive phases. The first stage (stage 1) presents with nonspecific symptoms such as headache, nausea and fever, and vague CNS symptoms, such as behaviour changes, irritability, drowsiness and vomiting. Stage 2 is marked by signs of meningeal irritation and cranial nerve palsies involving mainly nerves III, VI and VII. Stage 3 is characterised by raised intracranial pressure and altered sensorium. Some stage 3 patients present in a coma. Seizures may occur at any stage. Late presentation is common in developing countries; tuberculomas are more common in the older child, present with focal seizures or with symptoms and signs of raised intracranial pressure and may coexist with meningitis in up to 10% of cases (fig. 1).

Diagnosis Lumbar puncture is mandatory. The cerebrospinal fluid (CSF) shows a clear hyper-concentrated fluid with high protein (>0.4 $g \cdot L^{-1}$), low glucose (<60 $mg \cdot dL^{-1}$) and a high white cell count of 100–1000 $cells \cdot mL^{-1}$ of which at least 80% are lymphocytes. Acid-fast bacilli staining and culture of CSF rarely yield mycobacteria. Partially treated bacterial meningitis, and viral and fungal meningitis (especially

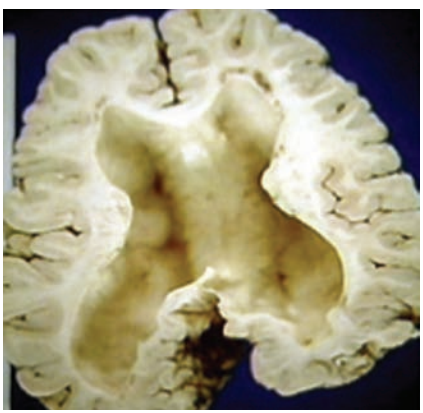

Figure 1. A transverse section of the brain showing dilated ventricles in a child who died of TBM.

cryptococcal meningitis in HIV-positive children) should be ruled out.

Complications include hydrocephalus, seizures and cranial nerve palsies. Learning difficulties, deafness, blindness and hemiplegia may persist in the long term.

Imaging in CNS TB MRI with gadolinium enhancement is the most sensitive test for detecting the extent of leptomeningeal disease and is superior to CT scanning in detecting parenchymal abnormalities such as tuberculomas, abscesses and infarctions.

A CT scan with contrast enhancement can show meningeal enhancement, hydrocephalus and focal infarcts from vasculitis. Tuberculomas appear as hyper dense, rim-enhancing lesions 1–5 cm in dimension. Neurocysticercosis has a similar appearance and needs to be differentiated from tuberculomas, especially in developing countries.

Miliary TB Classic miliary TB refers to millet-like (1–5 mm) seeding of TB bacilli in the lung as evidenced by radiography. Very young and/or immunocompromised children, such as HIV infected or severely malnourished children, are usually affected and miliary TB tends to develop soon after primary infection from an adult source case.

Clinical features Progressive symptoms similar to other forms of pulmonary TB develop over days or weeks and the diagnosis is then apparent on the pathognomonic chest radiograph (fig. 2).

Diagnosis Chest radiographs show the typical, bilaterally distributed, miliary nodules in the majority of cases. Lymphocytic interstitial pneumonitis (LIP) and opportunistic infections such as *Pneumocystis jirovecii* may present with a similar picture in HIV-infected children.

The TST may be negative in miliary TB as disseminated disease may cause TST anergy. This should never rule out TB. Fundoscopy may identify retinal tubercles. Gastric washings or induced sputum for

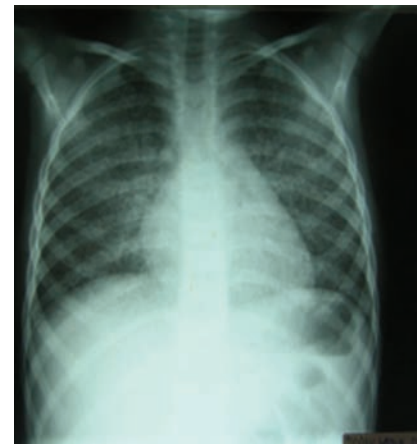

Figure 2. Miliary TB. Chest radiograph of a 2-year-old boy showing bilateral distribution of miliary nodules.

acid-fast bacilli and culture should be performed; culture might be positive in up to 50% of cases.

Chest CT has a higher sensitivity and specificity compared to radiography in displaying the nodules. It is useful in resolving suggestive but inconclusive chest radiography findings. Ultrasonography may reveal diffuse liver disease, splenomegaly and para-aortic lymph nodes. A head CT scan or MRI scan may show involvement of the CNS. Echocardiography helps to exclude pericardial involvements.

Pleural TB Pleural TB occurs in 2–38% of cases of pleural TB in children and may be a manifestation of primary or reactivation disease. Primary pleural TB results from a hypersensitivity reaction to bacilli in the pleural space. The effusion usually develops 6–12 weeks after infection.

Clinical features Pleural TB is more common in adolescents. It presents with chest pain, cough, shortness of breath, weight loss, fatigue and anorexia. Examination reveals wasting, pyrexia, respiratory distress, dullness to percussion and reduced breath sounds, mimicking pneumonia. Effusion is usually unilateral and more common on the right.

Diagnosis Radiological examination reveals effusion, mediastinal shift, parenchymal consolidation, bulging lung fissures and hilar or mediastinal adenopathies. Pleural aspiration and analysis shows straw coloured fluid, an exudative lymphocytic effusion with 1000–6000 white blood cells per μL, protein >4 $g \cdot dL^{-1}$ and glucose level <70 $g \cdot dL^{-1}$. Elevated pleural fluid ADA levels (>40–60 $Units \cdot L^{-1}$) can support the diagnosis. Sputum acid-fast bacilli and culture should be performed on sputum, pleural fluid and pleural biopsy specimen; however, pleural fluid is rarely acid-fast bacilli positive. Culture may be positive in 40–60% of cases. Histopathological examination of pleural tissue demonstrates granulomata with or without caseous necrosis.

Pericardial TB TB can involve the pericardium in ~1–2 % of cases and causes ~70% of all cases of large pericardial effusions. Most cases of constrictive pericarditis in developing countries and ~4% of cases in industrialised countries are due to TB.

Clinical features Common presenting symptoms include shortness of breath, cough, fever and weight loss. Chest pain is less common. Hepatomegaly and jugular venous distension are common. Cardiac tamponade has been noted in up to 90% of cases. Pulsus paradoxus and pericardial rubs are occasionally demonstrated.

Diagnosis Chest radiograph shows cardiomegaly in >90% of cases and may also demonstrate features of active TB. ECG shows nonspecific ST and T-wave abnormalities. Echocardiography shows non-TB specific features; effusion with fibrinous strands on the visceral pericardium. CT scans show pericardial effusion and thickening. Typical changes in mediastinal lymph nodes are seen in almost 100% of cases.

Pericardiocentesis is both diagnostic and therapeutic and shows blood-stained exudative fluid with high protein and high leukocyte count, with lymphocyte and monocyte predominance. ADA levels of 30–60 $Units \cdot L^{-1}$ indicate disease and aid therapeutic decisions. Acid-fast bacilli in pericardial fluid or pericardial tissue histology establish the definitive diagnosis. Myocardial TB is very rare and remains mainly a *post mortem* diagnosis. It presents with arrhythmias, conduction blocks, valvular insufficiency and CHF.

Skeletal TB is seen in 1–2% of all childhood TB cases. TB bacilli get deposited at the bone site forming a caseating focus, which then causes bone trabecular destruction. 50% of children have concurrent active pulmonary TB at the time of diagnosis. Most affected children are in their second decade of life except for TB dactylitis, which is common among children <5 years of age. Symptoms often begin 1–3 years after primary TB infection and diagnosis is often delayed because of lack of exposure history, nonspecific symptoms and lack of systemic illness. The most common manifestations are spondylitis (TB of the spine), arthritis and osteomyelitis.

Spinal TB constitutes ~50% of skeletal TB cases and mostly involves the thoracolumbar spine (Pott's disease). The infection spreads to involve the adjacent tissues initially and intervertebral disc later on in the process. Contiguous spread to the paraspinal muscles results in abscesses. Swelling, pain and tenderness at the site are the most common presenting symptoms. Gibbus (swelling and angulation along the spine) may be observed on clinical examination. Features of paraparesis or quadriparesis due to spinal cord compression may be observed.

Diagnosis MRI is the imaging modality of choice and determines the extent of soft tissue involvement and the level of cord compression. Radiography of the spine later in the disease progression shows loss of height of vertebral bodies, bony erosions, periosteal reaction, sequestra and vertebral collapse. Chest radiograph may demonstrate active pulmonary disease in 50% of cases. CT scans demonstrate bony sclerosis and destruction. Histopathological examination of bone biopsy specimen showing granulomatous lesions confirms

Table 1. Extrapulmonary TB treatment regimen

Manifestation	Drug regimen	Dosage	Duration of treatment
Intensive phase			
All forms of extrapulmonary TB	HRZE	H 10 mg·kg^{-1}·day^{-1} R 15 mg·kg^{-1}·day^{-1} Z 35 mg·kg^{-1}·day^{-1} E 20 mg·kg^{-1}·day^{-1}	2 months
Continuation phase[#]			
Pleural, pericardial, abdominal and renal	HR	H 10 mg·kg^{-1}·day^{-1} R 15 mg·kg^{-1}·day^{-1}	6 months
CNS TB	HR	HR as above	10 months
Skeletal TB	HR	HR as above	10 months

H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol. [#]: a thrice weekly regimen is used in the continuation phase but this is not recommended in high HIV prevalence settings, except where the child is HIV negative and DOTS (directly observed treatment, short-course) is well established.

the diagnosis. Acid-fast bacilli stains of bone specimen are often negative but culture may be positive in up to 75% of cases.

TB arthritis is usually a monoarticular disease affecting the large weight-bearing joints; the hips or knees are involved in ~30% of cases.

Clinical features resemble those of spinal TB. The diagnosis is established through radiography of the affected joint and reveals joint effusion, periarticular osteopenia, irregularity of the bone cortex, lytic lesions and periosteal new bone formation. Decreased joint space and widening of the intercondylar notch in the knee are observed in advanced disease. Marked joint destruction and fibrous or bony ankylosis are seen in end-stage disease. An ultrasound scan demonstrates joint effusion and aids the aspiration for acid-fast bacilli and culture. MRI demonstrates marrow changes, joint effusions and cartilage and bone erosions. Joint fluid aspiration or synovial biopsy is necessary for confirmation of diagnosis.

Tuberculous osteomyelitis is a very rare form of skeletal TB in children. Lesions are either solitary or multifocal.

Clinical features are local pain, swelling and tenderness of the skull vault, hands, feet and ribs with forearm bones and clavicles often involved. Short bones of the hands and feet may be affected in younger children (TB dactylitis). Systemic symptoms may be observed.

Diagnosis Radiography shows soft tissue swelling, osteoporosis, cystic bone changes and sequestrum. An infiltrative pattern resembling Ewing's sarcoma, fungal infection and chronic pyogenic osteomyelitis may sometimes be seen. Cyst-like cavities with expansion of the diaphysis, the so-called ''Spina ventosa'', may be seen. BCG osteomyelitis presents similarly and can occur a few months to 5 years post-BCG vaccination. Culture of the BCG strain establishes this differential diagnosis.

Abdominal TB is generally less common in children. It may complicate untreated pulmonary TB in ~6–38% of cases. Abdominal TB due to *M. bovis* can result when unpasteurised milk is ingested, but this is now rare.

Clinical features Abdominal TB is more common in older children and adolescents, and usually presents as enteritis or peritonitis. Patients suffer with chronic abdominal symptoms over several months: vague abdominal pain, abdominal mass, anorexia and vomiting in association with

weight loss. Physical examination shows a distended abdomen that feels "doughy" on palpation. Abdominal TB could present acutely with intestinal obstruction, perforation and peritonitis as a complication of adhesions.

Diagnosis CT scans show bowel wall thickness, ascites and the abdominal viscera and detect para-aortic and mesenteric lymphadenopathy and calcifications, which are often also visible on ultrasound. Chest radiography may reveal abnormality in 50–70% of patients. Evaluation of ascitic fluid shows lymphocytic exudates; acid-fast bacilli and culture are positive in up to one-third of patients.

Other forms of disseminated TB include renal TB and cutaneous TB. Both are extremely rare in children.

Treatment of extrapulmonary TB

The treatment of EPTB follows the same basic principles as for pulmonary TB. Treatment is divided into intensive and continuation phases. The intensive phase rapidly eliminates the majority of TB bacilli and prevents the emergence of drug resistance. The continuation phase eradicates dormant organisms. The recommended drug regimen is shown in table 1.

Corticosteroids

Corticosteroids are indicated in children with TB meningitis, TB pericarditis and possibly also in severely ill children with disseminated TB (miliary). The recommended treatment is prednisone 1–2 $mg \cdot kg^{-1}$ daily orally for 4–6 weeks in addition to TB drugs. The dose can be tapered to stop over 2–4 weeks, depending on resolution of symptoms.

General considerations

Any child presenting with disseminated forms of TB should be screened for HIV or other forms of immunodeficiencies, if known to be HIV negative.

Prolonged treatment with several drugs, possibly also including anti-retroviral therapy, requires ongoing support for parents and children and regular clinical reviews to assess response to treatment, adherence and possible side-effects/interference of medication. Drug dosage should be adjusted according to the patients' weight. Children with proven or suspected multidrug-resistant (MDR)-TB should be treated by experts and within the context of a well-functioning MDR-TB control programme. Hospitalisation is mandatory during the initial phase for disseminated forms of TB.

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Epidemiology and phenotypes of bronchial asthma and wheezing disorders

Franca Rusconi, Ben D. Spycher and Claudia E. Kuehni

Studies of the epidemiology of asthma have flourished in the last 30 years, reflecting the fact that the disease is common in developed and developing countries, the aetiology still largely unknown, and costs are high. This section explains how asthma is assessed in epidemiological surveys, describes time trends and prevalence differences by age and sex, explains the concept of asthma phenotypes, and summarises the current knowledge on natural history and long-term outcome.

Assessment of asthma in epidemiologic studies and time trends

Paediatric asthma guidelines emphasise that asthma remains a complex clinical diagnosis, which cannot be made by a single measurement or test. Physicians diagnose asthma on the basis of medical history, physical examination and assessment of reversibility of airway obstruction. In epidemiological studies, the most common approach uses questionnaires to ascertain whether subjects have had symptoms of asthma or have ever received a diagnosis of asthma from a physician.

Key points

- Asthma and wheezing disorders are heterogeneous conditions in terms of risk factors, age of onset, clinical phenotype, severity, response to treatment and long-term course.
- Despite a large body of research, the factors explaining time trends and international disparities in asthma prevalence remain largely unknown.
- Both severity of asthma and lung function show a track from early childhood to adulthood.
- It is important to study phenotype and clinical course of wheezing illness early in life when it might still be possible to modify the natural history of the disease.

The prevalence of asthma diagnosis and symptoms is dependent on the awareness of the disease in the populations studied and on diagnostic labels. The same child might be diagnosed with ''asthma'' by one doctor and with ''wheezy bronchitis'' by another. Thus, the preferred approach to assessing asthma prevalence in epidemiological studies is based on symptoms, particularly current wheeze (wheeze during the past 12 months).

The International Study of Asthma and Allergies in Childhood (ISAAC) is a major initiative involving nearly 2 million schoolchildren aged 6–7 and 13–14 years from >100 countries. It was designed to compare prevalence of asthma, rhinitis and eczema between countries (phase I, 1994–1995) and their trends over time (phase III, 5–10 years later) using standardised questionnaires (Asher *et al.*, 2006). Key findings included the high prevalence of asthma symptoms and asthma diagnosis in English-speaking countries and Latin America (>20% in most centres), intermediate prevalence in Western Europe, and low prevalence (<5%) in Eastern Europe, with a clear northwest–southeast gradient. The lowest prevalence is found in Africa and Asia with the exception of affluent

countries such as Singapore and Japan. In most high-prevalence regions, particularly English-speaking countries, prevalence of current wheeze changed little between phase I and III, and even declined in some cases, while most countries with low and intermediate prevalence reported increases. Other recent reports of time trends in Western countries, outside of ISAAC, also suggest that prevalence of wheeze might have reached a peak (Patel *et al.*, 2008). Virtually all countries reported increases in the lifetime prevalence of an asthma diagnosis, irrespective of the prevalence of wheeze. This might indicate better recognition and diagnosis of the disease, and more frequent use of the diagnostic label, which is considered less stigmatising today than it has been in previous years.

Wide variations of asthma prevalence were found within genetically similar groups; therefore, environmental and cultural factors are likely to play a role in explaining regional and temporal variations. However, the asthma risk factors studied (*e.g.* infant feeding, diet, maternal smoking, immunisations, allergens and air pollution) explain only a small part of the regional variability and time trends (Asher *et al.*, 2010).

Studies in migrants also point to the importance of socio-cultural and environmental factors. These studies generally found a steep increase in prevalence among groups migrating from low- to high-prevalence areas, particularly among those who were born in the host country or migrated during the first years of life. Unfortunately, numerous changes occur simultaneously in migrants, so it is difficult to disentangle the role of environmental factors (*e.g.* climate and allergens), behaviours (diet and smoking) and social factors that might affect their interaction with the healthcare system; for example, the likelihood of being diagnosed and treated (Kuehni 2011). Asthma risk factors are described in detail in the Genetic and environmental factors in bronchial asthma and wheezing disorders section in this *Handbook*.

Prevalence by age and sex

Only a few cohort and cross-sectional studies have described changes in asthma symptoms from infancy to adulthood. Existing studies suggest that the prevalence of current wheeze is highest in infants and toddlers, then decreases slightly to remain relatively stable throughout the school years. However, the relevance of different trigger factors changes strongly with age: while virally induced wheeze decreases, wheezing episodes triggered by pollen or exercise become more common with age.

Sex differences in asthma also change with age. In many (but not all) surveys, young boys are reported to have more wheeze and asthma than girls. In adolescence, the pattern changes and new-onset wheeze becomes more frequent in females. Explanations for this include age-related differences in the growth of the airways and lung parenchyma, sex-specific differences in environmental exposures and exercise, hormonal changes occurring during puberty, changes in symptom reporting, and sex-related underdiagnosis and under-treatment in female adolescents (Almqvist *et al.*, 2008).

Asthma phenotypes

Wheezing disorders might comprise several distinct phenotypes, possibly representing different disease entities (Silverman *et al.*, 1997). If this is true, early distinction of phenotypes would allow more focused research into aetiology and pathophysiology, prescription of treatments and preventive measures targeted to the phenotypes, and improvement in the prediction of long-term outcome. Classical approaches for distinguishing asthma phenotypes have relied on trigger factors or time course. A distinction by the main triggers led to the definitions of:

- episodic viral wheeze (wheeze occurring episodically only during viral infections);
- multiple-trigger wheeze (wheeze also occurring in response to other factors such as crying, laughter, exercise or allergens, and often associated with atopy).

While the prevalence of the former decreases during the first years of life, the latter becomes relatively more frequent, is more persistent and more likely to be diagnosed as "asthma" (Brand *et al.*, 2008). However, these phenotypes, based on triggers of wheeze only, show limited stability through early childhood, suggesting that triggers of wheeze alone are not sufficient to distinguish underlying disease processes or that the disease processes change in some children throughout this period (Spycher *et al.*, 2012).

An alternative approach distinguishes children based purely on the time course of wheezing episodes during childhood. A common distinction is between:

- early transient wheeze (wheezing only during the first 2–3 years of life);
- persistent wheeze (wheezing beginning in early life and persisting up to school age);
- late-onset wheeze (beginning to wheeze after the age of 3 years) (Martinez *et al.*, 1995).

Novel statistical approaches in large cohorts have distinguished more temporal patterns (Henderson *et al.*, 2008). Classifications by time course, however, have the disadvantage that they can only be applied retrospectively, once a child has reached a certain age. Therefore, they cannot be used to decide how to treat a preschool child or inform parents about the likely prognosis.

Recently, multidimensional approaches have been used whereby phenotypes are defined based on a wider range of concurrently assessed features using statistical methods such as latent class analysis (Spycher *et al.*, 2010). These analyses can include different asthma-related symptoms and measurements such as lung function, bronchial responsiveness, atopy or exhaled nitric oxide simultaneously, and identify groups that are relatively homogeneous with respect to these features. Such phenotypes are closer to the clinical situation, where a number of patient characteristics are evaluated by the physician simultaneously. The phenotypes defined by these methods have confirmed some of the previously suggested patterns such as transient viral wheeze and persistent atopic wheeze. Currently, phenotype research is thriving, and it is important to keep in mind that phenotype definitions only have value if they improve patient care or lead to a better understanding of disease processes.

Natural history and long-term prognosis

Childhood asthma is characterised by a highly variable time course differing by age of onset, duration of symptomatic periods, and remissions and relapses. This complicates the study of the natural history of asthma. Nevertheless, long-term prospective studies have revealed important aspects of the disease.

In one of the oldest cohort studies, the Melbourne Asthma Study (Australia), a population-based sample of 7-year-old children with a history of wheeze and an asymptomatic control group were followed over several decades (Phelan *et al.*, 2002). The study found consistent associations between severity of symptoms in childhood, defined by frequency of wheeze, and persistence of asthma up to the age of 42 years: children with frequent episodes in childhood had more severe asthma and a lower FEV_1/FVC throughout adolescence and adulthood. Eczema, hay fever or allergic sensitisation in childhood also tended to result in more severe asthma later in life.

In the Dunedin birth cohort (New Zealand) (Sears *et al.*, 2003), children with persistent wheeze throughout follow-up were more likely to be sensitised to common allergens and had lower FEV_1/FVC ratios at 26 years of age than nonwheezers. In both the Melbourne and Dunedin studies, the lung function deficit was already established by school age, suggesting an early loss of lung function in some asthmatic children and that lung function tracks over time into adulthood. These and other studies show that a considerable proportion (20–30%) of children with asthma at school age continue to have symptoms as adults, although some experience long asymptomatic periods.

A limitation of these older cohort studies is that respiratory symptoms and lung function were first assessed at school age. Thus, information on the first years of life was lacking. More recent cohort studies that have followed children prospectively from fetal life or birth and have assessed lung function in infancy, before the onset of disease, can shed more light on this critical period (www.birthcohorts.net). Importantly, it was suggested that lung function deficits might be congenital in some children, while in others they are probably a consequence of severe asthma. These hypotheses must be tested using repeated measurements of lung function from birth to late childhood. Long-term follow-up of these cohorts will clarify which children with persistent asthma are at risk of developing irreversible airway obstruction, the clinical hallmark of COPD (Martinez, 2009).

Several approaches have been taken to predict the long-term prognosis of young children with wheezing illness based on risk factors such as symptom severity, markers of atopy, parental history of asthma and environmental exposures (Savenije *et al.*, 2012). However, the ability of currently available prediction scores to identify children who go on to have asthma in later childhood has been disappointing. The most important commonly assessed predictor of future asthma is severity of current symptoms (frequency and severity of wheezing episodes) (Leonardi *et al.*, 2011). The additional prognostic value of investigations such as blood eosinophils or exhaled nitric oxide remains to be shown. In addition, currently proposed prediction models have been developed for specific age groups, and might not be generalisable to older or younger children.

In summary, the concept of an early window of susceptibility, beginning in fetal life, and the tracking of certain characteristics of asthma from childhood to adulthood, including severity and impairment of lung function, stress the importance of characterising the clinical course of the disease early in life, when, in principle, it is still possible to modify natural history.

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Genetic and environmental factors in bronchial asthma and wheezing disorders

Oliver Fuchs and Erika von Mutius

Asthma is a disease with a strong genetic background. Asthma heritability, *i.e.* the variance caused by genetic factors, has been estimated to be between 35% and 95%. Asthma heritability can be explained by genetic or by epigenetic effects. Understanding the genetic disease background is important, as it offers the opportunity of new therapies or even preventive measures. Moreover, it helps to understand the overlap between pathogenic pathways or aetiologies of asthma-related traits and intermediate phenotypes such as allergic rhinitis, atopic eczema, IgE levels or lung function parameters, *e.g.* bronchial hyperresponsiveness (BHR). So far, there is evidence for both common and distinct aetiological pathways. For the latter, loci identified to be associated with lung function were not related to asthma, implying that causal pathways are distinct. It is still unclear whether these reflect diverse pathways or whether some phenotypes share a number of them, at least partly.

Key points

- For childhood asthma and wheezing disorders both genes and the environment play a role, which is why they are complex diseases.
- Genetic studies have identified numerous risk loci for childhood asthma, in particular the GSDMB-*ORMDL3* locus on 17q21, which has replicated numerous times and has the strongest effect on childhood-onset asthma found to date.
- Epidemiological observations have identified both protective environments and risk factors associated with childhood asthma and wheezing disorders. The most robust and consistent finding relating to risk is ETS exposure, particularly maternal smoking during pregnancy.
- Gene–environment interactions, for example ETS, and the association of the 17q21 locus could be established in relation to childhood asthma.

Historically, different methods have been used to assess genetic associations with asthma-related traits. Table 1 displays all existing approaches, their concepts as well as their individual benefits and downsides relating to study design, sample size requirements and need for replication. The first studies were genome-wide family-based linkage studies and subsequent positional cloning. Generating hypotheses to be tested in subsequent analyses, they led to the discovery of various genetic loci and genes related to asthma, *e.g. ADAM33* (potential role in airway remodelling), *SPINK5* (role in integrity of airway epithelium), or *STAT3* (IgE level). Based on the hypothesis that they were asthma-related due to biological, pathophysiological or functional relevance, the majority of genetic variants associated with asthma, however, were discovered by candidate-gene approaches. Within these studies, numerous genetic variants, such as *CD14* (involved in innate immunity), *TGFB1*, *ADRB2*, *NOS1–3* (roles in lung function, lung growth and development, allergic airway inflammation) have been identified.

Emerging high-throughput techniques helped to detect asthma-related genetic loci in large populations. Genome-wide association studies (GWAS) included several hundred thousand single-nucleotide polymorphisms (SNPs) across the whole human genome. Due to decreasing costs, their number is steadily increasing. Until the end of 2012, 1489 GWAS, 22 thereof on asthma, were listed on www.genome.gov/gwastudies. The first asthma GWAS described the *GSDMB-ORMDL3* locus on chromosome 17q21. This locus was replicated in independent populations and has the strongest effect on childhood-onset asthma. Being involved in intracellular Ca^{2+} flux and possibly contributing to airway remodelling, there is also a plausible mechanism related to *ORMDL3*. The GABRIEL Consortium performed the largest GWAS for childhood asthma to date. Seven loci, *IL18R1*, *HLA-DQ*, *IL33*, *SMAD33*, *IL2RB*, *GSDMA*, and *GSDMB-ORMDL3*, were identified. More recently, it has become possible to apply extensive sequencing of whole genomes for the discovery of mutations associated with childhood wheeze and asthma. As whole-genome sequencing is still overly expensive, whole-exome sequencing, *i.e.* analysing enriched coding sequences (exons) of the human genome, may be a way to go until whole-genome sequencing, including other but putatively nonetheless important non-coding sequences such as introns, will become affordable in large studies.

Unfortunately, the genetic basis of asthma is as yet unknown. Instead of discovering "the" asthma gene or a few genes with strong effect sizes, analyses to date discovered several loci each with small effects. With relatively low positive predictive values even for highly associated risk alleles, the utility of genetic data in personalised medicine for diagnostic or even predictive testing of asthma in the individual is still science fiction. Nevertheless, current evidence has promoted the field on a population level. An example for this is the population under study in the GABRIEL Consortium mentioned above. Here, at least 38% of childhood-onset asthma could be explained by the seven identified genetic loci. Figure 1 displays the genetic loci discovered in asthma GWAS until the end of 2012.

What is the best approach to identify genetic variants conferring risk for development of childhood wheeze and asthma? As all methods have their advantages and disadvantages, they may play a role altogether and consequently, there will be trade-offs for their benefits and downsides. Moreover, careful disease phenotyping is necessary as childhood asthma is not one disease entity but many. If one is interested in discovery and analysis of genes conferring only modest effect sizes, GWAS and candidate gene approach would be favourable. If one is interested in rare variants, sequencing might be the best approach, perhaps even family-based linkage studies (table 1).

The epigenome

In addition, alterations in gene expression by activation and deactivation of genes without any changes in the underlying DNA sequence may influence the risk of childhood asthma and wheezing disorders. This is called the epigenetic effect. It can be mediated by methylation of cytosine to 5-methylcytosine and *vice versa* mostly at sites with a cytosine in linear sequence with a guanine base on the same DNA strand, leading to gene silencing. Epigenetic effects can also be mediated by non-coding RNA species (such as miRNAs) and through alterations of chromatin by histone modification (methylation, acetylation, ubiquitinylation, phosphorylation and sumoylation).

The possible role of epigenetics in asthma is highlighted by several findings. So far, pure genetics explain only limited heritability. Moreover, affected mothers transmit asthma more often to their offspring than affected fathers, *i.e.* there is a clear parent-of-origin effect for asthma, possibly due to maternofetal immune-interactions or to imprinting. However, epigenetic studies in asthma are complex and their possible use is still unclear. First of all, unlike genetic

Table 1. Methods to assess genetic associations with asthma-related traits

Best for	Approach	Concept	Comparisons	Advantages	Disadvantages
Study of common variants	Currently done: candidate-gene approach	Hypothesis driven Includes genes *a priori* thought to be asthma-related due to biological, pathophysiological or functional relevance or known to be associated with asthma SNP analysis within genes or regions of interest, targeted SNP analysis possible, tagging of non-represented SNPs by analysis of SNPs in LD	Frequency of alleles in gene of interest of individuals with asthma *versus* healthy controls Risk of asthma can be computed depending on study design (case control: OR; prospective: RR).	Cheap Results can be rapidly interpreted Straight-forward because hypothesis driven	Limited as it relies on existing evidence Does not lead to discovery of genes or SNPs
	Currently done: GWAS	Hypothesis free, can be hypothesis generating SNP analysis covering the whole genome, tagging of non-represented SNPs by analysis of SNPs in LD	SNPs of whole genomes of individuals with asthma *versus* healthy controls Risk of asthma can be computed depending on study design (case control: OR; prospective: RR)	Is becoming cheaper, several platforms available May lead to discovery of genes or SNPs High resolution due to proceeding SNP discovery Imputation of additional SNPs in LD to covered variants possible	Limited to common SNPs (usual MAFs are 1–5%) and to SNPs represented on platform or that can be tagged (needs LD) Large sample sizes and replication in at least one independent population are needed
Study of rare variants	Currently done: sequencing, either genes, exomes or whole genomes, so-called "next-generation sequencing"	Can be both hypothesis free (exome or whole genome) or hypothesis driven (gene), may generate new hypotheses Enables analysis of DNA sequence and thus of all sequence variation	Gene of interest or exomes as well as whole genomes of individuals with asthma *versus* healthy controls Risk of asthma can be computed depending on study design (case-control: OR; prospective: RR)	May reveal rare variants (MAFs below thresholds of GWASs) Enables fine-mapping of ROIs	Expensive Can be difficult to interpret, computational and bioinformatic analysis is demanding Large sample sizes and replication in at least one independent population are needed
	Historically and currently done: linkage study followed by positional cloning study	Hypothesis free, can be hypothesis generating Gene identified by genome-wide linkage study Genomes screened with genetic markers evenly dispersed over whole genome Linkage: marker is inherited together with disease more often than expected by chance	Studied in families (usually with two affected siblings and unaffected parents) Risk of asthma computed as log of odds in favor of linkage (LOD score) Identification of genes or SNPs by fine-mapping (positional cloning) is possible Further analyses are needed to define gene function	May lead to discovery of new ROI or gene, perhaps SNP of interest May also lead to discovery of rare variants Requires relatively few markers	Relatively expensive Laborious and time intensive Needs families Needs several steps for discovery of gene of interest Limited resolution

LD: linkage dysequilibrium; OR: odds ratio; RR: relative risk; MAF: minor allele frequency; ROI: region of interest.

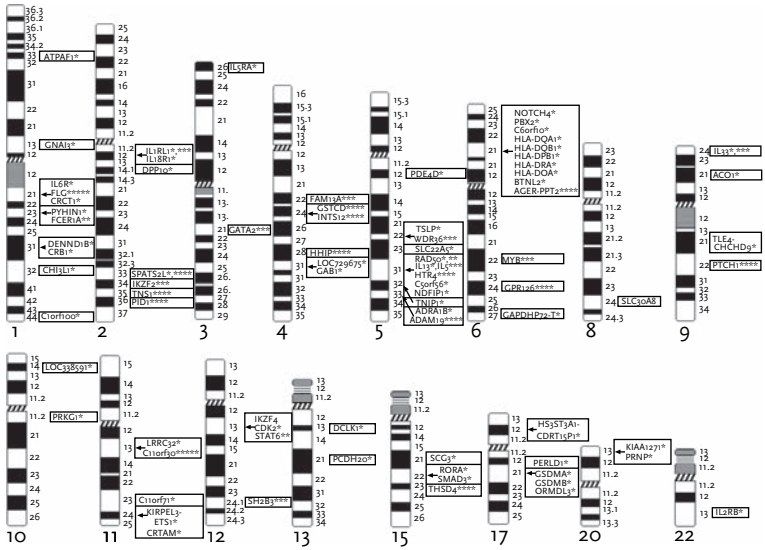

Figure 1. Genetic loci discovered in GWASs until the end of 2012 on asthma (*) and related traits: IgE levels (**), eosinophil count (***), lung function (****) and atopic dermatitis (*****). Locus positions are shown down to chromosome, region and bands. Arrows represent partly sub-bands. Short arms of chromosomes (p) face upwards and long arms (q) face downwards. Data courtesy of D. Vercelli (Arizona Respiratory Center, Tucson, AZ, USA; personal communication). Image courtesy of M. Rocchi (University of Bari, Bari, Italy; personal communication).

variants, epigenetic modifications may be in a constant state of flux. It is difficult to decide when to measure and what cell types or tissue to analyse. Likewise, their relative contribution to gene expression and especially their heritability across generations is unknown.

There is evidence from both animal and human studies for epigenetic regulation in asthma and wheezing disorders. Mouse studies demonstrated an influence of maternal methyl-donor rich diet on BHR, airway inflammation and serum IgE levels in offspring. Also exposure to environmental microbes can act by epigenetic regulation as shown by a study in mice where prenatal administration of the farm-related bacterial species *Acinetobacter lwoffii F87A* prevented an asthmatic phenotype in the offspring. In immunology, epigenetic mechanisms are known to be involved in T-cell differentiation (*e.g.* by modification of the *IFNG* promoter for T-helper (Th)-1 cells, as well as for Th2, and of *FOXP3 for* regulatory T-cells (Treg)). Thus, epigenetic modification may possibly impact asthma with Th2-skewing, as it is known that such immune responses contribute to asthma development. Here, human studies have demonstrated the impact of air pollution as an environmental factor on *FOXP3* methylation and Treg cell function in asthmatic children. Furthermore, epigenetic effects on more intermediate outcomes such as atopy and allergic airway inflammation, lung function and on childhood wheeze subtypes are also supported by data derived from human studies. Due to ethical constraints, human studies have examined epigenetic effects in cells outside the lung, mostly peripheral blood cells, but also in possibly more relevant buccal and nasal cells or in cells from sputum. Such easily obtained material might be useful for markers of childhood asthma as demonstrated by the fact that hypo-methylation in *Alox12* even in peripheral blood cells was associated with

persistent wheeze. For exhaled nitric oxide as a marker of allergic airway inflammation data are conflicting.

The environment

There is evidence that the environment plays a significant role as populations with very similar genetic backgrounds show different rates of childhood asthma and wheezing disorders. Epidemiological observations have identified protective environments and risk factors associated with the development of childhood asthma and wheezing disorders. The most robust and consistent finding conferring risk is environmental tobacco smoke (ETS) exposure, particularly maternal smoking during pregnancy. In numerous studies, these exposures have been shown to be associated with an increased risk of wheezing and childhood asthma. Passive smoke exposure through other family members also increases the risk of wheeze and childhood asthma in many studies. Interestingly, the ban on tobacco smoking in public places established in Scotland in 2001 significantly decreased the rates of hospitalisation for asthma by ~15%. Moreover, active smoking in children and adolescents has been related to increased risk for new-onset or progression of asthma in this age group.

With respect to outdoor air pollution, studies relating to the density of car traffic, in particular truck traffic on roads in close proximity to the child's residence, have been most conclusive. Here, particles with aerodynamic diameters between 2.5 μm ($PM_{2.5}$, able to enter the alveoli) and 10 μm (PM_{10}, too large to enter the alveoli), ozone and nitrogen dioxide were demonstrated to affect lung growth and to be associated with reduced lung function and airway inflammation in children, even prenatally. This underlines the importance of adverse effects during the most vulnerable phases of lung development early in life and it is not limited to outdoor air pollution. Indoor parameters in addition to ETS may play a role. Besides pollutants resulting from indoor heaters and fireplaces (carbon monoxide, nitrogen dioxide, polycyclic aromatic hydrocarbons, volatile organic compounds (VOCs) and PM), VOCs and formaldehyde from new furniture, for example, have been related to childhood asthma. Moisture damage, as well as mouldy spots indoors, has been shown to increase the risk of childhood asthma and wheezing disorders.

Importantly, viral infections in early life have been related not only to asthma exacerbations but also to the development of childhood wheeze and asthma, especially if they occur against a background of early atopic sensitisation. In turn, the role of allergen exposure has been highly debated. There is evidence that indoor allergen exposure is a determinant for the development of allergic sensitisation towards this particular allergen. In contrast, allergen exposure has not convincingly been associated with the development of childhood asthma and wheezing disorders. Avoidance of house dust mite exposure has not achieved a reduction in asthma risk. However, carers of children who are already sensitised and allergic to indoor allergens such as house dust mite, cat or dog dander should clear indoor environments of these allergens as they may trigger symptoms. Lifestyle factors have also been shown to play a role. These include maternal diet during pregnancy as well as diet in early and later childhood, in particular breastfeeding, a Mediterranean diet and vitamin intake. BMI and obesity have been debated for a number of years. These might be related to a changed inflammatory state, especially due to central obesity, increased insulin resistance and further metabolic alterations, which may lead to asthma. Furthermore, there is evidence that, particularly in adolescent females, an increase in body weight, which may be related to early menarche, is a determinant for new onset of asthma in these subjects. The role of physical activity remains unclear. Reduced physical activity may be a consequence of asthma and wheeze rather than a causal factor for the new onset of disease.

In the context of protective environments, studies have consistently shown that growing up on a traditional farm reduces the

risk for asthma and hay fever. These studies have consistently been reproduced in many countries worldwide. The important exposures relate to contact with farm animals, their fodder and unprocessed cow's milk which have been identified in a number of studies. The protective farm effect on asthma is, at least in part, attributable to environmental bacteria and fungi, which are highly prevalent in these environments. Experimental studies using microbes cultured from farming environments confirm the preventive effect of exposure for the development of allergic asthma in mice.

The role of gene–environment interaction

Given the high prevalence of asthma, it is of major public health relevance to elucidate the effects of genes and the environment in the study of pathological pathways in asthma. By fixing one parameter in the equation, it is possible to disentangle their individual impacts. As highlighted above, one may identify genetic factors by studying populations sharing similar environments; by studying populations sharing the same genetic background but living under different environmental conditions, one can identify relevant environmental impacts. However, asthma and wheezing disorders probably result from a joint effect of genes and the environment and their interaction, *i.e.* the dependence of effects by one factor on the presence or absence of another factor. Technological progress has advanced the field of gene–environment interactions in asthma, as the analysis of gene–environment interactions on a genome-wide level, *i.e.* gene–environment-wide interaction studies (GEWIS) have been introduced recently. This poses a challenge to even highly advanced computational systems. In addition to what has been mentioned for the study of genetic and epigenetic effects, there is probably even more complexity in gene–environment interactions analysis. Moreover, the time-point when exposures have the biggest effect on the outcome under study has to be taken into account (window of opportunity). Thus, for gene–environment interaction studies there is a clear need for similar stringent quality control and replication and the same necessities in study design and careful phenotyping as discussed previously.

There are examples for gene–environment interactions in the field of asthma and wheezing disorders on different levels of analytical approach. The first level is that of a known candidate gene and a well-defined environmental exposure with suspected gene–environment interactions, such as in the interaction of endotoxin (a component of the cell wall of Gram-negative bacteria) with the gene for its receptor *CD14* for the risk of asthma and/or atopy. Another example is ETS exposure and the 17q21 locus. Here it has been shown that the increased risk for childhood-onset asthma is further increased by ETS exposure in early life, itself known to confer a risk for early-onset disease. The first GEWIS for asthma assessed gene–environment interactions in the field of the protective farm effect on asthma in children. Neither significant interaction of farm-related exposures with common SNPs nor with previously published genetic markers of asthma was found.

Thus, in the field of asthma and wheezing disorders, few gene–environment interaction mechanisms have been established although epidemiological studies have demonstrated numerous environmental exposures associated with asthma and studies to date on the genetic background have identified a number of asthma-associated loci. Future research will have to take into account windows of opportunity for exposures under study as well as better characterised wheezing phenotypes.

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Acute viral bronchiolitis

Fabio Midulla, Ambra Nicolai and Corrado Moretti

Definition

Bronchiolitis is an acute viral respiratory infection involving the terminal and respiratory bronchioli in infants, resulting in small airways obstruction. Bronchiolitis is a clinical diagnosis but, despite its high frequency, its definition is still controversial. The American Academy of Pediatrics subcommittee defines bronchiolitis as a disorder in infants <24 months of age that is most commonly caused by a viral lower respiratory tract infection characterised by wheezing. In contrast, European guidelines define bronchiolitis as a seasonal viral illness in infants <12 months of age characterised by nasal discharge, cough, tachypnoea, retractions and bilateral crackles. These definitions reflect differences in how the disease is interpreted and the North American definition, in particular, might engender an overlap between bronchiolitis and early wheezy bronchitis.

Key points

- Bronchiolitis is the first episode of acute viral infection of terminal and respiratory bronchioli in infants <1 year of age.
- Symptoms of bronchiolitis are moderate-to-severe respiratory distress with rales at auscultation.
- Supportive therapies aim to keep the upper airways clear, and the infant oxygenated and hydrated.
- A bronchodilator mixed with 3% hypertonic saline might be tried and this combination should be continued only if it achieves a documentable clinical benefit.

Epidemiology

Bronchiolitis is the most frequent infectious disease in children <1 year of age (90% of patients are 1–9 months of age), and is the leading cause of hospitalisation in this group of infants. Bronchiolitis is epidemic between November and April. Annually, 11 out of every 100 infants have bronchiolitis and 11–13% of patients require hospitalisation. Each year 150 million new cases of bronchiolitis are reported worldwide. Only 1–3% of infants require admission to intensive care, particularly those in whom risk factors are present.

Aetiology/risk factors

Bronchiolitis is caused by viruses. The most common viruses responsible are respiratory syncytial virus (RSV), human bocavirus, rhinovirus, human metapneumovirus, influenza A and B, and parainfluenza viruses 1–3.

Risk factors for severe bronchiolitis are age <3 months, male sex, low socioeconomic conditions, maternal smoking and RSV infection. Other risk factors for severe bronchopulmonary are prematurity with bronchopulmonary dysplasia and coexisting co-morbidities, such as cardiovascular diseases, immunodeficiency and chronic respiratory diseases. The only protective factor is maternal breastfeeding.

Pathophysiology

Viral respiratory infection results in respiratory epithelium necrosis, loss of

epithelial cilia, collection of desquamated airway epithelial cells, lymphocyte and neutrophil infiltration within terminal and respiratory bronchioli, and oedema around the airway. Cellular debris, inflammatory cells and fibrin cause airway obstruction. Mucus plugs can partially or totally occlude the bronchioli. When the bronchioli are completely occluded, atelectasis develops; if bronchioli are only partially occluded, diffuse air trapping occurs (fig. 1).

The increase in airway resistance and decrease in dynamic lung compliance increase the work of breathing. Atelectasis and air trapping result in hypoxaemia and increased carbon dioxide due to an altered ventilation/perfusion ratio. Tachypnoea, increased work of breathing and reduced feeding can cause dehydration with metabolic acidosis.

Diagnosis

Bronchiolitis is commonly diagnosed on clinical grounds alone without help from diagnostic tests. The criteria for the diagnosis of bronchiolitis include exposure to other children or adults with respiratory viral infection, age <12 months, preceding upper respiratory illness and signs of acute lower respiratory illness (respiratory distress, low oxygen saturation, rales and, rarely, wheezing). Chest radiographs and blood tests are required only if suggested by clinical indications; blood gas analysis is recommended only in more severe cases. Rapid virus detection could reduce antibiotic use.

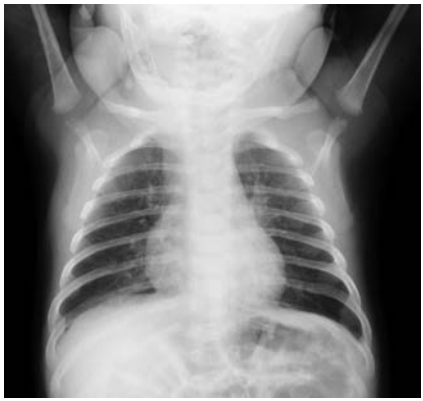

Figure 1. Chest radiograph of an infant with severe acute bronchiolitis showing diffuse air trapping and peribronchial thickening.

Symptoms

The natural history of bronchiolitis is of a self-limited disease that usually lasts for 3–7 days with an average duration of hospitalisation of 3.9 days. A small minority of infants, especially those with associated comorbidities, may require intensive care and mechanical ventilation.

The initial symptoms of bronchiolitis are rhinorrhoea and cough, sometimes accompanied by a low-grade fever. The first clinical symptom could also be episodes of apnoea, especially in preterm infants, but most infants with bronchiolitis manifest tachypnoea, retractions, nasal flaring, rales at auscultation and hypoxaemia. Other symptoms might include dehydration with metabolic acidosis. SIADH (syndrome of inappropriate secretion of antidiuretic hormone) is common in infants with severe respiratory distress and can cause hyponatraemia and accidental fluid overload. Bronchiolitis is a ''dynamic disease'' and its clinical characteristics can quickly change.

Admission criteria include respiratory distress, apnoea, tachypnoea, oxygen requirement, poor feeding, dehydration, continuous clinical assessment of airway clearance requirement, underlying chronic disease, and inappropriate social and family conditions.

The major discharge criteria are oxygen saturation that stably remains >90–94% in room air in the absence of respiratory distress, and adequate daily oral intake (>75% of usual intake) at a level to prevent dehydration followed by adequate parental care and family education about the potential duration of acute symptoms.

Indications for intensive care unit consultation and admission include failure to maintain S_{pO_2} >92% with oxygen

therapy, deteriorating respiratory status with exhaustion, and recurrent apnoea.

Supportive therapy

General management includes therapies intended to reduce the work of breathing (keep upper airways clear by using vasoconstrictors and nasal suction), and to restore clinical stability (oxygenation and hydration). Heart rate, respiratory rate and S_{pO_2} should be monitored for at least the first 24 h. A small minority of patients with severe bronchiolitis need airway support either *via* CPAP or mechanical ventilation (fig. 2).

In infants with mild bronchiolitis, breast feeding should be supported and small volume and frequent feeding should be encouraged. Nasogastric feeding should be considered in infants with severe bronchiolitis and intravenous hydration should be given only if nasogastric feeding is not possible or in infants with severe dehydration. Intravenous fluid should be administered carefully to avoid fluid overload (SIADH).

According to the American Academy of Pediatrics oxygen should be administered only when saturation at room air is $<$90% in the absence of respiratory distress, while the Scottish Intercollegiate Guideline Network guidelines recommend the use of oxygen until oxygen saturation remains permanently $>$95%. Oxygen is usually administered *via* nasal cannula or a head box. Recent evidence shows that oxygen can be given efficaciously with heated humidified high-flow nasal cannula; its presumed role is reduction of the work of breathing, prevention of dynamic airways collapse and improvement of gas exchange.

Indications for CPAP include severe respiratory distress, a need for an inspiratory oxygen fraction (F_{IO_2}) $>$0.5 or the presence of apnoea. It is hypothesised that the addition of heliox to CPAP, transforming turbulent gas flow into laminar gas flow, could improve the washout of carbon dioxide as well as oxygenation in the newly recruited airways with a consequent decrease of the work of breathing. Unfortunately, the potential benefit of CPAP in preventing mechanical ventilation could not be evaluated.

Pharmacological therapy

Current clinical evidence shows that bronchodilators produce small short-term improvements in clinical scores. A trial with salbutamol is justified in infants with severe respiratory distress. Inhaled salbutamol should be continued only if clinical examination documents a significant clinical response (*e.g.* decreased respiratory rate or an improvement in S_{pO_2}).

Nebulised racemic adrenalin provides better short-term improvement in the clinical score than placebo, particularly in the first 24 h. Clinical trials have shown adrenaline to be superior to placebo and salbutamol. Inhaled adrenalin should be continued only if clinical examination documents a significant clinical response.

A recent Cochrane Review of seven trials showed that nebulised 3% hypertonic saline alone or together with a bronchodilator effectively reduces the length of hospitalisation among infants with nonsevere acute viral bronchiolitis, and improves clinical severity scores in outpatient and inpatient populations. Hypertonic saline, through osmosis, causes water to move from the interstitium into the airway thereby decreasing interstitial oedema and mucosal viscosity.

Current evidence provides no support for a clinically beneficial effect of systemic or inhaled glucocorticoids.

No evidence justifies using antibiotics in bronchiolitis because it is a viral disease and affected infants rarely undergo bacterial superinfection. Antibiotic treatment should be recommended only in infants with severe bronchiolitis requiring intubation, a group in whom bacterial superinfection is more common.

Nebulised DNase and montelukast are not indicated in the treatment of bronchiolitis. In infants with a history of prematurity with episodes of apnoea, caffeine appears to be a rational choice of treatment.

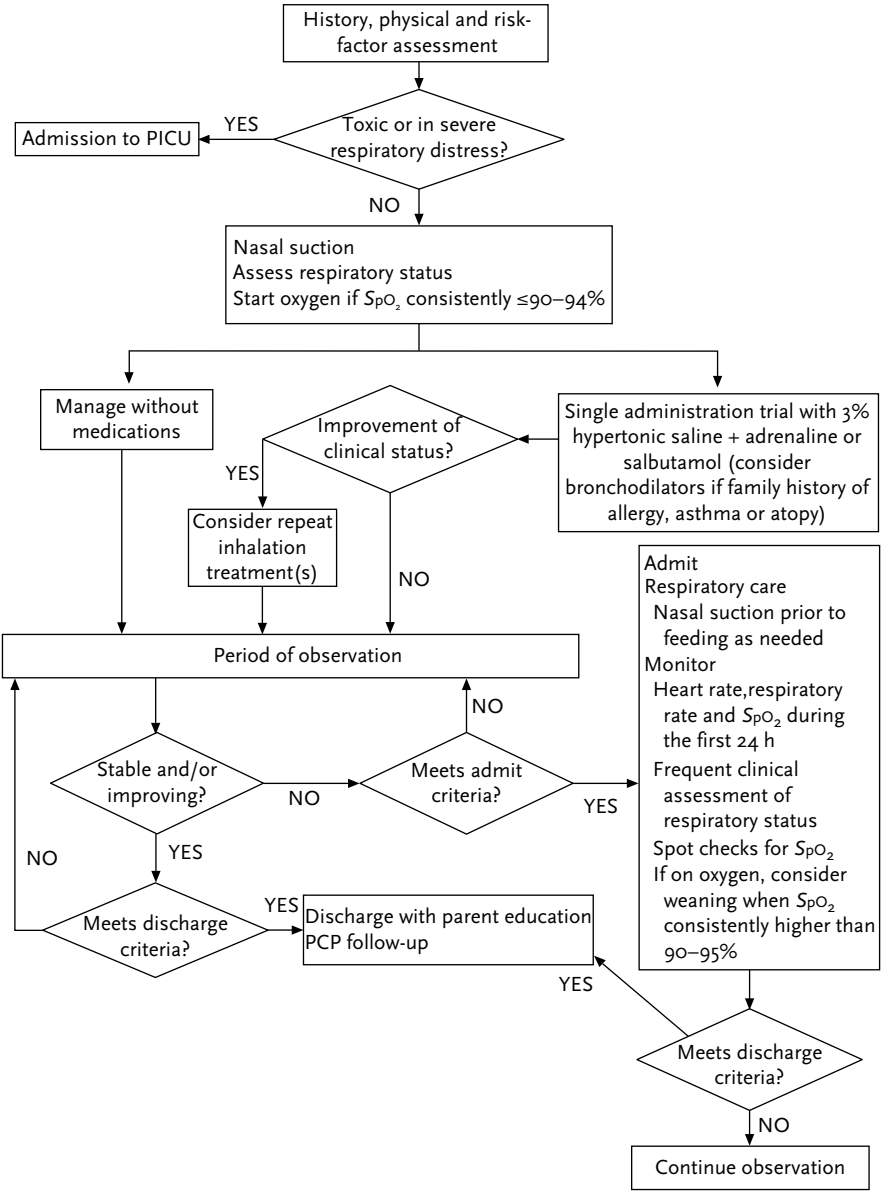

Figure 2. An algorithm for the management of bronchiolitis in the emergency department. PICU: paediatric intensive care unit; PCP: primary care physician.

Prevention and prophylaxis

Preventative measures include adequate healthcare professional education about epidemiology and control of viral infection, such as washing the hands before and after caring for patients with viral respiratory symptoms and single rooms for infected patients. Equally important, adequate local policies should restrict hospital visiting by those with symptoms of respiratory infections.

Palivizumab is a humanised monoclonal RSV antibody licensed for preventing the development of severe diseases arising from an RSV infection. Palivizumab prevents hospital admission for RSV infections, but does not decrease length of stay or oxygen requirements for those who are hospitalised. Palivizumab is a useful therapeutic option in infants <12 months who have severe comorbidity (extreme prematurity, congenital or acquired lung diseases, congenital heart disease and immune deficiency).

Prognosis and follow-up

Mild respiratory symptoms may last for ~3 weeks after bronchiolitis. About 50% of children with bronchiolitis may have episodes of wheezing in later years. The most important risk factors for recurrent and persistent wheezing after bronchiolitis are rhinovirus infection and a positive family history for atopy.

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Preschool wheezing

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Wheezing and dyspnoea in preschool children are among the most common presenting symptoms in paediatric practice. Approximately one in three children will have at least one episode of wheeze before their third birthday. There is much clinical heterogeneity in phenotypes of children with preschool wheeze, which appears to be similar between populations. Due to this heterogeneity, and despite its common occurrence, relatively little evidence is available on the pathophysiology and treatment of wheezing in preschool children. Therefore, considerable controversy exists in the literature about the classification and the treatment of preschool wheezing disorders. To end this controversy, the underlying pathophysiology and aetiology of preschool wheezing disorders need to be properly understood.

Key points

- Despite the favourable natural history in the majority of children with wheeze during preschool years, symptoms in this age range can be severe or frequent, justifying maintenance treatment.
- Limited information is available on the pathophysiology of recurrent wheeze in preschool children, which is likely to be complex and multifactorial. As a result, one-dimensional classification systems (*e.g.* episodic viral *versus* multiple-trigger wheeze) are of limited value in diagnosis and management.
- ICS are recommended as first choice maintenance therapy in children with frequent or severe symptoms irrespective of phenotype. Montelukast is an alternative maintenance treatment option, although it is less effective than ICS.
- If symptoms persist despite maintenance treatment ongoing exposure to relevant inhalant allergens and tobacco smoke, poor adherence or inhalation technique, alternative diagnoses and relevant comorbidity should be excluded before stepping up therapy.

Epidemiology

Much of the knowledge on recurrent wheeze and dyspnoea in preschool children comes from a series of well-designed, large-scale birth cohort studies. The most well-known of these was conducted in Tucson, AZ, USA. The main results of this landmark study, the Tucson Children's Respiratory Study, are as follows:

- 826 infants were followed from birth;
- during the first 3 years of life 30% of children had had at least one episode of wheeze and half of these children had wheezed more than once;
- 60% of wheezy preschool children ceased to wheeze before the age of 6 years (transient wheeze associated with maternal smoking and with wheeze occurring only during viral colds);
- 40% continued to wheeze after their sixth birthday (persistent wheeze associated with eczema, maternal asthma and elevated cord blood IgE).

In contrast with asthma in school-aged children, which is more likely to persist throughout childhood, many wheezy preschool children outgrow their symptoms by school age. This prompted efforts to identify factors that could predict persistence of preschool wheeze into school age, and to classify preschool wheezing disorders into different phenotypes with different treatment response or outcome.

Predicting the outcome of preschool wheeze

Despite differences between studies, atopy during early childhood has consistently been identified as the most important risk factor for wheeze persisting beyond the sixth birthday, in a dose–effect relationship: the more allergens the child is sensitised to, and the stronger the degree of sensitisation, the greater the likelihood the child's wheeze is going to be persistent. Although asthma risk indices constructed of different risk factors are significantly associated with persistent wheeze in groups of children in birth cohort studies, they have not been validated prospectively, and the predictive value of these indices is too poor to allow meaningful prediction of outcome of preschool wheeze in individual cases.

Classification of preschool wheeze

The finding in the Tucson study that wheeze occurring only during viral colds was associated with transient wheeze suggested that exclusive viral-induced wheeze in early childhood might be an innocuous disease, which is likely to disappear when children get older. However, this hypothesis is not supported by follow-up studies, which showed that the majority of children with episodic viral wheeze (EVW) seen in secondary care continue to wheeze beyond the age of 6 years.

In 2008, a European Respiratory Society (ERS) Task Force report proposed to distinguish two wheezing phenotypes in preschool children. 1) EVW: wheezing in discrete episodes associated with viral upper respiratory tract infections (URTIs) and no symptoms between episodes; and 2) multiple-trigger wheeze (MTW): wheeze both in discrete episodes and between episodes, with numerous triggering factors including viral colds, mist, exercise, *etc.* (table 1). Based on the evidence available at that time, this distinction was considered to be both clinically plausible (most experts in the ERS Task Force felt they could distinguish these phenotypes reliably based on the patient's history) and meaningful, because the few published studies appeared to support the view that inhaled corticosteroids (ICS) were the treatment of choice for MTW, and that EVW might respond more favourably to maintenance treatment with montelukast. The ERS Task Force acknowledged that these recommendations were likely to change with new evidence becoming available.

Limitations of the EVW–MTW phenotype distinction

Although the ERS Task Force classification system has been widely adopted, it has been criticised as being too simple to capture the multidimensional nature of preschool wheezing, and it has been suggested that EVW and MTW do not represent different phenotypes, but rather different degrees of severity of the same disease. In addition, the classification system is hampered by the fact that viral colds are the main cause of exacerbations, both in EVW and in MTW. Evidence from a range of recent studies suggests that the ERS classification system should be reconsidered.

First, prospective studies have shown that these phenotypes are not stable over time; when repeatedly taking a history from parents about their preschool child's wheeze symptoms, the symptom pattern changes over time from EVW to MTW and *vice versa*. Secondly, the distinction between EVW and MTW does not take the severity and frequency of episodes of wheeze into account, while in clinical practice these factors are more important in determining the initiation and choice of maintenance therapy than the temporal pattern of symptoms. Thirdly, although statistically significant differences in physiology and pathology between the two phenotypes have been demonstrated, the two phenotypes also show considerable clinical overlap.

Table 1. Different classification systems for preschool wheeze

Atopic *versus* non-atopic wheeze
Atopic wheeze (or allergic asthma): three or more episodes of wheeze and dyspnoea AND demonstrated sensitisation to inhalant or food allergens
Non-atopic (or viral) wheeze: three or more episodes of wheeze and dyspnoea, only occurring during URTIs, AND no evidence of allergic sensitisation to inhalant or food allergens
EVW *versus* MTW
EVW: wheezing during discrete time-periods, often in association with clinical evidence of a viral cold, with absence of wheeze between episodes
MTW: wheezing that shows discrete episodes, but also symptoms between episodes
Mild and infrequent wheeze *versus* severe or frequent wheeze
Mild and infrequent wheeze: wheeze with little impact on daily life of affected children, and with a low frequency of episodes (less than one episode per month)
Severe or frequent wheeze: wheeze with considerable impact on daily life of affected children (requiring hospital admission or emergency room visit), or with a high frequency of episodes (two or more per month)
Data from Brand *et al.* (2008), Pedersen *et al.* (2011), and Schultz *et al.* (2011).

With respect to inhaled steroid treatment, a systematic review showed that ICS are effective in reducing preschool wheeze, irrespective of the reported symptom pattern (EVW or MTW). A recent large trial in the USA showed that daily nebulised low-dose budesonide was no more effective in reducing the number and severity of wheezing episodes in preschool children than intermittent use only during symptomatic episodes. While episodic nebulised budesonide was no more effective than episodic use of montelukast in preschool children with viral-induced wheeze, daily use of nebulised budesonide was more effective than daily montelukast in children aged 2–8 years with mild persistent wheezing.

Different ways to classify preschool wheeze

Based on the available evidence, several classification systems of preschool wheeze have been proposed (table 1). None of these systems is universally accepted, which is not surprising given the limited evidence on which they are based. There is no consensus on the preferred terminology.

Diagnostic approach to preschool children with recurrent wheeze and dyspnoea

Wheeze is a nonspecific symptom, which may be caused by a range of clinical conditions. The initial diagnostic approach to a preschool child with wheeze is aimed at excluding serious underlying conditions, which usually present in the form of ''atypical wheeze'' (table 2). A detailed history and thorough physical examination when the child is symptomatic are usually sufficient to exclude atypical wheeze. If history and physical examination suggest the possibility of atypical wheeze, specific further diagnostic testing is indicated.

The majority of preschool children presenting with troublesome wheeze and dyspnoea will have ''typical wheeze'', after exclusion of the unlikely causes listed in table 1. Because parents differ from physicians in their understanding of the term ''wheeze'', confirmation of the presence of wheeze by a physician is recommended before initiating therapy. In children with confirmed typical wheeze, the only potentially useful diagnostic test is a test of allergic sensitisation (either skin-prick test or measurement of specific IgE to a panel of allergens in blood) for classification purposes (table 1).

Treatment of acute episodes

The initial treatment of choice in episodes of acute wheeze is an inhaled bronchodilator

Table 2. Atypical wheeze: warning signs and possible underlying conditions

Warning sign	Possible underlying causes
Persistent symptoms from birth	Tracheobronchomalacia and PCD
Productive wet cough as a main symptom	PCD, CF, immune deficiency and TB
Never completely symptom free	Tracheobronchomalacia, vascular ring, foreign body aspiration and neonatal chronic lung disease
Failure to thrive	CF and immune deficiency
Recurrent pneumonia	CF and immune deficiency

PCD: primary ciliary dyskinesia.

such as salbutamol, preferably by metered-dose inhaler-spacer combination because this is more effective than treatment delivered by a nebuliser. Oral corticosteroids are less effective in preschool children with an episode of acute wheeze than in older children with asthma, and are only recommended in children who require hospitalisation and supplemental oxygen for a severe exacerbation, or those with atopic wheeze. Pre-emptive high-dose ICS for viral induced wheeze, at the start of a viral upper airway infection and continued until this is resolved, although effective, is not recommended because of its effect on growth.

Maintenance treatment

Principles of maintenance treatment are outlined in table 3, and these are in line with asthma guidelines in older children and adolescents. Based on the realisation that parental cooperation is necessary to ensure optimal effects of therapy, the first, and perhaps most important, step of maintenance therapy is to achieve and maintain a therapeutic alliance with patients and parents. Tailored self-management education is needed to ensure that parents understand how and why treatment works. A recommendation to reduce exposure to tobacco smoke can only be achieved if this is discussed with parents in a constructive and non-judgmental fashion. Tailored self-management education is most effective when it is delivered repeatedly, addresses parental concerns and cognitions, and incorporates parents' treatment goals for their child. If sensitisation to aeroallergens has been demonstrated, reducing the exposure to these allergens is likely to be effective, although evidence in this area is lacking.

Because wheezing in preschool children largely occurs in discrete episodes with sometimes relatively long symptom-free intervals, parents should understand that the effect of maintenance therapy can only be judged after the child had one or more subsequent URTIs. This may require prolonged continuation of medication, which parents will be more likely to provide when they trust, and can collaborate constructively with, their child's physician.

The choice of whether or not to initiate maintenance therapy in preschool children with wheeze depends primarily on the severity and frequency of episodes. After a systematic review of all available studies using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology, the Dutch Paediatric Respiratory Society, in collaboration with the Dutch Cochrane Centre, recommended ICS as maintenance treatment in preschool children with troublesome wheeze, irrespective of wheezing phenotype. Although inhaled steroids do not alter the long-term outcome or persistence of wheeze, they are effective in controlling symptoms, which is why their use in preschool children with troublesome wheezing symptoms is justified. There is no preference for any specific inhaled steroid preparation. The assumed superiority of

Table 3. Principles of maintenance treatment of preschool children with recurrent wheeze

Therapeutic alliance with parents and patient
Non-pharmacological therapy
Self-management education
Maximal reduction of passive smoke exposure
When sensitised to aeroallergens reduce aeroallergen exposure
Repeated scheduled follow-up
Pharmacological therapy
Inhaled salbutamol on demand
Train and maintain correct inhalation technique
If repeated troublesome symptoms and parents motivated for maintenance therapy then start low-dose ICS or montelukast
If low-dose ICS do not control symptoms
Check inhalation technique and adherence to treatment
Exclude relevant comorbidity or alternative diagnosis
Add additional controller (inhaled steroid, montelukast or long-acting β-agonist)

inhaled steroid preparations with ultrafine particles is theoretical, with no evidence from randomised trials to support their use. Although data on side-effects of long-term use are lacking, inhaled steroids in this age group appear to be safe.

Montelukast is a reasonable alternative as a controller therapy, although it is less effective than ICS in children with recurrent wheeze.

If symptoms fail to improve sufficiently during inhaled steroid or montelukast maintenance treatment, physicians should exclude reasons for failure of such therapy before starting additional medication. Treatment failure can often be explained by insufficient adherence to medication, poor inhalation technique, an alternative diagnosis such as bronchomalacia, or relevant comorbidity such as allergic rhinitis. If these are properly addressed and treated, and symptoms remain problematic, addition of other controllers (montelukast, ICS or long-acting β-agonists) can be considered. There is no evidence from randomised trials to prefer any add-on treatment schedule over another. Most cases of troublesome preschool wheeze can be controlled effectively by inhaled steroids or montelukast alone, or by a combination of controller medications.

Because of preschool wheezing's favourable natural history, maintenance treatment should be tapered off when the child is completely symptom free for 3–6 months, or for 12 months in children who have had a serious exacerbation requiring long-term hospitalisation or admission to intensive care.

Conclusion

Recurrent wheeze in preschool children is common. Due to the limited amount of evidence on its complex and multifactorial pathophysiology, different classification systems with associated treatment recommendations have been proposed, none of which can be recommended for universal use at present. After excluding cases with atypical features, most patients with severe recurrent wheeze in this age range can be managed effectively by ICS or montelukast, either alone or in a combination regimen. Mild intermittent wheeze can be treated with an inhaled bronchodilator only.

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Bronchial asthma

Mariëlle Pijnenburg and Karin C. Lødrup Carlsen

Asthma is the leading chronic disease in children in the Western world, affecting 5–20% of school-age children in Europe. Asthma prevalence has increased during the last two decades, although this trend seems to being levelling off, at least in high-income countries. Childhood asthma is a serious public health problem for several reasons. First, asthma causes considerable morbidity and healthcare utilisation. High frequencies of sleep disturbances due to asthma (up to 34%), absence from school (23–51%) and limitation of activities (47%) have been reported in several studies. Asthma is the third-ranking course of hospitalisation in children and the major cause of school absenteeism due to chronic disease among children in the USA (www.afaa.org). In Europe, unscheduled emergency visits to healthcare accounted for 47% of total asthma costs in infants and 45% in children; 7% of all children reported at least one hospitalisation. Secondly, as asthma is associated with reduced growth of lung function and lung function at a young age is a determinant of lung function in adult life, optimal treatment is of major concern for long-term prognosis.

The main characteristics of asthma are reversible airway obstruction and airway hyperresponsiveness; chronic inflammation of the airways plays a central role in the pathogenesis of asthma and anti-inflammatory treatment with inhaled corticosteroids (ICS) is the treatment of choice. A stepwise approach to asthma management has been suggested by all international guidelines, and the ultimate goal of asthma treatment is to achieve and maintain clinical control with the least possible unwanted effects.

Key points

- There is no universally accepted definition of asthma, although reversible airway obstruction, airway hyperresponsiveness and chronic inflammation are key features.
- There is accumulating evidence that the interaction between respiratory viral infections and atopy is important in the cause and pathogenesis of atopic asthma.
- Airway remodelling is a common feature in adult severe asthma but this is less clear in childhood, particularly as to when it starts and what elicits the process.
- The ultimate goal of asthma treatment is to achieve and maintain clinical control with a minimum of side-effects and to reduce future risks to the patient.
- There is no uniform definition of severe childhood asthma and several criteria are used such as the need for or use of high-dose corticosteroids, severe and/or frequent exacerbations, chronic asthma symptoms, or reduced lung function.
- Severe childhood asthma should be referred to and managed in specialised paediatric units.

The underlying mechanisms of asthma are poorly understood. However, there is accumulating evidence that the interaction between respiratory viral infections,

against a background of atopy, is important in the cause and pathogenesis of atopic asthma.

Diagnosis

Diagnosing asthma may be challenging, particularly in infants and pre-school children, and no universally accepted definition of asthma exists that embraces children from infancy to post-puberty. Difficulty in studying asthma arises from the fact that asthma is not a single disease but a compilation of diseases presenting as a syndrome or a collection of symptoms. Particularly in childhood, reversible bronchial obstruction may be a final common feature of a number of different diseases with distinct aetiologies, and different environmental and genetic associations. However, most cases of asthma start in childhood and early-life asthma, particularly in boys, is a significant risk factor for later COPD, and the severity and number of obstructive episodes in early childhood appear to be reasonable predictors for later on-going childhood asthma.

Several phenotypes of asthma have been described and are being identified, commonly based upon the time of presentation of ''wheeze'' within the first part of childhood. However, phenotypes based on the presence or absence of allergic sensitisation, eosinophilic or noneosinophilic inflammation, or response to treatment are also recognised. The asthma-like clinical presentations often referred to as ''wheezy'' disorders in children are common prior to signs or documentation of allergic markers, although nonallergic childhood asthma is common in many areas.

With this background, various definitions are used, and common to them all are reversible airway obstruction and chronic airway inflammation. Thus, a descriptive and pragmatic approach is necessary in the clinic, as the diagnosis will elicit targeted treatment.

Classical symptoms of asthma are wheeze, cough (particularly at night or during exertion), dyspnoea and chest tightness.

The main features, therefore, for diagnosing asthma are:

- history taking,
- objective documentation of reversible bronchial obstruction,
- allergy and bronchial hyperresponsiveness (BHR) testing,
- assessing airway inflammation whenever possible.

The medical history should focus on symptoms of bronchial obstruction or cough, triggers of these symptoms, and should include all items in figure 1, with attention to the age-specific questions. Furthermore, triggers of symptoms are distinct from inciters of asthma development, mechanisms of the latter being less clear. Common triggers of symptoms are viral infections, exercise, allergen exposure and irritants such as tobacco smoke.

Pathophysiology

Asthma is a chronic inflammatory airway disease characterised by reversible airway obstruction and BHR. However, there is no current consensus on the underlying pathophysiology of asthma throughout childhood. This said, the underlying chronic inflammation is often characterised by eosinophilic activity and allergic inflammation, but nonallergic asthma is not uncommon in childhood.

Bronchial obstruction is a result of bronchial muscle constriction, acting particularly through the β-receptors, as well as mucosal oedema and increased airway secretions resulting from airway inflammation. All contribute to reduced airway flow, which is reflected in reduced lung function and classical symptoms such as wheezing, dyspnoea and coughing. Reversibility of the bronchial obstruction may occur spontaneously or with bronchodilators (particularly β_2-agonists), whereas anti-inflammatory medications, such as corticosteroids, are necessary to reduce the underlying pathophysiological causes of bronchoconstriction (see later).

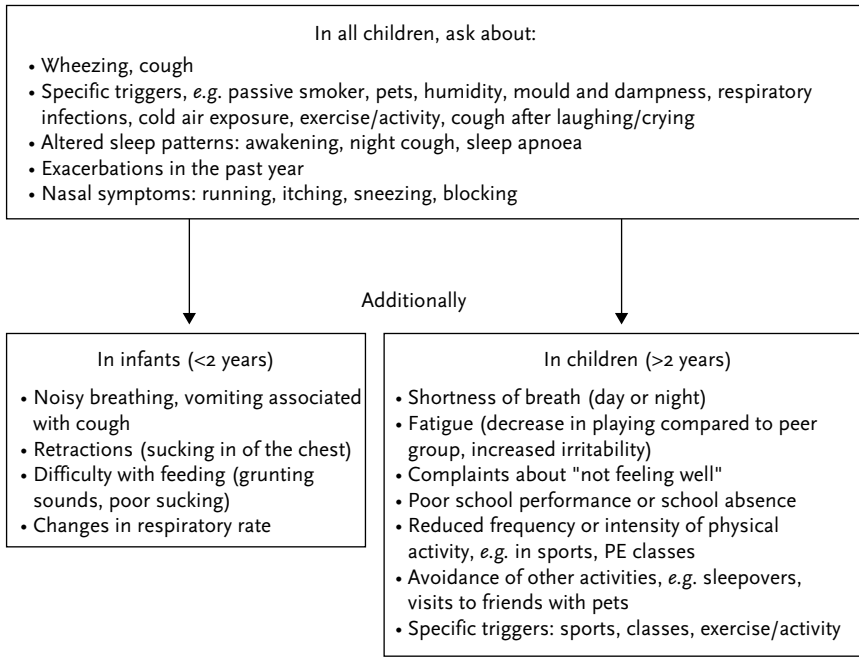

Figure 1. Specific symptoms that should be asked in assessing asthma diagnosis. PE: physical education. Informaton from Bacharier et al. *(2008).*

Airway inflammation The underlying airway inflammation in asthma is generally considered to be eosinophilic. However, the strength of the association between atopic sensitisation and asthma varies, and most sensitised subjects do not have asthma. Allergen exposure may, in some, lead to a break in natural tolerance, triggering allergic inflammation, and an allergen-specific immune response involving T- and B-lymphocytes. The innate immune system is, in effect, the barrier between the organism and external environment, being the important first line of defence against infections and intruders. The adaptive immune system, however, classically involves (T-)cellular responses to antigens (or allergens), typically with production of specific IgE antibodies from B-cells, and adapts to environmental challenges.

The allergic response is initiated when an allergen binds to the high-affinity receptor for IgE (FcεRI) on the antigen-presenting cells (APCs) that facilitate presentation to the T-cells. IgE is synthesised in the presence of interleukins (ILs) (*e.g.* IL-4 and IL-13) and other cytokines. The allergic inflammation is characterised by a T-helper cell (Th) type 2 cascade involving Th2 cytokines and other immune mediators. It is currently believed that directing naïve T-cells to Th1 *versus* Th2 immunity involves regulatory T-cells (Tregs), a process which is important in tolerance development and suppression of allergic inflammation.

In addition, dendritic cells in the airway epithelium facilitate uptake of allergens bound to FcεRI. Such mechanisms are probably propagated through defects in barrier function that have recently been shown in the airway epithelium of asthmatic subjects.

Viral infections are important triggers of symptoms and exacerbations of asthma in childhood, whereas many children with

''viral wheeze'' may later not have asthma. Recent studies suggest that respiratory viruses, possibly (subtypes of) human rhinovirus in particular, may play a role in triggering the immune system. The mechanisms are currently not known, although several hypotheses exist, including an immune circle in asthma development in which repeated airborne irritant stimuli (such as allergens or viruses) evoke cycles of inflammation, giving intermittent inflammation resulting in episodic symptoms at first. However, with repeated insults, the inflammatory resolution becomes less complete, leading to tissue repair and regeneration that may set off prolonged periods of pathological changes. These periods may progress to deterioration in respiratory function and, perhaps, to remodelling.

A potential causal association between allergic sensitisation and viral infection is currently the focus of research, and is has been suggested that allergic sensitisation precedes rhinovirus-induced wheezing. Another aspect of the damaged epithelium in asthma is the reduced ability to handle viruses in an optimal way. It appears that reduced ability of airway epithelial cells to produce interferon-γ may lead to cytotoxic cell death and subsequent dissemination of viruses, rather than apoptosis, possibly explaining the prolonged symptomatic viral infection observed in asthmatics.

BHR is a common, but not obligate, feature of childhood asthma. It typically presents as a general liability to develop symptoms by exposure to various physiological or environmental stimuli, exercise being a classical childhood asthma symptom trigger. The underlying mechanisms for BHR development are not clear but may involve barrier dysfunction as well as possibly neural parasympathetic mechanisms involving heat and fluid exchange over the epithelium. BHR is a modest, but significant, risk factor for later asthma and tends to decrease through childhood.

The role of lung function reductions in the development of asthma in contrast to lung function decline with chronic asthma is not entirely clear. There is no doubt that asthma is associated with reduced lung function as well as a more rapid decline in lung function compared to healthy individuals. In a few birth cohorts, reduced lung function has been found to precede asthma in some, but not all children with asthma.

Airway remodelling, being a common feature in adult asthma, is less clear in childhood, particularly as to when it starts and what elicits the process. Nevertheless, lung function reductions in older children are likely to reflect structural changes in the airways such as subepithelial reticular basement layer thickening, epithelial cell disruption, imbalance of proteases and antiproteases, and neoangiogenesis (remodelling).

Management

Several guidelines address asthma treatment in adults and children.

This section discusses management of asthma in children aged $\geqslant$5 years. For children under the age of 5 years, please see the section on Pre-school wheezing in this *Handbook*. Details on aerosols, delivery of drugs to the lung, inhaler devices and instructions on optimal inhaler technique can be found in the Aerosol therapy section in this *Handbook*.

Nonpharmacological management Most nonpharmacological interventions in asthma have limited effect and often lack sufficient evidence, except for avoidance of active or passive smoking. Exposure to environmental tobacco smoke (ETS) is associated with decreased lung function from birth, increases the risk of asthma development, increases the frequency and severity of asthma symptoms, decreases asthma related quality of life and is associated with persistent asthma in adults. Smoking cessation by parents/caregivers or children themselves should be vigorously encouraged and supported.

In obese patients, weight reduction may increase general health and improve asthma control, although this has not been proven for children. It has been suggested that

rapid weight gain during early life is associated with increased risk of developing asthma.

Single measures are unlikely to reduce exposure to house dust mite (HDM) allergens and have not been effective in reducing asthma symptoms. An integrated approach aimed at reduction of HDM allergens may have some clinical benefit in selected children but has not been recommended for all HDM-allergic asthmatic children.

In general, in pet-allergic children, removal of these animals from the home is advised to gain adequate asthma control, although this has been questioned.

There are no dietary interventions that have been proven beneficial in asthma, although regular intake of fruits and vegetables have been associated with reduced risk of developing asthma.

Aim of asthma treatment The ultimate goal of asthma treatment is to achieve and maintain clinical control and to reduce future risks to the patient. The level of clinical control is defined as the extent to which asthma manifestations, like daytime symptoms, night waking, the use of reliever medication and the ability to carry out daily activities including exercise, have been reduced by treatment. The future risk to the patient includes loss of control, exacerbations, accelerated decline in lung function and side-effects of treatment. Ideally, treating patients with asthma should take into account both aspects. The Global Initiative for Asthma (GINA) guidelines suggest discerning three asthma control levels (controlled, partly controlled and uncontrolled), which guide step-up or step-down asthma treatment (table 1). Although this is a working schema and has not been validated, it enables physicians to assess asthma control systematically and adjust treatment accordingly.

A stepwise treatment approach for asthma has been proposed by all international guidelines (fig. 2). In patients with uncontrolled asthma, step-up treatment should be considered. Before stepping up treatment, there is an absolute need to check adherence to treatment, inhaler technique and ongoing exposure to triggers (table 2). In a patient unresponsive to treatment, one should confirm that the symptoms are due to asthma and consider comorbidity like untreated allergic rhinitis, obesity or gastro-oesophageal reflux disease. Step down should be considered if patients are well controlled for 3–6 months, and the lowest step and dose of treatment that maintains control should be sought.

At each step, short-acting β_2-agonists (SABA) should be provided for quick relief of symptoms (step 1).

If children have symptoms and/or need rescue SABA more than twice a week, wake up at least one night a week or have had any asthma exacerbation during the last year, maintenance treatment with ICS should be started (step 2). ICS at a low–moderate dose are the recommended controller treatment for patients of all ages in step 2. The starting dose of ICS may depend on severity of disease and will usually be 200–400 $\mu g \cdot day^{-1}$ for chlorofluorocarbon (CFC)-containing beclomethasone dipropionate (BDP) and budesonide preparations, and 200–250 $\mu g \cdot day^{-1}$ for fluticasone, mometasone and ultra-fine CFC-free beclomethasone preparations. The advised starting dose of ciclesonide in children 12 years and older is 160 $\mu g \cdot day^{-1}$. One should be aware that although ICS are highly effective in reducing asthma symptoms, improving lung function and reducing airway hyperresponsiveness, these effects do not persist when discontinuing treatment.

Alternative controller medications are leukotriene modifiers, which may be appropriate for patients who are unable or unwilling to inhale ICS.

If children are uncontrolled at low–moderate doses of ICS, there are three treatment options: add inhaled long-acting β_2-agonists (LABA), increase the dose of ICS or add a leukotriene receptor antagonist (LTRA). Presently, there is no evidence for superiority of one of the strategies over the other. While the interindividual response

Table 1. Levels of asthma control

Assessment of current clinical control (preferably over 4 weeks)			
Characteristic	**Controlled (all of the following)**	**Partly controlled (any measure present in any week)**	**Uncontrolled**
Daytime symptoms	None (twice or less per week)	More than twice per week	Three or more features of partly controlled asthma present in any week[+,§]
Limitation of activities	None	Any	
Nocturnal symptoms/ awakening	None	Any	
Need for reliever/ rescue treatment	None (twice or less per week)	More than twice per week	
Lung function (PEF or FEV1)[#,¶]	Normal	<80% predicted or personal best (if known)	
Assessment of future risk (risk of exacerbations, instability, rapid decline in lung function, side-effects)			
Features that are associated with increased risk of adverse effects in the future include: poor clinical control, frequent exacerbations in the past year[+], admission to critical care for asthma, low FEV1, exposure to cigarette smoke, high-dose medications			

[#]: not reliable for children aged ⩽5 years; [¶]: without administration of a bronchodilator; [+]: any exacerbation should prompt a review of maintenance treatment to ensure it is adequate; [§]: by definition, an exacerbation in any week makes that an uncontrolled week. Reproduced and modified from GINA (2012) with permission from the publisher.

may vary significantly, no predictors of response to one of the three options has been identified, highlighting the need to regularly monitor and appropriately adjust each child's asthma therapy.

The British Thoracic Society (BTS) and GINA guidelines favour the addition of inhaled LABA in step 3 treatment. LABA should always be an add-on treatment to ICS therapy and should never be used as single agents. If effective, LABA should be continued, and if ineffective, LABA should be stopped and the dose of ICS should be increased. If this treatment is (partly) ineffective, LTRA could be added. It is important to note that individual variations in the susceptibility to side-effects of steroids may render some children, even those on low doses, at risk of adrenal axis suppression.

National guidelines may differ from the BTS and GINA guidelines and should be consulted on a local level. In addition, considerations of the safety of LABA in children, the convenience of their use, individual patient preferences and costs may guide treatment choices in individual patients.

Although healthcare varies between and within countries, it should be emphasised that children who are not controlled on step 3 treatments should be referred to a paediatrician specialised in asthma care. Assessment of a possible wrong diagnosis, lack of treatment adherence or persistent exposure to untoward environmental factors should be considered. In step 4, ICS dose should be optimised to 800 $\mu g \cdot day^{-1}$ BPD or equivalent together with LABA and/or LTRA. Low-dose, sustained-release theophylline may provide some benefit in addition to medium–high dose ICS and LABA, although generally the clinical effects have been small.

Step 5 treatment should be confined to paediatric specialists in asthma management. Regular systemic corticosteroids might be considered in step 5, although side-effects severely limit their

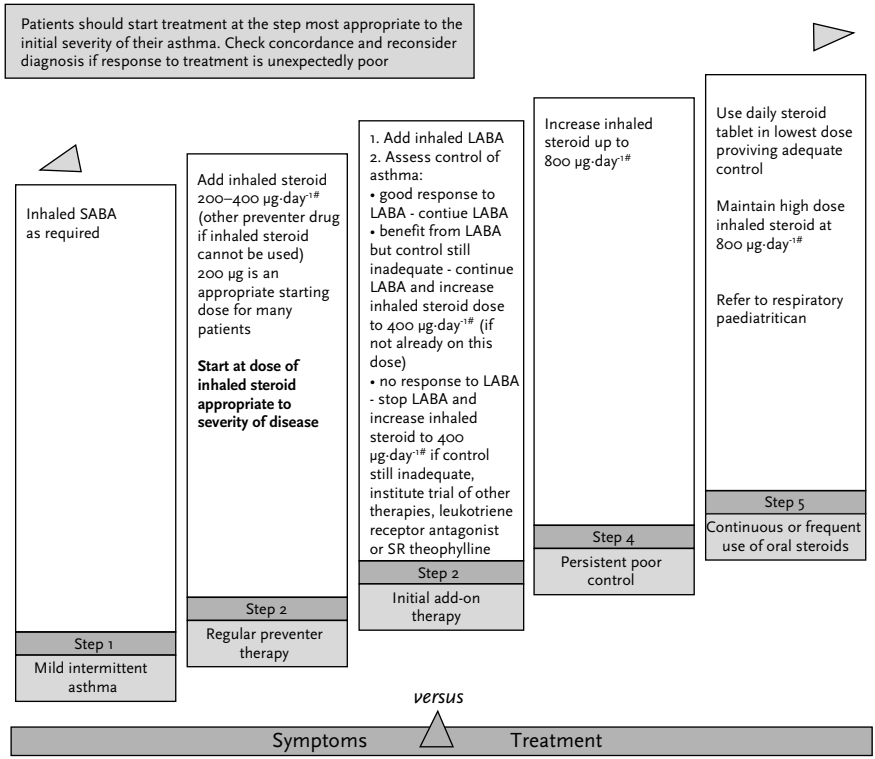

Figure 2. Stepwise management of asthma treatment in children aged 5–12 years. #: BDP or equivalent. Reproduced and modified from BTS et al. *(2012) with permission from the publisher.*

use. Monoclonal antibody therapy is an option in children from the age of 6 years with elevated total IgE between 76–3000 IU·mL^{-1}. Omalizumab reduces asthma exacerbations and ICS dose, and improves asthma-related quality of life; however, its long-term safety and efficacy are not clear.

Table 2. Factors to be assessed in poorly controlled asthma, before step-up treatment

Adherence to treatment
Inhaler technique
Exposure to triggers (tobacco smoke, allergens)
Allergic rhinitis
Is it asthma?
Comorbidity

Other options that might be considered in step 5 are intramuscular triamcinolone and experimental therapies like macrolide antibiotics, cyclosporine, methotrexate and subcutaneous terbutaline, and other, rare treatment options.

Treatment of asthma exacerbations For treatment of asthma exacerbations, consultation of (inter)national guidelines is highly recommended as local policies may differ between countries and settings, and guidelines are not uniform on all points. Most mild–moderate exacerbations might be treated in a community setting, whereas moderate–severe exacerbations should be treated in acute care settings.

The severity of the asthma exacerbation is assessed by a brief history and physical examination. Important signs and

symptoms are the ability to talk in sentences, pulse rate, respiratory rate, breath sounds, use of accessory muscles, retractions, oxygen saturation, degree of agitation, conscious level and (if possible) peak expiratory flow (PEF) or FEV_1 (table 3).

With moderate or severe exacerbations, treatment should be initiated immediately.

Children with an asthma exacerbation who do not respond adequately to β_2-agonists and/or are in need of supplemental oxygen and/or have severe asthma should be admitted to hospital. A follow-up visit within a short time after discharge by a general practitioner or asthma specialist should be arranged.

There is no absolute limit at which oxygen therapy should be instituted. However, oxygen *via* a facemask or nasal cannulae should be administered if oxygen saturation is <94%, although the BTS guidelines accept a lower limit of 92%.

In children with mild–moderate exacerbations, β_2-agonists delivered *via* a pressurised metered-dose inhaler (pMDI)–spacer combination are usually sufficiently effective. Two to four puffs of β_2-agonists should be administered one at a time and inhaled *via* tidal breathing, and repeated at 10–20-min intervals for the first hour as needed. However, nebulised β_2-agonists should be considered in moderate–severe exacerbations if there is insufficient effect from pMDI–spacer administration. Addition of an inhaled anticholinergic, like ipratropium bromide 0.5 mg, may be beneficial.

Severe or life-threatening exacerbations should be treated with nebulised salbutamol 5 mg or terbutaline 10 mg at intervals of 10–20 min. Some countries use subcutaneous injections of adrenaline.

Systemic steroids should be given in all but the mildest exacerbations. After starting inhalation therapy, oral prednisolone is equally effective as parenteral prednisolone; however, in children with altered consciousness or who vomit, intravenous corticosteroids are preferred. In children, the advised dose is 1–2 $mg \cdot kg^{-1}$ prednisolone for 3–5 days up to a maximum of 40–60 mg.

Intravenous magnesium sulphate in a dose of 40 $mg \cdot kg^{-1}$ (maximum 2 g) administered over 15 min may be considered in children unresponsive to 1 h of adequate treatment.

If the response to intensive nebulised treatment and prednisolone is poor, children should be referred to a paediatric intensive care unit (PICU). Intravenous salbutamol or terbutaline may be considered even before transport to the PICU under close monitoring of heart rate, arterial blood gases and serum potassium. The starting dose is 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ continuously.

Monitoring

Asthma is a chronic disorder with a variable course, which makes regular follow-up of asthmatic children necessary. Traditionally, subjective parameters like symptoms, and more objective measures such as spirometry, PEF and BHR, are used to assess asthma control and disease activity.

Table 3. Assessment of severity of asthma exacerbation in children aged >5 years

Moderate exacerbation	Severe exacerbation	Life threatening exacerbation
Able to talk	Too breathless to talk	Agitation
SpO_2 ⩾92%	SpO_2 <92%	drowsiness, confusion
Heart rate ⩽120 beats·min^{-1}	Heart rate >120 beats·min^{-1}	risk factors for near fatal asthma
Respiratory rate ⩽30 breaths·min^{-1}	Respiratory rate >30 breaths·min^{-1}	Silent chest
PEF ⩾50% best or predicted	PEF <50% best or predicted	PEF <30%
	Use of accessory muscles	PCO_2 >45 mmHg
	Chest retractions	PO_2 <60 mmHg

PCO_2: carbon dioxide tension; PO_2: oxygen tension.

In daily practice, parents, children and their physicians usually estimate asthma control and make therapeutic decisions on subjective symptom assessments. Validated questionnaires may be of help in the standardised assessment of asthma control in the clinic and for research purposes. There are several questionnaires available, such as the Asthma Control Questionnaire (ACQ), the Asthma Control Test (ACT) and the Childhood Asthma Control Test (C-ACT), the Asthma Therapy Assessment Questionnaire (ATAQ) and the three-item Royal College of Physicians (RCP_3) questionnaire. The C-ACT has been developed for detecting uncontrolled asthma in children aged 4–11 years; the ACT and ACQ have been validated for children aged $\geqslant$12 years. The seven-item version of the ACQ has five questions on symptoms and additionally includes FEV_1 and use of rescue β_2-agonists. Standardised questionnaires seem attractive in measuring asthma control as they are cheap, easy to use and interpret, and give a quick impression on asthma control. They provide a reproducible, objective measure that may be repeated over time and may improve communication between the patient/parent and physician. However, no data are available on the potential of such questionnaires to improve asthma outcome in children.

The GINA guidelines suggest the use of symptoms and lung function to assess asthma control, and make a difference between controlled, partly controlled and poorly controlled asthma (table 1). Subsequently, the level of asthma control guides medication adjustments.

In patients older than 5–6 years, spirometry or PEF should be measured during clinic visits to assess asthma control and detect possible decline in lung function. FEV_1 is preferred over PEF, as PEF may be completely normal while severe airway obstruction is present. The presence and degree of airway obstruction has short- and long-term prognostic value for asthmatic children, and is an independent predictor of future risk. Guidelines recommend assessing lung function and bronchodilator response at least yearly.

Contrary to adults, in children, adjusting the dose of ICS to symptoms and BHR did not result in more symptom-free days compared to titrating treatment to symptoms only. However, in a subgroup of children with few symptoms but hyperreactive airways, monitoring BHR resulted in improved lung function.

Recently, much attention has been paid to markers of inflammation, like the exhaled nitric oxide fraction ($F_{E}NO$) and eosinophils in induced sputum, as objective tests to monitor asthmatic patients. However, titrating ICS based on $F_{E}NO$ levels or on sputum eosinophils has not been shown to be effective in improving asthma outcomes in children. Whether $F_{E}NO$ may be of help in diagnosis, phenotype-specific treatment, decisions on starting and stopping ICS, or monitoring adherence remains to be shown.

At every visit, use of rescue β_2-agonists, exacerbations, asthma symptoms and limitations in physical activity, oral corticosteroid use, school absenteeism, inhaler technique, and adherence to treatment should be checked.

Before stepping up treatment, one should consider low adherence, poor inhaler technique, adequate avoidance of risk factors, allergic rhinitis, (passive) smoking, other aggravating factors and comorbidities.

Self-management Although self-management education including written action plans clearly leads to improved outcomes in asthmatic adults, this has not been shown for children. To date, there is a lack of studies comparing the effect of providing a written action plan *versus* no written action plan in children and adolescents. However, symptom-based action plans seem superior to peak flow-based action plans for preventing acute care visits in children. There is some evidence that combined interventions aimed at self-management (*e.g.* information, self-monitoring and action plan, or educational and environmental measures) may reduce asthma exacerbations in children who

Table 4. Particular features that contribute to severity of asthma by age group

Infancy	Underlying pathophysiology and clinical characteristics poorly understood Viruses are the most common precipitating factors Many conditions to be considered in the differential diagnosis Difficulty in objective documentation of bronchial obstruction Many with problems in the first year of life remit long term in the second year
Preschool age	Viruses are the most common precipitating factors Compliance with management largely depending upon carers Some difficulty in objective documentation of bronchial obstruction or airway inflammation
School age	Allergy is frequent Symptoms often precipitated by exercise Compliance with management still depending upon carers Evaluation of lung function easy Indirect evaluation of airway inflammation relatively easy
Adolescence	Clinical expression is variable Tendency to deny symptoms Risk-taking behaviour common Low compliance Psychological problems Treatment may be difficult

Reproduced and modified from Hedlin *et al.* (2010).

visited the emergency room for asthma. The optimum setting and content for such educational interventions and relative effectiveness of the various components are largely unknown.

In general, a written personal action plan is recommended for all children with asthma and, in particular, for children with poorly controlled asthma. Furthermore, parental education in asthma is recommended to improve assessment of the child's disease as well as adherence to treatment.

Problematic, difficult or severe asthma

Severe asthma is relatively rare, occurring in approximately 4–5% of children with asthma and 0.5% of the general child population. However, there is no uniform or generally accepted definition of severe childhood asthma, and several criteria are used, such as the need for or use of high-dose corticosteroids, severe and/or frequent exacerbations, chronic asthma symptoms, or reduced lung function. Thus, severe or difficult asthma may be related to wrong diagnosis, exposure to environmental factors such as allergens, tobacco smoking and irritants that worsen the disease, nonadherence to therapy, psychosocial issues, or true severe asthma that is resistant to therapy.

Each age group has particular features that contribute to the severity of asthma, as outlined in table 4.

In contrast to adults, children with severe asthma may not yet have developed remodelling, although increases in smooth muscle and evidence of reticular membrane layer are frequently found. Furthermore, the inflammation in childhood severe asthma may appear to be eosinophilic without the classical Th2 inflammation, in contrast to the more commonly neutrophilic inflammation in adults.

Managing children with severe asthma requires a systematic approach to assess diagnosis, airway inflammation and therapeutic responses to corticosteroids. This should enable further differentiation of those children who have a true severe, therapy-resistant asthma, from those with the wrong diagnosis, those with asthma with significant comorbidities that need to be

addressed, and those with asthma that is not responding to treatment because of factors other than medication response. Only in those with severe therapy-resistant asthma may expensive and potentially hazardous cytokine-specific therapies be appropriate.

Treating severe asthma is challenging and includes medication that is not well documented in this age group, and should thus be referred to specialised centres with particular expertise in diagnosis and treatment of severe childhood asthma.

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Emerging therapeutic strategies

Giorgio Piacentini and Laura Tenero

Asthma is the most common chronic childhood disease and the major cause of hospitalisation for children. It is a chronic disease with repeated attacks of airways obstruction and intermittent symptoms of responsiveness to triggering factors, such as allergens, smoke, exercise or viral infection.

In the majority of asthmatic patients, symptoms can be controlled with a stepwise approach according to guidelines (Papadopoulos *et al*., 2012; Global Initiative for Asthma, 2011) with inhaled steroids, long-acting β_2-agonists (LABAs) and and leukotriene receptor antagonists.

However, the prevalence of severe and therapy-resistant asthma in a general paediatric population is 0.5% (4.5% of children with asthma). This group of patients presents ongoing chronic symptoms or severe exacerbations despite high-dose medication may benefit from new treatment strategies.

Key points

- New treatments based on interventions in the immunopathogenesis of asthma are currently under development and evaluation, especially in subjects whose symptoms are not controlled by current therapy.
- Omalizumab is a monoclonal human antibody which can antagonise the role of IgE in the pathogenesis of allergic asthma.
- IL-5 plays an important role in eosinophil activation and airway hyperresponsiveness and is involved in the induction of Th2 responses in the asthmatic airway.

Pharmacotherapy

Guidelines on paediatric management of asthma aim for control of symptoms, reduction of exacerbations, hospitalisation and emergency department visits, and improvement of quality of life.

Currently, after an initial classification of severity into the categories of mild, moderate and severe at the time of diagnosis, most guidelines propose that the level of treatment be considered on the basis of the evaluation of symptoms according to their presentation as intermittent or persistent, controlled or uncontrolled. Therapy is based on an increasing or decreasing stepwise approach according to the level of disease control.

Inhalation therapy, which facilitates administration of drugs directly into the airways, is currently the preferred route for most patients. The delivery of the drug directly to the site of disease results in a powerful therapeutic effect and minimises the occurrence of systemic side-effects.

Inhaled corticosteroids (ICS) are the most effective controller medications currently available. Their regular use reduces the severity of symptoms, decreases exacerbations and hospital admission, improves lung function and reduces hyperesponsiveness.

Critical issues regarding asthma treatment in children are the necessity of delivering

drugs at the site of the inflamed distal airway, the potential side-effects of long-term treatment with ICS and the difficulty of controlling symptoms. The ongoing need to solve these issues warrants research into new therapeutic strategies.

New strategies for asthma treatment

Various new treatments based on interventions in the immunopathogenesis of the disease are currently under development and evaluation to improve asthma control.

T-helper type 2 (Th2) inflammation, mediated by interleukin (IL)-4, IL-5, IL-9 and IL-13, plays a central role in the pathway of allergic asthma. Two different phenotypes of asthma patients based on high or low Th2-cytokine gene expression have been identified. ''Th2 high'' asthma patients present with elevated IL-5 and IL-13 expression in bronchial biopsies, serum IgE and blood and airway eosinophilia. These patients are those for whom the best response to ICS is expected, whereas subjects with ''Th2 low'' asthma phenotype represent a subgroup with clinical manifestations that are poorly controlled by current therapies since the disease is mostly related to nonallergic, steroid-unresponsive, mechanisms.

A number of alternative potential therapies have been proposed to prevent T-cell activation, to modulate Th1/Th2 differentiation, to inhibit Th2-related cytokines and to inhibit downstream mediators. In paediatric patients the inhibition of downstream mediators using anti-IgE has been shown to be an interesting emerging approach of practical application.

Omalizumab Omalizumab is a monoclonal human antibody that can antagonize the role of IgE in the pathogenesis of allergic asthma. A number of studies, mainly in adults, have demonstrated that omalizumab can reduce serum levels of free IgE, expression of IgE receptors on basophils and antigen stimulated histamine release. Studies performed with this new therapeutic strategy show that the treatment can reduce both early and late response as well as bronchial reactivity, improve asthma control, reduce exacerbations during corticosteroid therapy and allow a reduction of ICS dose. In 2009, the licence for the use of omaluzimab was extended to include children aged 6–12 years as an add-on treatment for poorly controlled asthma in patients with severe persistent allergic disease.

Though the treatment needs to be administered in a controlled clinical setting with a period of observation after injection, this therapy has become increasingly popular in the past few years. It can be considered as an option in children with IgE-mediated sensitisation to one or more allergen, with chronic symptoms, recurrent severe asthma exacerbations and resistance to high doses of ICS and LABAs.

Omaluzimab has been shown to be safe and beneficial in children through 1-year trial, but long-term safety and efficacy have not yet been demonstrated.

Children and adolescents with severe persistent asthma with positive skin prick test for allergen and with reduction of FEV_1 (<80% predicted) who are treated with ICS have been shown to benefit from improved quality of live with when treated with omalizumab.

Analysis of a subgroup of subjects from a study evaluating the effect of omalizumab as add-on treatment in inadequately controlled severe asthmatics suggests that patients with IgE levels below 76 $IU \cdot mL^{-1}$ are less likely to benefit.

Although free IgE is extensively and rapidly suppressed after commencing treatment with omalizumab, it may take up to 3 months before clinical symptoms equilibrate at a new level.

Although omalizumab brings clinical benefits, treatment costs are high, and while some authors have concluded that omalizumab produces sufficient improvement in clinical outcomes in difficult-to-treat, persistent allergic asthma to justify the cost, other studies have suggested that the clinical benefits may not offset the high cost of treatment. The UK

National Institute for Health and Clinical Excellence has recommended that omalizumab should not be routinely used for the treatment of severe persistent allergic asthma in children aged 6–11 years.

TNFα blockers Some studies in adults have suggested that tumour necrosis factor (TNF)α may be a marker of severity in asthma and a target for biological therapy. TNFα is a cytokine produced by different cell types which plays a role in the innate immune response. It has been suggested that TNFα can contribute to the inflammatory response in asthmatic airways.

Studies evaluating the efficacy of the use of anti-TNFα therapy in asthma refractory to ICS have been published, and a significant improvement in methacholine airway hyperresponsiveness, as well as improvements in FEV_1 and in quality of life in patients with severe asthma treated with etanercept (a TNFα receptor IgG Fc fusion protein) have been reported. However, these studies have been carried out in adult patients; no evidence in children is currently available. Therefore, further investigations are needed in order to evaluate the benefits and the risks of this treatment in the paediatric population.

Vitamin D Recent research has shown that vitamin D has an important role in the modulation of the immune system response, especially through the inhibition of Th1 response and T-cell proliferation.

An epidemiological study suggested that low concentration of vitamin D in children with asthma is associated with more severe symptoms, frequent exacerbations, reduction in lung function and an increase in medication use. Vitamin D has been postulated to play an important role in the modulation of inflammatory response and maintenance of airway homeostasis as well as to have a role in the improvement of the anti-inflammatory action of glucocorticoids in patients with refractory asthma.

Though some observational studies show lower plasma levels of vitamin D in asthmatic patients as well as inverse associations between vitamin D and total IgE levels, eosinophil counts and lower mean FEV_1, the strength of this evidence needs to be further investigated. Clinical trials with vitamin D supplementation in children with asthma are warranted.

Macrolides Macrolides are commonly used as antimicrobial agents but they have been also demonstrated to have immunomodulatory and anti-inflammatory properties in the airway. Clinical trials have shown benefits of macrolides in the treatment of a spectrum of chronic inflammatory respiratory diseases.

The mechanism of action remains partially unexplained but it may be possibly due to their antibacterial and/or anti-inflammatory actions, which include reductions in IL-8 production and neutrophil migration and/or function.

Clarithromycin and azithromycin have been shown to exert an effect in reducing airway inflammation, with decreased airway oedema and TNFα, IL-1, and IL-10 concentrations. Furthermore, azithromycin has been demonstrated to reduce IL-5 production in children with atopic asthma, and to have a beneficial effect on the pathogenesis of asthma.

Nevertheless, positive effects of macrolides have not yet been fully demonstrated in clinical trials in asthma and recent studies have presented conflicting conclusions on the use of macrolides in routine clinical practice in patients with uncontrolled asthma. Further studies investigating the effects of macrolides in asthma management are, therefore, required.

Theophylline Theophylline may act through different molecular mechanisms to inhibit phosphodiesterase and adenosine receptor antagonism at therapeutic concentrations. Some studies show that low doses of oral theophylline increase histone deacetylase-2 (HDAC2) expression in alveolar macrophages in patients with COPD and it also downregulates inflammatory gene expression *via* effects on histone acetylases (HATs) and histone deacetylases (HDACs). In asthma, HAT levels are increased while HDACs are reduced; this is inverted by

glucocorticoids as well as by theophylline, with a reduction in IL-8, TNF-α and granulocyte-macrophage colony-stimulating factor (GM-CSF) in response to lipopolysaccharide. Moreover, theophylline may prevent downregulation of the β-receptors by β_2-agonists.

Through these mechanisms, theophylline has been demonstrated to re-establish steroid responsiveness, thus representing a potential new approach in steroid-resistant patients.

Anti-IL antibodies Eosinophils are major actors in airway inflammation and remodelling mechanisms in asthma. They release a wide range of mediators which can promote airway inflammation, induce epithelial damage and cause airway hyperresponsiveness.

The complex networks of cytokines and cells involved in the pathology of asthma provide scope for intervention with monoclonal antibodies that block cytokine– or chemokine–receptor interactions, to deplete cells expressing a specific receptor or to block cell–cell interactions.

Though, at present, anti-IgE is the only monoclonal antibody approved for asthma treatment in children, other antibodies have been clinically tested in asthma, including anti-IL-5, anti-IL-4, anti-IL-13, anti-TNFα, anti-CCR3, anti-CCR4 and anti-OX40L.

In particular, IL-5 plays an important role in eosinophil activation and airway hyperresponsiveness and it is involved in the induction of Th2 responses in the asthmatic airway. IL-5 also plays a role in the migration of eosinophils from the bone marrow to the blood circulation and subsequently to the sites of inflammation and it is also active in promoting the survival of eosinophils at the site of airway inflammation by preventing apoptosis.

The compelling evidence linking IL-5 to asthma pathology led to the development of therapies targeting IL-5 and a few studies have been performed in patients with severe asthma and sputum eosinophilia and hypereosinophilic syndromes.

These studies, performed in adult patients, demonstrate the utility of anti-IL5 but the general applicability of the studies is still under debate because of the the strict selection criteria used and the low numbers of participating patients. However, these studies explore a very attractive rationale for the modulation of eosinophils activity in asthma and demonstrate that anti-IL-5 antibodies represent a promising avenue for asthma therapy.

At present, no study on IL-5 in children has been published.

Conclusion

Different guidelines and consensus documents are currently available for asthma treatment. They all agree regarding the main objective of the treatment intervention, which is to achieve and maintain control of the disease, including reduction of exacerbations, need for emergency visits and hospitalisation.

The stepwise therapeutic model, with step-up of treatment in case of poor control is not always adequate to achieve control of symptoms and exacerbations in patients with severe asthma.

New strategies to improve asthma control have been proposed in recent years and are currently under development and evaluation.

New drugs are involved in the modulation of Th1/Th2 differentiation, inhibition of Th2-related cytokines and inhibition of the downstream mediators.

While omalizumab is currently approved for the treatment of severe persistent allergic asthma unresponsive to traditional theapy in children aged 6–11 years, other drugs are under evaluation to improve the control of the disease in clinical practice.

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Differential diagnosis of bronchial asthma

Giorgio Piacentini and Laura Tenero

Epidemiology

Although asthma is considered the most common condition presenting with wheezing, not all children who wheeze are affected by asthma. Wheezing can be an isolated symptom or it may be accompanied by cough, chest tightness, shortness of breath and dyspnoea in different clinical conditions. Recurrent wheezing is common in young children and population studies have shown that one third of children have had at least one episode of wheezing before the age of 3 years and 50% of children have had at least one episode by the age of 6 years. Recurrent wheezing is, therefore, a common condition in paediatric practice and the differential diagnosis represents a challenging clinical procedure for paediatricians. The main issue is to correctly distinguish between the different phenotypes of wheezing in pre-schoolers, for whom the diagnosis is further complicated by the lack of objective lung function measurements and biomarkers. Differential diagnosis may also be challenging in older children, due to conditions which may mimic asthma, such as dysfunctional breathing.

Key points

- Although asthma is considered the most common condition presenting with wheezing, not all the children who wheeze are affected by asthma. Recurrent wheezing is a common condition in paediatric practice and the differential diagnosis represents a challenge for paediatricians.
- The diagnosis of asthma is more difficult in preschoolers.
- The symptoms of asthma can be associated with other diseases.

Childhood asthma and wheezing are not synonymous, these terms characterise a number of conditions that may have different outcomes. Some children present with transient wheezing and have a reduction in pulmonary function at birth but do not go on to develop asthma, whereas other children have persistent wheezing and have an increased risk of developing asthma.

Definition of wheezing

Wheezing is noisy breathing that can be classically defined as a musical, high-pitched, airway-derived noise detectable during exhalation. Wheeze results from narrowing of the intrathoracic airways, which produces expiratory flow turbulence. Therefore, a number of different conditions, including airways narrowing, airways abnormalities, cystic fibrosis and bronchomalacia, may cause a child to wheeze. Although this definition is well known to medical personnel, parents and patients, it is often improperly used to describe respiratory symptoms that are not really wheezes. It is important to clearly define the features of the sound in order to confirm or reject wheezing as the appropriate descriptor of the symptom under consideration. Stridor, which is an inspiratory noise associated with extrathoracic or upper airway obstruction, is often confused with wheezing; however, its presence prompts consideration of an alternative differential diagnosis.

Clinical conditions presenting with wheezing

Alternative conditions must be taken into account before a diagnosis of asthma is defined permanently. Alternative causes of recurrent episodes of wheezing, especially in early childhood, are shown in table 1. The main differential diagnoses are respiratory infections, congenital and structural problems, foreign bodies, and gastro-oesophageal reflux. In children with severe, recurrent wheezing that is nonresponsive to inhaled corticosteroids, leukotriene receptor antagonists and/or bronchodilators, other diagnoses should be considered.

Major causes of wheezing to consider during diagnosis

Respiratory infections In children with persistent wheezing that does not respond to adequate inhaled corticosteroid treatment, viral and bacterial infections are frequent. The main pathogens involved are *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*. The chronic inflammatory response to infection may be related to persistent wheezing despite therapy. Antimicrobial therapy should be considered in these patients. Chronic cough is also a frequent symptom in young children that could be confused with asthma. In sinusitis, purulent rhinorrhea, sneezing and post-nasal drip are related to chronic cough, but sinusitis is often misdiagnosed especially if it persists for longer than 4 weeks. Chronic sinusitis requires a long course of antibiotics (10–15 days). Other respiratory infections causing wheezing and cough in children that could be confused with asthma are

Table 1. Differential diagnosis in bronchial asthma

	Symptoms and history	Medical findings
Respiratory infections	Fever Cough with respiratory distress Relatives with the same symptoms	Wheezing Rales Rhonchi
GORD	Frequent regurgitation Post-prandial vomiting Crying in supine position Nocturnal symptoms	Failure to thrive Loss of weight
Foreign body aspiration	"Cough/suffocation" with sudden onset Sudden cough	Bronchial breathing
Vocal cord dysfunction (VCD)	Shortness of breath, wheezing, stridor, or cough	Inspiratory flow–volume loop
Laryngomalacia	Inspiratory stridor present from birth	The volume loop is characterised by a "tooth" deflection in the inspiratory phase
Cardiovascular causes of airway compression	Recurrent respiratory difficulty, dyspnoea, dysphagia, wheezing and stridor Present from birth	Wheezing
Genetic disease	Recurrent dyspnoea Recurrent infections	Wheezing and dyspnoea
Congenital malformations	Respiratory symptoms at birth, but can remain asymptomatic for long periods	Malformations on radiological investigation

pertussis, bronchiolitis and epiglottitis. Cough and upper respiratory symptoms could also be related to tuberculosis, which may manifest without the typical symptoms (night sweats, haemoptysis, weight loss and fatigue). In this case it is necessary to perform chest radiography, which may show upper lobar infiltrates, cavitary infiltrates or adenopathy.

Gastro-oesophageal reflux disease (GORD) Infant wheezing that is unresponsive to bronchodilator therapy may be related to GORD or silent aspiration. GORD has been shown to be associated with chronic upper airway respiratory symptoms, including reactive airways disease, recurrent stridor, chronic cough and recurrent pneumonia in infants who do not respond to common anti-asthma medications (Bhatia *et al.* 2009).The gold standard for investigation of this problem is 24-h pH monitoring.

Foreign body aspiration In children with sudden cough and wheezing, the risk of inhalation of a foreign body should be considered. In this case, it is important to analyse the history and look for temporal relationships with onset of symptoms. Though chest radiography could be helpful if the foreign body is radiopaque or if indirect signs, such as peribronchial inflammation of mediastinal dislocation, develop, the diagnostic and therapeutic gold standard is bronchoscopy.

Airway abnormalities Laryngomalacia is the most common congenital abnormality and cause of stridor in children. The manifestations can vary from mild noisy breathing with feeding to life-threatening airway obstruction to failure to thrive. Stridor is inspiratory for the collapse of supraglottic airway structures. The volume loop is characterised by a ''tooth'' deflection in the inspiratory phase. Vocal cord dysfunction is a disorder characterised by an upper episodic and involuntary airway obstruction caused by adduction of the vocal cords, primarily on inspiration, inducing paroxysms of the glottis. This disease is often confused with refractory asthma as symptoms are intermittent shortness of breath, wheezing, stridor, or cough, which may be interpreted as uncontrolled or worsening asthma, leading to unnecessary therapy or step up in medication. The diagnosis could be suspected when there is a truncation of the inspiratory flow–volume loop. Direct visualisation during an attack permits definitive diagnosis. In these children the exhaled nitric oxide fraction (F_{ENO}) is expected to be normal.

Cardiovascular causes of airway compression Compression of the airways is a relatively common complication of congenital vascular malformation in children. The main symptoms are recurrent respiratory difficulty, dyspnoea, dysphagia, wheezing and stridor without other causes. The differential diagnosis may start from spirometric evaluation, but confirmation requires chest radiography, eventually with barium contrast, echocardiography, MRI, CT and bronchoscopy.

Genetic diseases Genetic conditions such as primary ciliary dyskinesia and CF may be relevant in the differential diagnosis in children presenting with recurrent dyspnoea.

Congenital abnormalities Congenital malformations of the lower airways are rare anomalies and include a wide spectrum of conditions with a broadly varying clinical presentation. Individuals with congenital lung malformations can present with respiratory symptoms at birth or can remain asymptomatic for long periods. Usually, the diagnosis requires an imaging evaluation. Depending on the pathophysiological mechanisms and structures involved, lung malformations can be divided into several categories: bronchopulmonary anomalies; combined lung and vascular abnormalities; and vascular anomalies.

Pulmonary sequestration is characterised by normal, nonfunctioning lung tissue that has no connection with the bronchial tree and receives its blood supply from the systemic circulation. Pulmonary sequestrations can be classified as extralobar or intralobar depending on their location in relation to the adjacent normal lung and on their visceral pleural covering.

Congenital cystic adenomatoid malformations are hamartomatous lesions, with focal dysplasia and anomalous development, and are characterised by a cystic mass of lung tissue with proliferation of bronchial structures and lung tissue showing aberrant, differentiated architecture, with various degrees of cyst formation. The most common symptoms are recurrent infections, and there have been reports of malignant transformation.

Congenital lobar emphysema, also known as infantile lobar hyperinflation, is a rare lung malformation. Entrapment of air in the affected lobe during the expiratory phase results in progressive distension and a consequent effect on lung structures and adjacent mediastinal mass. All this leads to breathing problems due to alteration of normal gaseous exchange.

Various terms have been used to designate *arteriovenous malformations*, including arteriovenous fistula, pulmonary arteriovenous aneurysm, pulmonary haemangioma, pulmonary cavernous angioma, and pulmonary telangiectasia.

Another differential diagnosis that should be considered is *bronchopulmonary dysplasia* (BPD). It is an important cause of morbidity and mortality in preterm infants. Its incidence in infants with birth weight $<$1500 g ranges 23–26%. BPD is defined as the presence of oxygen dependence to 36 weeks of post-conceptional age or at 28 days of life, in combination with persistent clinical respiratory symptoms and radiological pulmonary abnormalities. It is discussed in detail elsewhere in this *Handbook*.

Conclusion

The symptoms of asthma, not always specific, can be associated with other diseases, and differential diagnosis should always be considered to confirm or exclude a definitive diagnosis of asthma. Particular attention should be considered in preschool children in order to identify the specific phenotype of wheezing.

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Pathophysiology and epidemiology of allergic disorders

Karin C. Lødrup Carlsen

Allergic disorders include asthma, allergic rhinitis, allergic rhinoconjunctivits, atopic eczema, urticaria, food allergy and anaphylaxis. Allergic diseases are chronic and often complex diseases with environmental, as well as genetic, influences. With the recent "asthma and allergy epidemic" in the Western world, it has been suggested that environmental factors play a more important role in disease development than previously thought. In addition, more than 100 different genes are implicated in allergic diseases to some extent; however, there is no clear specific gene, suggesting a less prominent role of genes in the current epidemic of allergic diseases. Whether this is related to more abundant risk factors or the loss of potentially protective factors is not known. Current research is investigating whether environmental effects on genes causing epigenetic changes are involved in disease modification. However, neither the factor(s) nor the timing of triggers that off-set the immune system from normal development into an allergic inflammatory pathway are known.

Key points

- Manifestations of allergic diseases may appear at any age, but most commonly occur in childhood.
- The so-called "allergic march" portrays a succession from atopic eczema, through food allergy to inhalant allergy, often accompanied by asthma and subsequently allergic rhinitis, all of which commonly occur by school age.
- Viral infections are important triggers of symptoms and exacerbations of asthma in childhood; however, allergic sensitisation appears to precede viral infection in children with viral wheeze and allergic sensitisation who develop asthma.
- The observed increase in allergic diseases is particularly worrying since it not only affects the subjects with the diseases, but is likely to increase the burden of allergic disease in the offspring of the current younger generation.

Pathophysiology

Manifestations of allergic diseases may appear at any age, but most commonly occur in childhood. The so-called "allergic march" portrays a succession from atopic eczema, through food allergy to inhalant allergy, often accompanied by asthma and subsequently allergic rhinitis, all of which commonly occur by school age. Puberty is the second life-phase with major changes in allergic disease, and is when the male predominance of allergic diseases seen in childhood gradually changes into a subsequent female predominance after puberty. The causes of this change are not known, but hormonal changes with increasing allergic manifestation in females during puberty are considered a probable cause of the changing sex predominance.

Allergic sensitisation, particularly to mites, cockroaches, pollen and pet allergens, are among the strongest risk factors for asthma. However, allergic diseases may also occur in

individuals without detectable serum IgE or positive skin prick tests to allergens. Children with atopic eczema, asthma or asthma-like symptoms often lack detectable serum IgE antibodies, suggesting that there are alternative mechanisms for initiating the underlying inflammation. This is commonly seen as differing phenotypes of allergic diseases, with allergic sensitisation being a pivotal phenotypic criterion. This view is currently challenged, as allergy is probably not an all-or-nothing phenomenon, but rather a continuum of immunological mechanisms underlying allergic disease presentations. However, some common underlying pathophysiological mechanisms within and between allergic diseases are probable in view of the frequent comorbidity of allergic diseases, typically allergic rhinitis and asthma, or atopic eczema preceding asthma and allergic rhinitis.

In general, most individuals do not respond adversely to allergens. However, in some, allergen exposure leads to a break in natural tolerance triggering allergic inflammation (fig. 1), and an allergen-specific immune response that is maintained by host T- and B-cells. The allergic inflammation typically involves the production of specific serum IgE antibodies against allergens (allergic sensitisation). Allergic inflammation involves local, as well as systemic, immune cells and biomarkers of the innate and adaptive immune system (fig. 1). The allergic response is initiated when an allergen binds to the high-affinity receptor for IgE (FCεRI) on the antigen presenting cell (APC). The APC will then process the allergen into small peptides that will be presented *via* the major histocompatibility complex (MHC) class II molecules for recognition by the T-cells. The immediate allergic response involves isotype switching of a B-cell into IgE synthesis, a process that requires the presence of several interleukins (IL; such as, IL-4 and IL-13) and cytokines, resulting in a cascade of immunological events. In contrast to normal immune host responses to microbial products involving T-helper type 1 (Th1) lymphocytes, the allergic inflammatory cascade involves Th2 cytokines and other immune mediators leading to:

- survival of the Th2 cell;
- mast cell differentiation and maturation;
- B-cell isotype switching to IgE synthesis;
- maturation and survival of eosinophils;
- recruitment of basophils.

It is not known what triggers T-cells and how the naïve T-cells mature into Th2 immune-active cells. However, it is believed that directing naïve T-cells to Th1 *versus* Th2 immunity involves regulatory T-cells (Tregs), a process that is important in tolerance development and suppressing allergic inflammation.

The innate immune system is, in effect:

- the barrier between the organism and the external environment;
- an important defence against infections;
- the first line of defence against intruders.

Innate immune cells (such as mast cells), granulocytes, mononuclear phagocytes, lymphocytes and epithelial cells, express surface and internal receptors, including Toll-like receptors and those involved in recognising and removing microbial substances.

However, the adaptive immune system classically involves T-cell responses to antigens (or allergens), typically with production of serum IgE-antibodies from B-cells adapting to environmental challenges. In addition, dendritic cells (APCs in the airway and gut epithelium) (fig. 2) are not present at birth, but move from the bone marrow to the epithelium, possibly as a result of damage to the airway epithelium, like viral infections in asthmatic subjects. In subjects with established allergic sensitisation, the dendritic cells, which contain receptors that are able to attach to allergens, engulf the ''intruding'' allergen, processing them to form peptides that can be presented to the T-cell receptors as complexes formed with the MHC. The dendritic cell uptake of allergens is facilitated by allergens bound to FcεRI (fig. 1), which may be particularly abundant

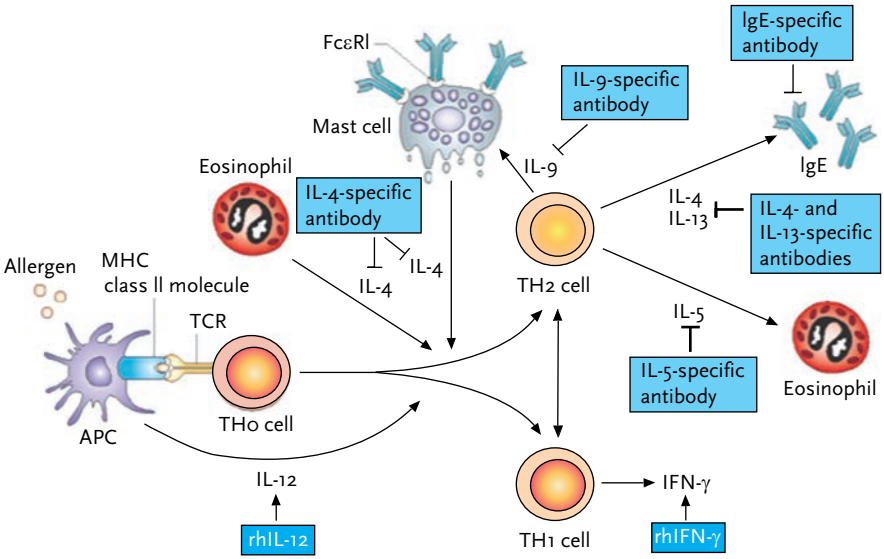

Figure 1. Schematic diagram showing the interplay between local, as well as systemic, immune cells and biomarkers of the innate and adaptive immune system in allergic inflammation. TCR: T-cell receptor; rhIL: recombinant human IL; IFN: interferon; rhIFN: recombinant IFN. Reproduced from Holgate (2008), with permission from the publisher.

as the cells move from the bone marrow to the mucosal lining.

Such mechanisms are probably propagated through defects in barrier function, and have recently been demonstrated in the airway epithelium of asthmatic subjects and the skin of subjects with atopic eczema, as well as in other allergic diseases. A link has been reported through a common genetic variant of filaggrin.

Viral infections are important triggers of symptoms and exacerbations of asthma in childhood, whereas many children with "viral wheeze" will not go on to develop asthma. Recent studies suggest that respiratory viruses, possibly (sub-types of) human rhinovirus in particular, may play a role in triggering the immune system. The mechanisms are not known, but a series of interactions between antiviral and atopic inflammatory pathways mediated by local activation of myeloid cell populations are probable in the airways, as well as in the bone marrow. A recently hypothesised immune cycle in asthma development suggests that repeated airborne irritant stimuli (such as allergens or viruses) evoke cycles of inflammation leading to intermittent inflammation and initially resulting in episodic symptoms. However, with repeated insults the inflammatory resolution becomes less complete leading to tissue repair and regeneration, which may trigger prolonged periods of pathological changes. These periods may progress to deterioration in respiratory function and perhaps to remodelling. A commonly asked question, the answer to which is not clear at present, is what is the role and potential interaction between allergic sensitisation and viral infections in eliciting disease development, in contrast to both viruses and allergens being potential triggers of disease exacerbations? However, it was recently deduced that allergic sensitisation appears to precede viral infections in children who have both conditions. Another aspect of the damaged epithelium in asthma is the reduced ability to handle viruses in an

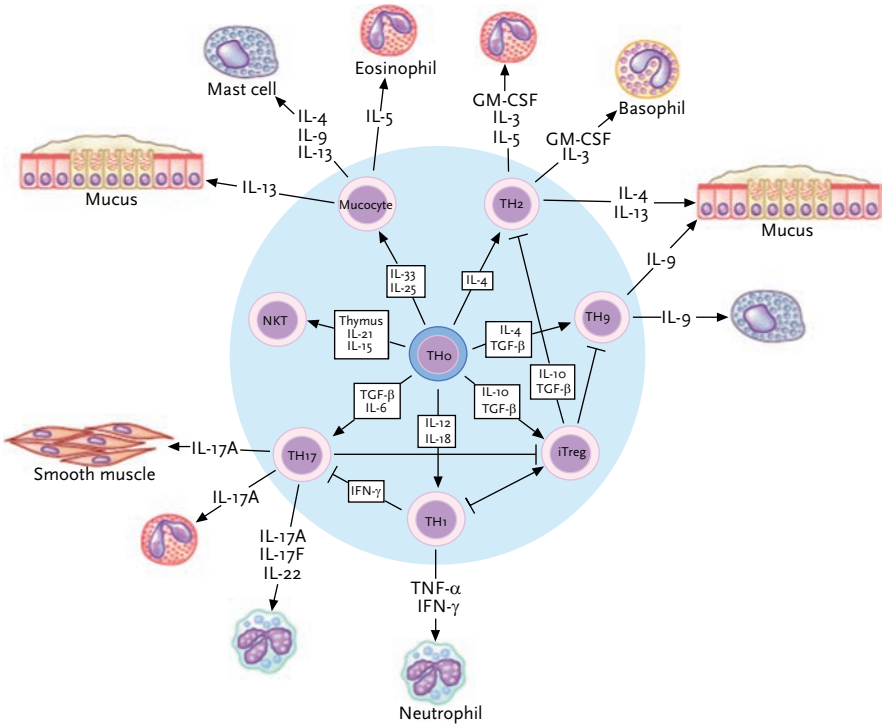

Figure 2. Different T-cell subtypes are involved in the pathogenesis of asthma. Cytokines and contact signals, together with dendritic cells and the thymic epithelium, drive the inflammatory process into various cell lines (blue circle), maintaining inflammatory responses involved in asthma and airway hyperreactivity. GM-CSF: granulocyte-macrophage colony-stimulating factor; TNF: tumour necrosis factor; IFN: interferon; NKT: natural killer T-cell; Th: T-helper; iTreg: inducible regulatory T-cell. Reproduced and modified from Holgate (2012), with permission from the publisher.

optimal way. It appears that the reduced ability of airway epithelial cells to produce interferon-γ may lead to cytotoxic cell death and subsequent dissemination of viruses, rather than apoptosis, possibly explaining the prolonged symptomatic viral infection observed in asthmatics.

Bronchial hyperresponsiveness (BHR) is a common, but not necessary, feature of childhood asthma. BHR typically presents as a general tendency to develop symptoms *via* exposure to various physiological or environmental stimuli, with exercise being a classical childhood asthma symptom trigger. The underlying mechanisms for BHR development are not clear, but may involve barrier dysfunction, as well as possibly neural parasympathetic mechanisms involving heat and fluid exchange over the epithelium. BHR is a modest, but significant, risk factor for later onset of asthma and tends to decrease throughout childhood.

The role of lung function reductions in the development of asthma, in contrast to lung function decline with chronic asthma, is not entirely clear. There is no doubt that asthma is associated with reduced lung function as well as a more rapid decline in lung function compared to healthy individuals. In a few birth cohorts, reduced lung function has been found to precede asthma in some, but not all, children with asthma.

Airway remodelling is a common feature in adult asthma but this is not as clear in

childhood, particularly with reference to when it starts and what elicits the process. Nevertheless, lung function reductions in older children are likely to reflect structural changes in the airways, such as subepithelial reticular basement layer thickening, epithelial cell disruption, imbalance of proteases and anti-proteases, as well as neoangiogenesis (remodelling).

Epidemiology

Allergic diseases in children have increased over the past decades to epidemic proportions. In a recent Swedish birth cohort study from 1994, >50% of 12-year-old children had at least one allergic disease, and 7.5 % had at least two diseases out of atopic eczema, asthma or allergic rhinitis.

In the International Study of Asthma and Allergy phases I–III, asthma prevalence varied up to 15-fold in the >50 included countries and almost 200 000 6–7-year-old children and 300 000 13–14-year-old children. In 2001–2003, the prevalence of current asthma symptoms in 6–7-year-olds ranged from 5.0% (Nigeria) to 37.6% (Costa Rica) with respective figures in 13–14-year-olds ranging from of 5.1% (Georgia) to 31.2% (Isle of Man). The corresponding figures for allergic rhinitis were 2.2% (Iran) to 24.2% (Taiwan) for 6–7-year-olds and 4.5% (Baltic countries) to 45.1% (Paraguay) in 13–14-year-olds, and for atopic eczema were 2.0% (Iran) to 22.3% (Sweden) and 1.8% (Georgia) to 21.8% (Morocco), respectively. Overall, since the mid-1990s, an increase in allergic disease prevalence has been found more often than a decrease, most often in the younger age group and particularly for atopic eczema. In Europe, pooled data from 11 birth cohorts (>14 000 children) demonstrated a mean prevalence of current asthma in children aged 6–10 years of 8.1%; approximately half of the children had concomitant allergic sensitisation, 7.7% had current allergic rhinitis and 29.5% had allergic sensitisation, demonstrating large variations between countries and cohorts.

The prevalence of food allergy is more difficult to assess due to the relatively large difference between perceived and documented (usually by food challenges) symptoms of food allergy. However, in a recent study in Australia, 13% of 1-year-old children with atopic mothers were found to have a food allergy whereas 4% of those with a non-atopic mother had confirmed a food allergy. However, cow's milk allergy has been reported in up to 40% of 5–16-year-olds, but was only confirmed in 5%. Anaphylaxis is increasing, and although there are shortcomings in definitions and methodology, an annual incidence rate of 0.4–9% has been reported, with peanuts and tree-nuts being the most common triggers. In a recent Swedish study the population incidence was found to be 32 per 100 000 person, with food involved in 92% of the episodes.

The observed increase in allergic diseases is particularly worrying since it not only affects the subjects with the diseases, but is likely to increase the burden of allergic disease in the offspring of the current younger generation.

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In vivo and *in vitro* diagnostic tests in allergic disorders

Gunilla Hedlin

Many children who start to wheeze during airway infections in early life will improve with age when infections become less frequent and the airways grow. There is, however, a large group of children who start with viral wheeze and continue to develop persistent asthma. In many of these children, IgE-mediated allergy will play an important role as a trigger of symptoms. In some, allergy testing will confirm an IgE-mediated sensitisation sometimes preceding the clinically relevant allergy. In others, asthma symptoms at allergen exposure will appear before sensitisation can be confirmed. Thus, although allergy is a common cause of symptoms of asthma and often of asthma exacerbations, it is not always clear what role a specific allergen plays in the severity of the disease. This is particularly obvious when the relationship between exposure and symptoms is not clear. In pollen allergy, the relationship between exposure and symptoms is easy to assess using pollen count reports. There is usually no need to confirm a relationship between sensitisation, exposure and symptoms by any other means than taking a history and performing a skin prick test (SPT) and/or an analysis of allergen-specific IgE in serum. In animal dander allergy there is also a clear relationship between exposure and allergic symptoms, yet this may not always be the case. Exposure to dander present on clothes, hair or on surfaces at home and school or in other public places constitutes an invisible source of allergen. Under these and other circumstances it can be difficult to evaluate the impact of allergy on a child's symptoms. These examples highlight the importance of performing a careful, thorough, diagnosis of allergy before the decision is made to take action on allergen avoidance and/or initiate immunotherapy. The allergens responsible for causing asthma symptoms have to be confirmed.

Key points

- Allergy is a common trigger of asthma.
- Allergy can start at any age.
- Allergy testing should be performed in all children with asthma.

Prevalence of allergic sensitisation

Allergic sensitisation can start at any age and is a common phenomenon. In the US National Health and Nutrition Survey 54% of 10 500 participants had one or more positive SPT to one or more of 10 allergens. The sensitisation rate had more than doubled between the tests performed during 1976–1980 and 1988–1994. Similar trends have been seen in European longitudinal and/or cross-sectional population-based studies. In a Swedish study of the sensitisation rate in schoolchildren the prevalence of one or more positive SPT increased from 21–30% between 1996 and 2006.

Diagnosis of allergy

History The first and foremost step in the evaluation of children with asthma is a careful detailed history. Important questions include family history of allergic disease, known triggers of symptoms, frequency and severity of symptoms, other signs of atopic

Table 1. Advantages of allergy testing

SPT	Serum IgE
No blood sample needed	No need to withhold antihistamines
Reliable with good extracts	Reliable with validated methods
Immediate results	Always available
Visible results	Can be used when skin is impaired

disease like rhinitis without relation to colds, atopic dermatitis and adverse reactions to food. In some children allergic rhinitis may precede asthma and act as a predictor of an increased risk of asthma. Early development of eczema and/or food allergies can also be signs of risk of later allergic asthma in children.

Allergy sensitisation testing: practice and interpretation The most common mode of allergy testing is *in vivo* testing by the SPT; usually the test of choice. The alternative is *in vitro* testing, which is analysis of allergen-specific IgE antibodies in serum. Both tests have advantages and disadvantages (table 1).

SPTs should be performed with well-standardised extracts. Usually a panel of aeroallergens are used. The test is applied by drops of allergen extract on the volar side of the forearm. The drops are then punctured by a needle-like device (fig. 1). After 15–20 min any wheal and skin flare reactions are recorded and the longest diameter of each wheal is measured. A wheal diameter $\geqslant$3 mm is considered a significant skin reaction. A false-negative test result can be seen when the patient has ongoing antihistamine therapy, ongoing dermatitis and/or when a topical corticosteroid has recently been applied on the skin. A false-negative result can also be seen at an early stage of sensitisation or if sensitisation is weak. A false-positive SPT can be seen if the child suffers from dermographism or when sensitisation does not reflect clinical allergy; in the latter case the history is more important than the test result, although a positive test can precede the clinical allergy. In food allergy that subsides, such as egg and milk allergy, the skin sensitivity can remain after the child has developed tolerance. A SPT can be performed at any age but skin reactions tend to be smaller in young children (table 2).

IgE in serum can be analysed for:

- single allergens,
- allergenic molecules (components) of single allergens,
- a mix of allergens (mix of rodents, moulds and dust mites),
- for screening purposes by a multi-allergen test, including the common SPT panel of allergens (table 3).

The *in vitro* IgE measurement and the SPT result usually agree, but not always. If the SPT does not agree with the history IgE in serum should be measured before rolling out a suspected allergy. Analysis of serum IgE can be performed at any age or any time; current pharmacotherapy does not interfere with the test result. Negative test results in young children should be interpreted with caution. Low specific-IgE levels (0.1–0.35 $kUa \cdot L^{-1}$) can indicate sensitisation. There are a number of companies that provide assays for the *in vitro* IgE antibody tests. Most commonly, a solid phase matrix with allergen extract is used.

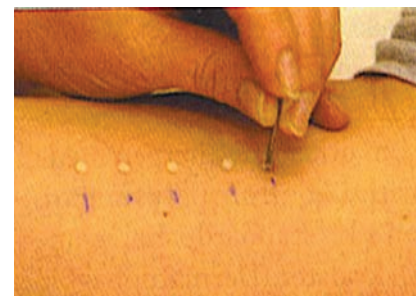

Figure 1. Performance of a SPT.

Table 2. Interpreting allergy test results

Allergy can be an asthma trigger in spite of a negative allergy test
Allergic sensitisation may not have any relation to asthma symptoms
The degree of sensitisation (*e.g.* wheal size and antibody level) may or may not reflect disease severity
SPT and *in vitro* IgE tests often agree but sometimes both tests are needed
When allergy testing and history disagree there can be a need for an allergen challenge test, if allergy needs to be confirmed or excluded

After adding the patient's serum an anti-IgE antibody is added and the amount of bound allergen-specific IgE in the patient's serum is analysed. The result is usually expressed in arbitrary mass units ($kUa \cdot L^{-1}$).

Allergen challenge tests While *in vitro* tests or SPTs are good enough for confirming pollen and animal dander allergy, it may be necessary to perform allergen provocation tests in the eyes and/or the nose to confirm a dust mite or mould allergy. Bronchial allergen challenge is rarely indicated. It can be dangerous in children with asthma, inducing a severe asthmatic reaction, and should be avoided.

Nasal and conjunctival allergen challenges can be important if there is doubt about the impact of the specific allergy on the severity of symptoms. This may be the case when allergen immunotherapy is considered. The rationale is to avoid treating a child whose symptoms are mainly caused by other factors in spite of confirmed allergen sensitisations.

Table 3. Common panels of allergens included in SPT and/or IgE antibody screening

Tree pollen (relevant for geographical area)
Grass pollen (relevant for geographical area)
Weed pollen (relevant for geographical area)
Animal dander
Cat
Dog
Horse
Dust mite
Mould
Alternaria
Cladosporium

Food challenges, open or double-blind, are sometimes warranted to confirm an allergy but also to support development of tolerance, which is common in children with, for instance, milk and egg allergy.

Total IgE measurements in serum are mainly needed when treatment with anti-IgE (omalizumab) is considered, an injection therapy with monoclonal anti-IgE antibodies. Dosing is based on the patient's age, weight and level of total IgE.

Molecular diagnosis in allergy is usually performed by measuring IgE antibodies towards individual allergenic components. An alternative is microarray-based testing against multiple recombinant or purified natural allergen components. This has made it possible to analyse IgE antibodies to numerous allergen components of many common allergens simultaneously in small samples of serum (20 uL). The allergen components can be classified by protein families. This detailed analysis improves the possibility to identify antibodies to proteins that cross-react between different allergens from a sensitisation that is species specific. Currently, the only commercially available component resolved microarray diagnostic method is the Immuno Solid phase Allergen Chip microarray (Phadia, Uppsala, Sweden).

Allergy diagnostics is an important part of the evaluation and management of children with preschool wheeze and asthma. Together with a careful history it is one of the first steps in identifying possible triggers

in children of all ages. Allergy becomes more common as a trigger in children with recurrent wheeze and is a major cause of symptoms and exacerbations in children with persistent and/or seasonal asthma.

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Anaphylaxis

Antonella Muraro

Anaphylaxis is a serious allergic reaction that is rapid in onset and may result in death. The epidemiology of the disease is hindered by difficulties in timely assessment of symptoms and in the lack of proper coding according to the International Classification of Disease. In addition, anaphylaxis in infants and children might be even more difficult to recognise and needs a high degree of suspicion. However, although no exact incidence can be established, based on current data it is reasonable to assume that 1–2% of the population may be affected, with food and drugs being the most common cause of anaphylaxis.

Triggers

The most common causes of anaphylaxis are food allergens, medications and hymenoptera venoms. Less frequently, anaphylaxis can be triggered by physical exercise, aeroallergens and contact with latex, radiocontrast media and ethanol. Almost all episodes are IgE-mediated reactions, although sometimes other, non IgE-mediated, immunological mechanisms might be involved, or there may be direct mast cell activation such as in physical exercise. Idiopathic anaphylaxis, *i.e.* when the cause is unknown, is also relatively common.

In contrast with older patients, in which drugs and hymenoptera venom are the main causes, food allergens are the most common trigger of anaphylaxis in children. Among them, cow's milk, egg, peanuts, tree nuts and seafood are most frequently reported.

Key points

- Anaphylaxis is a serious allergic reaction that is rapid in onset and may result in death.
- The most common causes are food allergens, medications and hymenoptera venoms.
- Infants are usually not able to describe symptoms; therefore, physicians need to have a high index of suspicion in order to diagnose anaphylaxis.
- Adrenaline is the medication of choice for anaphylactic episodes.

Clinical manifestation and diagnosis

The diagnosis of anaphylaxis is primarily based on clinical symptoms and signs, as well as a detailed description of acute episodes, including antecedent activities and events occurring within the preceding minutes to hours.

Typically, exposure to a triggering allergen is followed by rapid development of symptoms over minutes to several hours. Investigation is mandatory, especially if exposure to a likely allergen is reported. Sudden onset of urticaria, swelling of the oropharynx, rhinorrea, cough, breathing difficulties, vomiting and progressive abdominal pain, pallor, irritability and sleepiness (*i.e.* hypotension) should be carefully evaluated in any allergic child. In infants, anaphylaxis may be even more difficult to recognise because they are usually unable to describe the symptoms. Moreover, some signs of

anaphylaxis, such as irritability, flushing, hoarseness, drooling, regurgitation, loose stools, colicky abdominal pain and somnolence, may be difficult to interpret since they are quite common in this age group.

Recently, the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network have established three diagnostic criteria, allowing 95% of anaphylaxis events to be diagnosed (table 1).

In both adults and children, the time course of the reaction may be:

- Uniphasic, occurring immediately after exposure and resolving with or without treatment in minutes to hours;
- Biphasic, recurring after the apparent resolution of initial symptoms, usually about 8 h after the first reaction;
- Protracted, persisting for hours or days following the initial reaction.

Role of laboratory tests

The diagnosis is hampered by the lack of reliable markers of the disease. Serum tryptase, which should be obtained 15 min to 3 h after onset of the symptoms, has low sensitivity and specificity and its level is typically normal in food anaphylaxis. Histamine blood levels obtained 15–60 min after onset may also be useful. However, both tests are not universally available, not performed on an emergency basis and not specific for anaphylaxis. A recent report highlights the possible role of platelet-activating factor in the pathogenesis of more severe reactions.

Management

The management of anaphylaxis encompasses both the treatment of acute episodes and the preventive strategies in the community to avoid recurrences and new cases.

Basic management As with the treatment of any critical patient, the treatment of

Table 1. Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria are fulfilled
Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (*e.g.* generalised hives, pruritus or flushing and swollen lips-tongue-uvula), and at least one of the following:
Respiratory compromise (*e.g.* dyspnoea, wheeze-bronchospasm, stridor, reduced PEF and hypoxaemia)
Reduced BP or associated symptoms of end-organ dysfunction (*e.g.* hypotonia (collapse), syncope and incontinence)
Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
Involvement of the skin-mucosal tissue (*e.g.* generalised hives, itch-flush and swollen lips-tongue-uvula)
Respiratory compromise (*e.g.* dyspnoea, wheeze-bronchospasm, stridor, reduced PEF and hypoxaemia)
Reduced BP or associated symptoms (*e.g.* hypotonia (collapse), syncope and incontinence)
Persistent gastrointestinal symptoms (*e.g.* cramping abdominal pain and vomiting)
Reduced BP after exposure to known allergen for that patient (minutes to several hours):
Infants and children: low systolic BP[#] (age specific) or >30% decrease in systolic BP
Adults: systolic BP <90 mmHg or >30% decrease from that person's baseline
PEF: peak expiratory flow; BP: blood pressure. [#]: defined as <70 mmHg at 1 month to 1 year of age, <70 mmHg+[2 × age] at 1–10 years of age and <90 mmHg at 11–17 years of age.

Table 2. Grading of severity of anaphylactic reaction

Grade	Skin	GI tract	Respiratory	Cardiovascular	Neurological
Mild	Sudden itching of eyes and nose, generalised pruritus, flushing, urticarial and angioedema	Oral pruritus, oral "tingling", mild lip swelling, nausea or emesis, mild abdominal pain	Nasal congestion and/or sneezing, rhinorrhoea, throat pruritus, throat tightness and mild wheezing	Tachycardia (increase >15 beats·min^{-1})	Change in activity level plus anxiety
Moderate	Any of the above	Any of the above, cramping abdominal pain, diarrhoea and recurrent vomiting	Any of above, **hoarseness, "barky" cough, difficulty swallowing, stridor, dyspnoea and moderate wheezing**	As above	"Light headedness" and a feeling of "impending doom"
Severe	Any of the above	Any of the above, loss of bowel control	Any of the above, **cyanosis or saturation <92%,** respiratory arrest	**Hypotension[#] and/or collapse, dysrhythmia, severe bradycardia and/or cardiac arrest**	Confusion, loss of consciousness

The severity score should be based on the organ system most affected. Bold indicates a mandatory indication for the use of adrenaline. GI: gastrointestinal. [#]: defined as systolic blood pressure <70 mmHg at 1 month to 1 year of age, <70 mmHg+[2 × age] at 1–10 years of age and <90 mmHg at 11–17 years of age.

anaphylaxis begins with a rapid assessment and maintenance of airway, breathing and circulation. Patients experiencing acute anaphylaxis should be kept in a position of comfort, which usually involves lying recumbent or semi-recumbent. This accomplishes two therapeutic goals:

- preservation of fluid in the circulation (the central vascular compartment), an important step in managing distributive shock;
- prevention of empty vena cava/empty ventricle syndrome, which can occur within seconds when patients with anaphylaxis suddenly assume or are placed in an upright position.

Patients with this syndrome are at high risk for sudden death and unlikely to respond to adrenaline, regardless of route of administration, because it does not reach the heart and therefore cannot be circulated throughout the body.

After removing exposure to the trigger (if possible), if any of the three criteria of anaphylaxis outlined in table 1 are fulfilled, the patient should receive adrenaline immediately.

Adrenaline is the medication of choice for anaphylactic episodes; all other medications should be regarded as ancillary. Prompt injection of adrenaline has been associated with better outcomes. A severity score can be helpful in the diagnosis and in ensuring the timely administration of adrenaline (table 2).

The intramuscular route is acknowledged as the optimal route for adrenaline administration. Adrenaline in a concentration of 1 mg·mL^{-1} should be used in a dose of 0.01 mg·mL^{-1} body weight (maximum single dose 0.5 mg). This dosage can be repeated at short intervals (every 5–10 min) until the patient's condition stabilises.

Although frequently administered, the role and efficacy of antihistamines and corticosteroids in anaphylaxis has not yet been clarified. These medications should not be considered as first-line treatments for

Table 3. Indications for prescribing a self-injectable adrenaline device

Absolute indications	Relative indications
A previous cardiovascular or respiratory reaction to a food (and to other triggers such as insect sting or latex)	Any reactions to small amounts of a food including airborne or contact of the food allergen only *via* skin
Exercise-induced anaphylaxis (often also related to food)	History of previous, even mild, reactions to peanut or tree nuts
Idiopathic reaction	Remoteness of home from medical facilities
Child with food allergy and asthma	Food allergy reaction in a teenager

anaphylaxis as they do not act quickly. The efficacy of corticosteroids in reducing the risk of late-phase reactions has not been proven. High-flow oxygen should be given to any patient with respiratory symptoms or evidence of shock. Volume support with crystalloid solution or colloid expander is mandatory in the case of hypotension.

Long-term management *Identification of triggers* In order to identify the allergen, patients with a history suggestive of an anaphylactic reaction need urgent referral to an allergy clinic for a diagnostic assessment, based on clinical history and *in vivo* and *in vitro* examinations (skin prick test, intradermal test, prick-by-prick with raw food, IgE for suspected allergens and recombinant allergens, and oral challenges for food or drugs).

Risk reduction Strategies to avoid the precipitants should be customised taking into consideration factors such as age, occupation, activities, hobbies, living conditions and access to medical care. As most episodes of anaphylaxis occur in the community, children and their caregivers must know how to prevent further reactions and how to promptly recognise and appropriately manage any anaphylactic reactions that occur outside the hospital. Allergists, emergency physicians and general paediatricians/practitioners, as well as teachers and caregivers, need to develop a coordinated approach, including actions for primary and secondary prevention and emergency response, in order to prevent fatalities and improve quality of life of patients and families.

Prescription of self-injectable adrenaline The decision about whether to prescribe a self-injectable adrenaline device involves analysis of the risks of experiencing anaphylaxis, the benefits of a self-injectable adrenaline device, the risks associated with it and its cost on health services and individual families. Absolute and relative indications about prescribing adrenaline are shown in table 3.

Immunomodulation Venom immunotherapy is 95–100% and ~80% successful in wasp and bee sting allergies, respectively. Desensitisation protocols have also been established for some medications, such as a few antibiotics and nonsteroidal anti-inflammatory drugs, although they are only recommended in exceptional cases.

Food-induced anaphylaxis could theoretically be modulated by allergen desensitisation through immunotherapy, similarly to hymenoptera sting anaphylaxis. However, food allergen immunotherapy remains experimental and although several trials of oral tolerance induction are underway, this procedure is not yet recommended in routine clinical practice.

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Allergic rhinitis

Michele Miraglia Del Giudice, Francesca Galdo and Salvatore Leonardi

The allergic pathologies are frequent and bothersome diseases. In the past 30 years, epidemiological studies have shown that the prevalence of allergic rhinitis continues to increase worldwide although it is often underestimated, underdiagnosed and undertreated. Allergic rhinitis is the most frequent allergic, chronic disease in the paediatric population and is often associated with other allergic diseases. According to various epidemiological studies this disease affects more than 10% of children <14 years of age and 20–30% of adolescents and young adults.

Key points

- Allergic rhinitis is a symptomatic disorder of the nose characterised by itching, nasal discharge, sneezing and nasal airway obstruction induced by an IgE-mediated immune reaction after allergen exposure.
- According to ARIA guidelines, allergic rhinitis is divided into intermittent or persistent disease and the severity is classified as mild or moderate/severe depending on the severity of symptoms and their impact on social life, school and work.
- The diagnosis of allergic rhinitis is based on the concordance between a typical history of allergic symptoms and diagnostic tests.
- The therapeutic strategies of allergic rhinitis are patient education, pharmacotherapy and allergen-specific immunotherapy.
- The inflammation of the nasal mucosa may affect the eye mucosa, air sinuses, the ear and the lower airways.

Definition

Allergic rhinitis is defined as a symptomatic disorder of the nose characterised by:

- itching,
- nasal discharge,
- sneezing,
- nasal airway obstruction induced by an IgE-mediated immune reaction after allergen exposure.

It is accompanied by inflammation of the nasal mucosa and nasal airway hyperreactivity. Although it is not life threatening, it can have a significantly detrimental effect on a child's quality of life, and it may exacerbate a number of common comorbidities, including asthma and sinusitis.

Mechanisms

Allergic rhinitis is the result of IgE-mediated allergy and nasal mucosa inflammation. IgE is produced in the lymphoid tissues and locally in the nasal mucosa in response to common environmental allergens. When allergens bind to mast-cell-bound IgE, mast-cell degranulation occurs. Degranulation of mast cells results in the release of a myriad of biochemical mediators that regulate and/or mediate the different aspects of allergic inflammation.

Among other preformed mediators, histamine is released into the surrounding

tissues binding to H1-receptors on various target cells and eliciting a powerful allergic response (fig. 1). This response is characterised by an increase in vascular permeability and by stimulation of local nerve endings and mucus-secreting cells. The clinical manifestations of these biological activities include sneezing, rhinorrhoea, nasal and ocular itching, and red watery eyes. Thus, histamine is the key player in the acute allergic response.

Other important mediator classes involved in the acute-phase allergic response include prostaglandins (*e.g.* PGD2) and leukotrienes (*e.g.* LTC_4). Prostaglandins, of which PGD2 appears to be the most important, have vasodilatory and bronchoconstrictive properties. Prostaglandin D2 produces nasal inflammation in the acute phase, but does not appear to play a key role in chronic inflammation. Evidence derived from topical application of cysteinyl leukotrienes (cysLTs) in the nose and from the effects of leukotriene receptor antagonists (LTRAs) indicates that cysLTs contribute to nasal mucous secretion, congestion, and inflammation. CysLTs promote allergic inflammation by enhancing immune responses and the production, adhesion, migration and survival of inflammatory cells such as eosinophils.

Late-phase allergic reactions and chronic inflammatory changes involve many cell types including T-cells, mast cells and eosinophils. Eosinophilic inflammation also plays an important role. A T-helper (Th)2 response ensues with the release of interleukin (IL)-4 and IL-5. Eosinophils are increased in numbers and activated in the nasal mucosa of symptomatic allergic patients. They release proinflammatory mediators, including granule-stored cationic proteins, newly synthesised eicosanoids and cytokines. The major basic protein (MBP) is highly cationic and lacks enzymatic activity, and toxicity is believed to be mediated by enhanced membrane permeability resulting from interactions of the cationic protein with the plasma membrane. After allergen exposure, rhinitis can persist for several weeks. In the late phase the predominant symptom is nasal congestion. Eosinophils release mediators that can induce tissue damage, and pre-treatment with topical glucocorticoids reduces eosinophil infiltration and cytokine release.

Classification

The classification of allergic rhinitis was previously based on the time of exposure into seasonal or perennial. Perennial allergic rhinitis is generally caused by indoor

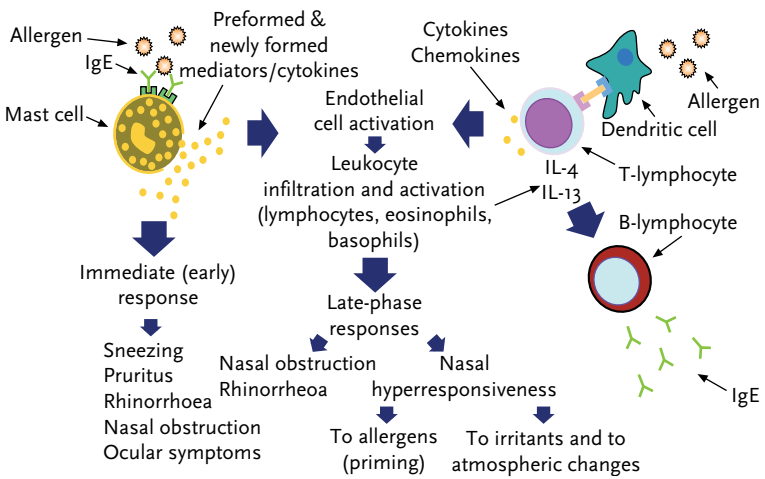

Figure 1. The nasal allergic response. Reproduced from Van Cauwenberger et al. *(2003) with permission from the publisher.*

allergens such as dust mites, moulds and animal danders. Seasonal allergic rhinitis is most frequently related to pollens or moulds.

Recently, an expert panel proposed a new classification of allergic rhinitis. In this classification allergic rhinitis was divided into "intermittent" or "persistent" disease and the severity of allergic rhinitis was classified as "mild" or "moderate/severe" depending on the severity of symptoms and their impact on social life, school and work (fig. 2).

This classification was proposed in the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, the first ever evidence-based guidelines for allergic rhinitis.

Another important aspect of the ARIA guidelines was to consider co-morbidities of allergic rhinitis. The eye, ear and lower airways are involved in allergic rhinitis. Interactions between the lower and the upper airways are well known; over 80% of asthmatics suffer from rhinitis and 10–40% of patients with rhinitis have asthma.

Diagnosis

The diagnosis of allergic rhinitis is based on the concordance between a typical history of allergic symptoms and diagnostic tests. Typical symptoms of allergic rhinitis that are reversible either spontaneously or with treatment include:

- rhinorrhoea,
- nasal obstruction,
- nasal itching,
- sneezing.

Other concurring symptoms may affect the eyes such as:

- lachrymation,
- conjunctivae itching,
- swelling.

Ocular symptoms are common, in particular in patients allergic to outdoor allergens. Allergic rhinitis due to pollen allergy occurs in the relevant seasons and there are large geographical differences. Apart from season and pollen exposure, other factors are also important for severity of symptoms including the weather: rain reduces the exposure and mild wind in dry weather may increase exposure, in addition wind may result in exposure far away from the source. Perennial allergens may be house dust mites (HDMs) as well as animal danders. The major cat allergen (Fel d 1) is transported in the air by particles <2.5 µm and can remain airborne for long periods. Fel d 1 is also adherent and can contaminate an entire environment for weeks or months after cessation of allergen

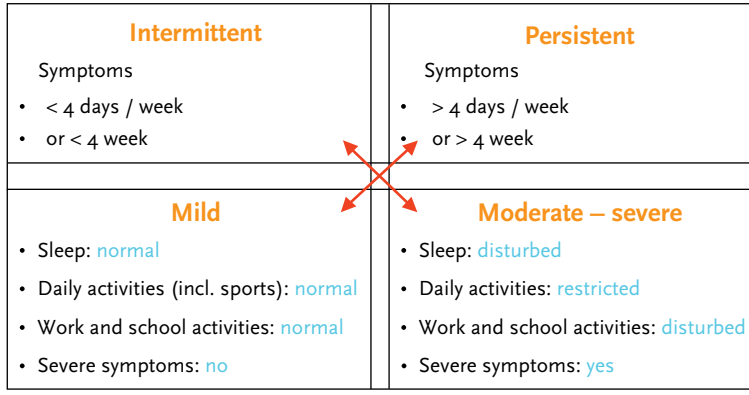

Figure 2. Allergic rhinitis classification. Reproduced from Bousquet et al. *(2001).*

exposure. HDMs are most often found in bedding, especially in humid environments. Since HDM allergy often induces late reactions, these children often experience nasal congestions and may also have symptoms during the daytime and seldom specifically in early morning. Allergic rhinitis due to HDM allergy also occurs most often in older children, though even young children may have allergic rhinitis and allergy to pollen as well as HDMs.

The main symptom of allergic rhinitis caused by perennial allergens is nasal congestion whereas conjunctival swelling, itching and watery discharge can occur. The congestion is a consequence of the inflammation that involves all the upper airways. Nasal congestion can result in chronic mouth breathing, associated with the development of a high-arched palate, upper lip and overbite. As a matter of fact, children often suffer from a sore throat caused by oral respiration. Other symptoms may include: coughing caused by post-nasal drip, cephalalgy caused by oedema of the nasal mucosa, and hearing impairment caused by tympanic dysfunction. Sudden night awakening and apnoea can affect sleep. Therefore, this alteration of sleep phase can affect the child in their everyday life and activities.

In children suffering from allergic rhinitis social problems can occur with embarrassing repeated actions, such as blowing their nose, grimacing in order to relieve their nasal itching or producing "strange noises".

Children with allergic rhinitis may have swelling and dark discolouration under the eyes due to congestion of small blood vessels beneath the skin in this area.

In children with persistent allergic rhinitis, the habitual manipulation of the nose due to chronic obstruction and itching is typically accomplished by pushing the tip of their nose with the palm of their hand in an upward motion: this action is known as the "nasal salute" or the "allergic salute". This may result in a persistent transverse hyperpigmented or hypopigmented line extending across the junction of the lower and middle thirds of the bridge of the nose named "nasal crease".

Clinical testing

Diagnostic tests are based on the demonstration of allergen-specific IgE *in vivo* or *in vitro*. A skin prick test (SPT) is recommended as the "gold standard" method for the diagnosis of IgE-mediated allergies in allergic rhinitis.

It has advantages of relative high sensitivity and specificity, rapid results, low cost and good tolerability. However, the quality of the allergens is very important and only standardised extracts should be used. Moreover, the skin of very young children may not be as reactive as older children and adults.

In children, the number of allergens to be tested is limited. The most important allergens in early childhood are HDM and animal dander but in older children pollens and moulds must be investigated.

The measurement of allergen-specific IgE in serum is available using either radio- or enzyme-labelled anti-IgE. This test has a diagnostic value similar to SPTs but it is more expensive than the latter. For this reason the measurement of allergen-specific IgE in serum is recommended if history of allergic symptoms and SPTs disagree, or in children affected by dermographism or widespread skin lesions, or during treatment by drugs affecting the reactions to SPTs, such as antihistamines.

However, the diagnosis of allergic rhinitis is based upon the coordination between a typical history of allergic symptoms and diagnostic tests. No diagnosis can be based solely on responses to SPTs in *in vitro* tests or nasal challenges. In some cases with a very clear history, *e.g.* with clear seasonal symptoms or mild symptoms and the child being well treated on symptomatic treatment, *e.g.* antihistamines in normal doses, further diagnosis with SPTs, specific IgE or even nasal challenges may not be necessary.

Recently, the nasal allergen provocation test has been needed to identify local allergic rhinitis. This new entity is a localised nasal allergic response in the absence of systemic atopy characterised by local production of specific IgE antibodies, a Th2 pattern of mucosal cell infiltration during natural exposure to aeroallergens, and a positive nasal allergen provocation test response with release of inflammatory mediators (tryptase and eosinophil cationic protein). Several non-allergic conditions can mimic allergic rhinitis symptoms, but because management differs in each case, it is very important to differentiate between allergic rhinitis and non-allergic rhinitis.

Management of a child affected by allergic rhinitis

The control of the nasal mucosa allergic inflammation is the goal of all the therapeutic strategies in the management of allergic rhinitis. The key points of the management of allergic rhinitis are patient education, pharmacotherapy and allergen-specific immunotherapy (fig. 3).

A lot of perennial allergens have been associated with allergic rhinitis, of which HDM and animal dander are the most important. Mould spores can provoke rhinitis and asthma as well. Patients allergic to furred pets may benefit from allergen avoidance at home, but they may encounter allergens on public transportation, and in schools and public places. A systematic review of dust mite allergen avoidance has shown that single measures are not effective in reducing symptoms of allergic rhinitis, although the general consensus is that allergen avoidance should lead to an improvement of symptoms. However, improving air quality by ventilating airtight homes to prevent a build-up of biological pollutants and volatile organic compounds (VOCs) may be useful.

Medications used for the treatment of allergic rhinitis in children are antihistamines (oral or topical), steroids, chromones and antileukotrienes, which are particularly useful when the allergic rhinitis is associated with asthma and immunotherapy.

Antihistamines Oral H1-antihistamines are effective against symptoms mediated by histamine (rhinorrhoea, sneezing, nasal itching and eye symptoms) but have nearly no effect on nasal congestion. Second-generation antihistamines are preferred and they may have some, though usually very

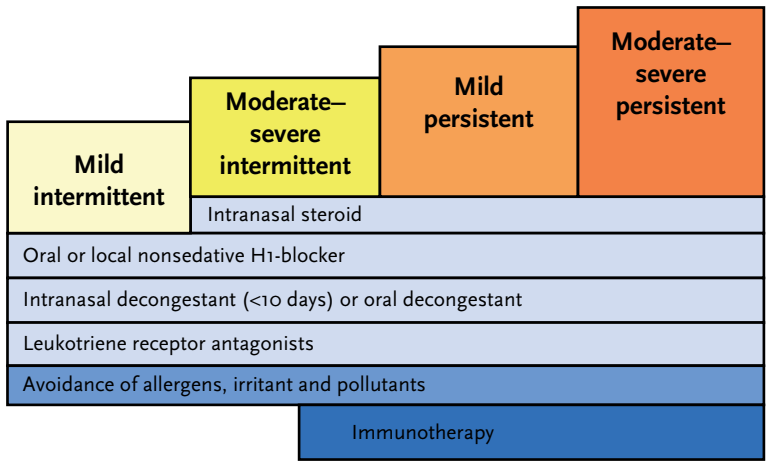

Figure 3. Management of allergic rhinitis: ARIA guidelines. Reproduced from Bousquet et al. *(2001).*

mild, sedative effect. The possible anti-inflammatory effect of some antihistamines is very modest and probably not clinically relevant. Oral H1-antihistamines have been shown to be safe and effective in children and also for long-term treatment. Nasal corticosteroids and oral antihistamines also result in an improvement of objective measurements of pulmonary function. Intranasal antihistamines have been found in some adult studies to be as effective as oral antihistamines, with fewer adverse effects but there are few data in children.

Corticosteroids The rationale for using intranasal corticosteroids in the treatment of allergic rhinitis is that high drug concentrations can be achieved at receptor sites in the nasal mucosa with a minimal risk of systemic adverse effects. Topical corticosteroids stabilise the membranes of mast cells and exert most of their effects *via* such membranes and partial blocking of the late phase reaction. The current intranasal preparations are well tolerated and can be used on a long-term basis without atrophy of the mucosa. Side-effects are generally mild (crusting, dryness and minor epistaxis).

Due to their mechanism of action, efficacy appears after 7–8 h of dosing, but maximum efficacy may require up to 2 weeks to develop. They are generally safe, and there is little evidence to support suppression of the hypothalamic–pituitary–adrenal axis (HPA axis) with prolonged use. The safety of intranasal corticosteroids is particularly relevant in paediatric and adolescent patients because these agents are widely used in this population. The effect of 6 weeks of once-daily treatment with beclomethasone dipropionate (BDP) nasal aerosol on HPA-axis function, as measured by 24-hour serum cortisol concentrations, in adolescent and adult subjects with perennial allergic rhinitis has been evaluated. The results of this randomised, double-blind, placebo- and active-controlled study, indicated that BDP nasal aerosol was not associated with HPA-axis suppression in adolescent and adult subjects with perennial allergic rhinitis.

The newer formulations of topical corticosteroids for allergic rhinitis, such as ciclesonide, fluticasone furoate and mometasone furoate, which have less systemic bioavailability, may be safer for long-term use. Fluticasone furoate nasal spray is a new topical intranasal corticosteroid with enhanced affinity for the glucocorticoid receptor and low systemic exposure, which has recently been approved in the USA for the treatment of seasonal or perennial allergic rhinitis in adults and in children aged $\geqslant$2 years. In well-controlled clinical trials, intranasal fluticasone furoate 110 µg once daily for 2 weeks in adults and adolescents with seasonal allergic rhinitis reduced nasal and ocular symptoms.

The treatment of rhinitis reduces asthma severity: asthma and allergic rhinitis commonly occur together, treatments for one condition could potentially alleviate the coexisting condition. The use of nasal corticosteroids in patients with rhinitis and asthma reduces not only rhinitis symptoms but also asthma symptoms and airway reactivity to methacholine challenge.

It should be made very clear that systemic treatment with corticosteroids for allergic rhinitis in children is not standard treatment, although a short course with low-dose prednisolone in some severe cases can be necessary: patients with severe symptoms who do not respond to other drugs or those who are intolerance to intranasal drugs may need to be treated with systemic corticosteroids (*e.g.* prednisolone, starting dose 10–15 $mg \cdot day^{-1}$) for a short period of time.

Allergen-specific immunotherapy Allergen-specific subcutaneous immunotherapy is not usually recommended before the age of 5 years. In older children the clinical efficacy of allergen-specific immunotherapy is well established for both rhinitis and asthma. Traditionally, immunotherapy has been administered by the subcutaneous route but the sublingual route is now available. Subcutaneous specific immunotherapy is burdened with a risk of inducing systemic side-effects. When treating rhinitis patients, the risk of serious anaphylactic reactions is

rather limited compared to treating asthma patients. The sublingual route is safer.

Allergen-specific immunotherapy is recommended for the treatment of patients with pollen and mite allergy and it may alter the natural course of allergic diseases. Indeed, administered to patients with rhinitis, immunotherapy appears to reduce the development of asthma (secondary prevention of asthma). The duration of immunotherapy is usually 3 years to show long-term efficacy after its cessation.

All these different treatments are to be modified or combined together depending on the:

- single case,
- age of the subject,
- duration of the symptoms,
- causal allergens,
- seriousness of the clinical symptoms.

The main goal of the therapy isn't just ending the symptoms, but preventing and treating all the possible complications that may affect the structures close to the nasal cavities and lower air system.

Comorbidities and complications

Allergic rhinitis cannot be considered as an isolated pathology. The inflammation that affects the nasal mucosa will consequently affect the eye mucosa, air sinuses, ear and lower airways.

The chronic exposure to perennial allergens, especially in domestic environments, induces a gradual nose occlusion that will be very subtle in its manifestation, therefore the subject will physically adapt to the symptoms. Permanent signs found in allergic rhinitis subjects can be malocclusion or misalignment of teeth and jaws and adenoidal face (long face syndrome). For subjects affected by allergic rhinitis the co-existence of multiple diverse conditions such as deviated septum, nasal turbinate dysfunction, sinusitis and adenoid hypertrophy can occur. Moreover, physical examination of the allergic rhinitis subject should also include an otoscopic examination. Children affected by allergic rhinitis are more prone to middle ear otitis and otitis media with effusion. A probable mechanism is that allergic inflammation in the respiratory epithelium at the entrance to and inside the Eustachian tube can result in tube dysfunction due to swelling in this region and possibly cause a secondary inflammation in the middle ear. In some cases there is a difficulty in the interpretation of the symptoms of nasal occlusion caused by allergy and often these symptoms get confused by the physical inflammatory cause (*e.g.* dental malocclusion combined with adenoidal obstruction).

Integrated handling of the allergic rhinitis may require the prevention of complications, therefore foreseeing the best treatment through the expertise of an otolaryngologist, surgeon or an orthodontist. Referring a patient for surgical treatment is the only solution in order to correct certain anatomical anomalies of the nasal bones, or removal of enlarged tonsils or adenoids, only in the case in which, along with the allergic inflammation, they aggravate nasal obstruction and breathing.

Numerous studies have demonstrated that allergic rhinitis may be a risk factor for both the onset and the worsening of asthma. The nasal and bronchial mucosa are characterised by the same pseudo-stratified epithelium and the ''united airways concept'' suggests that the respiratory system functions as an integrated unit. Support for this concept can be found in studies showing that pathophysiological processes involving the upper airways generally occur in conjunction with lower airway diseases and that diffuse inflammation often affects the respiratory mucosa at different sites simultaneously.

Finally, in relation to the close connection between lower and upper airways, the physical examination should always carefully investigate the breathing condition of the patient and consider lung function testing. Bronchial hyperreactivity (BHR) is characteristic of bronchial asthma. Patients with allergic rhinitis who do not report symptoms of bronchial asthma on

spirometry may show signs of BHR, which could indicate the presence of subclinical inflammation of the lower respiratory airway. The presence of bronchial hyperresponsiveness and concomitant atopic manifestations in childhood increases the risk of developing asthma and should be recognised as a marker of prognostic significance, whereas the absence of these manifestations predicts a very low risk of future asthma. Measurement of the exhaled nitric oxide fraction (F_{ENO}) may be considered a surrogate marker for airway inflammation. Forced expiratory flow at 25–75% of FVC ($FEF_{25–75\%}$) has been previously demonstrated to be able to predict BHR and bronchial reversibility.

Patients with allergic rhinitis due to pollen often display adverse reactions upon the ingestion of plant-derived foods as a result of IgE cross-reactive epitopes shared by pollen and food allergen sources. The symptoms of such pollen–food syndromes range from local oral allergy syndrome to severe systemic anaphylaxis. The best known association is between birch pollen and a series of fruits (including apple), vegetables and nuts.

Allergic rhinitis can often be a debilitating condition which, if untreated, can result in considerable health-related and economic consequences. For example, numerous studies have demonstrated that poorly controlled symptoms of allergic rhinitis contribute to decreased health-related quality of life (HRQoL), reduced sleep quality, daytime fatigue, impaired learning, impaired cognitive functioning and decreased long-term productivity.

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Atopic dermatitis

Paolo Meglio, Elena Galli and Nunzia Maiello

Atopic dermatitis (AD) is a chronic/relapsing, inflammatory skin disease that can affect 7.5% or more of children and about 1–3% of adults. In children, about 70% of cases start before age 5 years. The disease is characterised by recurrent, acute flare-ups on skin that often exhibits chronic eczematous pruritic skin lesions. Frequently, the platform of these manifestations is dry skin. Its impact on the quality of life of affected children is high.

Since the early attempts to clearly and comprehensively define diagnostic criteria, it has been evident that AD is a complex, multifactorial disease. Due to recent advances, we are now aware that an impaired skin barrier and complex immune dysregulation, sometimes including IgE-mediated mechanisms, are largely responsible for the symptoms. Moreover, complex interactions between genetic and environmental factors make the clinical spectrum of AD very variable (fig. 1).

Key points

- AD is a multifactorial disease.
- The environmental factors interact with skin and allergic genetic factors so that the clinical appearance is multifaceted and therapy is complex.
- Therapy mainstays are emollients, avoidance of irritants and allergens, topical anti-inflammatory drugs (mainly corticosteroids) and control of infections and pruritus.
- In a subgroup of children, early and severe manifestation of AD has been associated with an increased risk of asthma (the so-called ''atopic march'').

Clinical manifestations, diagnosis and monitoring

AD can present a broad spectrum of dermatological manifestations and over time various diagnostic criteria have been proposed. Those of Hanifin and Rajka (1980), are the most frequently used and consist of four major and 23 minor criteria based on consensus reached by experienced dermatologists. Even if such criteria are those used most frequently, they are less suitable for use as a diagnostic tool by nonspecialist or primary care doctors, due to their complexity. Moreover, they lack clinical validation. The UK's diagnostic criteria (Williams *et al.*, 1994), introduced with the aim of perfecting Hanifin and Rajka's criteria, are the best validated and indicate the six most useful criteria to use when diagnosing AD for children above 2 years of age.

AD may display three clinical aspects. In the acute phase, it manifests itself with vesicular, weeping and crusting eruptions. In the subacute phase, dry, scaly, erythematous papules that may converge into plaques may be present. Symptoms of chronic AD are dry, lichenified skin with papules and/or nodules and signs of scratchmarks (excoriations). Pruritus is almost invariably present in all three phases even if it varies in intensity, usually worsening in the early evening and at night. Normally, AD involves the large joint flexures (elbow flexure, wrist joint, popliteal region), forehead, face, eyelids, anterior and

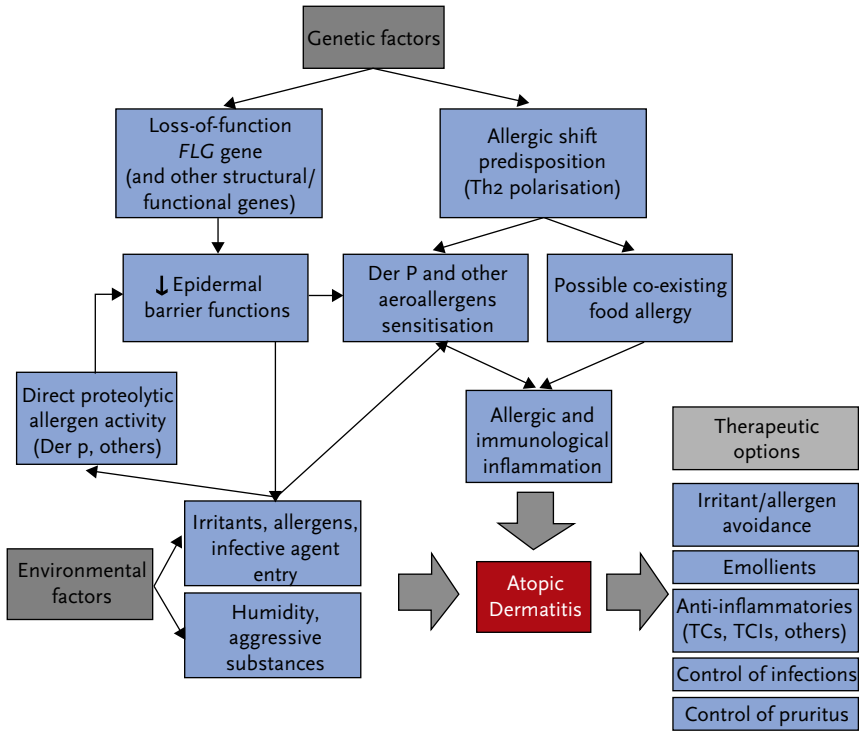

*Figure 1. AD is a multifactorial disease that arises from multiple genetic and environmental interactions. Genetic factors include complex epidermal barrier and immunological defects. Mutations of filaggrin (*FLG*) and other structural genes induce damage to epithelial barrier functions. In this way, cutis may become more permeable to irritants, allergens and infective agents. If an allergic predisposition also exists (T-helper (Th)2 polarisation), potential allergens that come into contact with the skin can provoke an allergic inflammation. Irritants can further worsen epithelial barrier functions. Moreover, AD cutis is defective in controlling infections, and* Staphylococcus aureus*, in particular, may in turn worsen AD. It is now hypothesised that if the damaged skin of a potential allergic subject comes into contact with a food allergen this can result in food allergy. Avoiding irritants/allergens, restoring epithelial barrier functions, fighting inflammation and controlling infections and pruritus are the mainstays of AD therapy. Der p:* Dermatophagoides pteronyssinus *allergen; TCs: topical corticosteroids; TCIs: topical calcineurin inhibitors.*

lateral neck and the dorsa of the feet and hands. This distribution can vary from patient to patient and can differ according to age.

Moreover, it should be remembered that all these divisions are artificial and that in any individual case, acute relapsing of subacute or chronic lesions may occur. Both the extent and severity may vary. Thus, AD presents a broad clinical spectrum ranging from minor and less severe forms (dry depigmented skin, hand eczema) to major, more extensive, severe forms, with widespread erythrodermic rash.

The distribution of lesions and the typology and severity of AD may vary according to the patient's age and disease activity. During infancy, AD generally presents more acute lesions mainly affecting the face, scalp, and extensor surfaces of the extremities. Bacterial secondary infection (impetiginisation) is frequent. In older children and in those with persisting AD,

symmetrical lichenification and localisation of rash to the flexural folds of the extremities are prominent. The sites of predilection are the face, neck, upper chest and shoulder girdle, large joint flexures and the back of the hands. Flattened inflammatory infiltrated lesions that may be hyperpigmented and have a tendency to confluence, may be a prominent feature.

A useful method to assess the severity of AD, named SCORAD (from SCORing and AD), was developed in the 1990s (European Task Force on Atopic Dermatitis, 1993) and has subsequently been validated. To calculate the SCORAD index, extension (parameter A), intensity (parameter B) and subjective symptoms (parameter C) must be taken into account.

- Extension is graded up to 100 and it is divided along the entire body according to the rule of nines. Slight differences exist between children under or over 2 years of age.
- Intensity is graded up to 18, with a severity score (0: no symptoms; 1: mild symptoms; 2: moderate symptoms, 3: severe symptoms) applied to six items (erythema, oedema/papules, scratchmarks, oozing/crust formation, lichenification and dryness).
- Subjective symptoms are itchiness and sleeplessness. They are calculated by means of two "visual analogue scales" graded from 0 to 10, with 20 being the maximum total score.

At this point, an arithmetical formula considering parameters A, B and C (A/5 + 7B/2 + C) is applied in order to obtain the SCORAD index, which ranges 0–103. Conventionally, AD is defined as mild with a SCORAD of <25, moderate with a SCORAD of 25–50 and severe with a SCORAD of >50. A variant of this method is the Objective-SCORAD (O-SCORAD), which excludes subjective symptoms from the evaluation. In this case, the maximum score is 83 (A/5 +7B/2) and AD is defined as mild with an O-SCORAD of <15, moderate with an O-SCORAD of 15–40, and severe with an O-SCORAD of >40.

Epidermal barrier dysfunction

Defects in the epidermal barrier due to genetic and/or functional alterations of structural proteins (filaggrin, loricrin, involucrin) and functional proteins (proteases and their inhibitors, antimicrobial peptides) play a critical role in the pathogenesis of AD. The most significant genetic factor is loss-of-function mutation found within the filaggrin (*FLG*) gene encoding profilaggrin, the ~500-kDa precursor for the structural protein FLG. It is detected in about 22% of patients with AD and is associated with early onset and persistence of the disease. *FLG* gene mutations are also implicated in immune dysregulation, as they are associated with increased allergen-specific CD41 T-helper (Th)2 cells. Moreover, epidermal homeostasis is regulated by proteases, including kallikreins, which are important for skin desquamation and the activity of which is tightly controlled by protease inhibitors.

Proteolytic activity from allergens (as well as possible IgE-linked activity) has been known to play a role in the pathogenesis of AD by directly affecting the structure and function of the epidermal barrier (including the tight junctions), thereby facilitating further penetration of allergens. This can possibly switch the non-IgE-associated form of AD to the IgE-associated form by driving dendritic cells to enhance Th2 polarisation. Moreover, in susceptible individuals, allergen-induced inflammation promotes Th2 and Th17 cytokines (interleukin (IL)-17) that in turn are able to stimulate keratinocytes to produce other pro-inflammatory cytokines and to downregulate *FLG* expression or the proper processing of profilaggrin.

FLG breakdown products, such as urocanic acid and pyrrolidone carboxylic acid, are important for maintaining an acidic pH that plays a critical role in regulating epidermal permeability, barrier homeostasis, epidermal antimicrobial barrier and stratum corneum integrity/cohesion, by regulating the activity of various enzymes including serine proteases and lipid-processing enzymes. Disorders in FLG expression and degradation also result in decreased

expression of the FLG-derived natural moisturising factor in AD skin.

In the lesions in AD patients, the pH of the skin has been reported to be significantly raised. This results in a reduced expression of proteins that inhibit colonisation by and growth of *Staphylococcus aureus*. Indeed, *S. aureus* colonisation and the resulting production of toxins are also due to the decreased production of anti-microbial peptides (defensins and cathelicidins), which are downregulated by the inflammatory AD micro-milieu. Decreased serum levels of the cathelicidin LL-37 have been observed in patients with AD, correlating to decreased vitamin D levels. Inflammation is further amplified by *S. aureus* toxins that aggravate the defects in the epidermal barrier (ceramidase) and induce IL-17 production by T-cells. Other negative effects of *S. aureus* colonisation are to upregulate the expression of the skin-homing receptor cutaneous lymphocyte-associated antigen on T-cells (CLA) and induced thymic stromal lymphopoietin (TSLP) that is able to activate dendritic cells with subsequent proliferation of naive $CD4^+$ T-cells and their differentiation into Th2 cells producing the inflammatory cytokines IL-4, IL-5 and IL-13, and Th17/Th22 cells producing IL-22 that is able to induce epithelial proliferation, possibly causing the thickened AD epidermis. Finally, *S. aureus*-specific IgE, generated by the immune system, can bind to FcεRI receptors on dendritic cells and initiate an IgE-mediated reaction to this microbe.

Pruritus

Pruritus (or itching) is the diagnostic hallmark of AD and has a significant impact on quality of life including agitation, anxiety, changes in eating habits, poor self-esteem, difficulty concentrating, and depression. Pruritus generally leads to scratching, which further damages the skin barrier function, so worsening inflammation (''itch-scratch cycle''). Patients with AD are often unaware of the extent to which they are scratching, especially during the night when increased transepidermal water loss may provide a plausible explanation for nocturnal exacerbations.

Even if histamine is the best-known pruritogen in humans, the histamine receptor (HR) 1 is unlikely to play a major role in AD, as the efficacy of non-sedating antihistamines in this disease is very limited. Indeed, recent studies showed that the HR4 plays a more important role inducing Th2 cell increases and IL-31 production, another important itch inducer in AD, particularly in severe forms. Moreover, the expression of IL-31's heterodimeric receptor (IL-31R) can be induced or upregulated in keratinocytes, monocytes, macrophages or dendritic cells by microbial factors (*S. aureus* superantigens and exotoxins, Toll-like receptor (TLR) agonists), as well as endogenous mediators of inflammation (proteases, such as trypsin, tryptase, cathepsins, kallikreins, PAF, prostaglandins, opioid peptides), including interferon (IFN)-γ.

Even if skin lesions in AD often result in increased density of the peripheral nerve fibres, including substance P-positive nerve fibres, the central sensitisation of itch-signalling systems seems to be a key feature of chronic pruritus in AD because of sensitisation of the spinal neurons in the dorsal horn, which leads to greater sensitivity to pruritic input. Two forms of central sensitisation are associated with pruritus: allokinesis and punctate hyperkinesis. Allokinesis is observed when touch- or brush-evoked itch occurs around an itching site. This is commonly seen in children with AD, where sweating, sudden changes in temperature, contact with fabrics and dressing and undressing induce severe pruritus. Punctuate hyperkinesis consists of an intense itching sensation in the area surrounding histamine induction. Stress may also induce or aggravate itch in AD with a neurogenic mechanism involving neuropeptides.

Immunological dysregulation and link to allergic diseases

Allergic diseases frequently coexist with AD. A significant association between early food

sensitisation and AD has been found, especially at an early age. Food allergy, which is generally the result of failure to develop tolerance, or the loss of pre-existing tolerance, may be caused by defects in immune or nonimmune intestinal barriers (*e.g.* a defective digestive process or abnormalities in the development of regulatory T-cells, soluble IgA, Peyer's plaques, and associated dendritic cells). Moreover, perturbation of the skin barrier allows allergen penetration that in turn triggers the activation of Langerhans cells, facilitating the subsequent uptake of antigens through the tight junction barrier of the epidermis. The Langerhans cells then presumably migrate to draining lymph nodes and activate antigen-specific T-cells. This can lead to Th2 responses and IgE production by B-cells. In humans, food allergen-specific T-cells have been isolated from lesional skin in patients with eczema.

It is proposed that in some individuals, allergic sensitisation to food may occur through low-dose cutaneous sensitisation and that early consumption of food protein induces oral tolerance. The timing and balance of cutaneous and oral exposure determines whether a predisposed child has allergy or tolerance. This suggestion rises from studies in which preschool children with low-dose exposure to peanut in the form of arachis oil applied to inflamed skin had an increased risk of peanut allergy at age 5 years. Randomised controlled trials supporting this hypothesis are expected soon. The grounds for this phenomenon come from animal models where it has been shown how sensitisation to ovalbumin (measured by sIgE production) occurs through epicutaneous exposure, following the removal of the stratum corneum or if the skin barrier is genetically impaired. This was not seen in mice exposed to ovalbumin *via* intraperitoneal injection. This assumption is reinforced by the fact that ovalbumin allergy has been demonstrated in a murine model for loss-of-function mutations in the *FLG* gene.

The atopic march Early manifestation of AD has been associated with an increased risk of asthma, suggesting that AD can be the first step in the so-called "atopic march". Like AD, asthma is also a complex genetic and multifactorial disorder with high prevalence in the paediatric population, largely attributable to the interactions between multiple genes and the environment. According to some longitudinal prospective studies, the relationship between AD and the subsequent onset of asthma is more evident if children with AD have a parental history of asthma, have had a severe, early onset of AD and if atopic sensitisations exist. Thus, the atopic march is not a general phenomenon as it affects only a subgroup of children with AD, in whom it is supposed that an *FLG* gene null mutation allows the skin to be attacked by a range of factors (irritants, allergens, house dust mites or *S. aureus* proteases) thereby predisposing such children to developing asthma.

Therapeutic options

Treatment of AD is aimed at suppressing inflammation, restoring the skin barrier and controlling itching. Various strategies and a broad number of treatments are available that can help achieve these goals. Optimal management is tailored to the patient and often involves multimodal strategies. Patient education to maximise compliance is essential.

Avoidance of irritants and allergens Irritants that worsen eczema should be assessed during medical evaluations. Textiles made of silver-loaded, seaweed-based cellulosic fibers have been shown to significantly reduce *S. aureus* colonisation without affecting the normal flora, and to decrease trans-epidermal water loss in patients with mild-to-moderate AD. Exposure to passive smoking, extreme temperatures and bright sunlight should be avoided. Preventing contact with the house dust mite may be useful if there is sensitisation, but also to prevent the proteolytic and irritative properties of mites. In very selected cases, especially if a certain food has been shown to cause immediate or very severe reactions, an elimination diet may be proposed.

Emollients Measures to restore the dysfunction of the skin barrier should be considered as first-line therapy, essential for effective treatment and prevention. For patients with mild-to-moderate eczema, topical therapy may be sufficient to control disease activity. Emollients may contain both occlusive substances that provide a lipid layer on the surface of the skin to slow water loss and increase moisture content in the skin, and humectants, which are substances introduced into the stratum corneum to increase its moisture-retaining capacity. They may be applied several times a day, especially after bathing, and their continued use during quiescence can reduce the tendency for eczema flares.

Topical corticosteroids Topical corticosteriods (TCs), of the appropriate potency and duration, remain the cornerstone of AD therapy for acute flare-ups, insofar as they have anti-inflammatory, immunosuppressive and vasoconstrictive properties and inhibit fibroblast activity. TCs are divided into seven classes based on potency, where class I is the strongest, and class VII the weakest. Commonly used options include low-potency (class VI and VII; *e.g.* hydrocortisone), mid-potency (class III–V; *e.g.* triamcinolone, mometasone, fluticasone) and high-potency (class I and II; *e.g.* fluocinonide, desoximetasone, betamethasone dipropionate, clobetasol) TCs. For the management of flare-ups, the use of mid-to-high potency TCs once/twice daily for up to 5 days/2 weeks (on the trunk and extremities) is generally recommended. Lower-potency steroids are recommended on the face, in young children or as a maintenance therapy. Steroid potency may be increased to control inflammation and once control is gained, TCs should be suspended or used intermittently. Recently this approach has been challenged by the proactive treatment concept that consists of a combination of predefined, long-term, low-dose, anti-inflammatory treatment applied to previously affected areas, in combination with liberal use of emollients. Twice-weekly application of fluticasone has been shown to significantly reduce the risk of relapses of eczema in a proactive strategy.

There is a need to address concerns regarding so-called ''steroid phobia'', which constitutes a barrier to TC use. Exaggerated fear and inappropriate withholding of TCs by patients, pharmacists, caregivers and the general community are significant barriers to successful management of AD.

Topical calcineurin inhibitors Topical calcineurin inhibitors (TCIs) work by inhibiting the phosphatase activity of calcineurin, blocking the expression of cytokines. They act ''downstream'' in the glucocorticoid receptor pathway and thus are thought to represent a more targeted way to contain inflammation and avoid possible adverse effects of topical corticosteroids. Tacrolimus and pimecrolimus may be used either as a monotherapy or as a combination or sequential therapy. The labelled indication is for application twice daily for up to 6 weeks as a second-line therapy for adults and children aged >2 years of age exhibiting an inadequate response or adverse effects to topical corticosteroids.

Treatment of skin infection Improving eczema with an anti-inflammatory regimen (TCs, TCIs) decreases staphylococcal colonisation, but patients with high numbers of colonising *S. aureus* may require a short-term topical treatment with topical antiseptics and/or topical antibiotics. In severe exacerbations, systemic antibiotic therapy may be helpful. Mycosis, dermatophytosis, streptococcal or viral infections should be treated only if present.

Ancillary therapy Oral sedating and nonsedating antihistamines have a limited role in the treatment of AD. Leukotriene receptor antagonists have not been developed for regular therapy of AD. Probiotics have been studied extensively to define their role in the treatment and prevention of AD in children. Unfortunately, the results are varied and, to date, inconclusive.

Complementary and alternative therapies There is evidence of growing interest in the use of complimentary alternative medicine to treat AD, such as Chinese herbal medicine, essential fatty acids,

phytotherapy, homoeopathy, acupuncture, bio-resonance, salt baths, and vitamins (especially vitamin D, if a low level/intake is documented) and minerals. To date, there is no evidence to support the use of complementary alternative therapies in routine treatment.

Systemic therapies Systemic agents are generally reserved for persistent, widespread and severe AD that is unresponsive to other therapies. Such patients should be treated by experienced specialists and therapies include corticosteroids, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil and, more recently, biological agents (soluble receptors, monoclonal antibodies, intravenous immunoglobulin and cytokines such as recombinant interferon, TNF and IgE/IL-5 pathway inhibitors).

Phototherapy Ultraviolet therapy can be a useful treatment for recalcitrant AD.

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Food allergy

Alessandro Fiocchi, Lamia Dahdah and Luigi Terracciano

Food allergy is an "adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food" (Boyce *et al*., 2010). This definition of food allergy includes IgE-mediated and non-IgE-mediated immune responses, or a combination of both, and is in agreement with recent international guidelines (Urisu *et al*., 2011; Fiocchi *et al*., 2010a; Sackeyfio *et al*., 2011) and statements (Burks *et al*., 2012). Table 1 shows specific food-induced allergic conditions on the basis of pathophysiology, with particular emphasis on respiratory manifestations.

Food allergens can cause reactions when ingested, touched or inhaled. Cross-reactivity can occur when a food allergen has structural or sequence similarity with a different food allergen or aeroallergen. More than 170 foods have been reported to cause IgE-mediated reactions but a minority of foods cause the majority of allergic reactions: peanuts, tree nuts, eggs, milk, fish, crustacean shellfish, wheat and soy (Boyce *et al*., 2010).

Key points

- Food allergy is on the rise especially in children.
- Its symptoms may include respiratory complaints.
- The presence of asthma is a negative prognostic factor for anaphylactic reactions.
- Severe asthma may be associated with food allergy.
- Currently, the treatment for food allergy treatment is avoidance, but OIT is a promising new approach.

Symptoms of food allergy (table 2) can occur within minutes to hours of ingesting the trigger food and can vary in severity from mild to life threatening. Co-factors of severe allergic reactions include co-ingestion of other foods, exercise and comorbid conditions. Food-induced anaphylaxis is the most serious, potentially lethal allergic reaction. Fatalities are primarily reported from allergic reactions to peanuts and tree nuts.

The natural history of food allergy resolution is variable and some patients reach tolerance (*i.e.* they develop a specific nonreactivity to the food). The time courses appear to be influenced by several factors.

- Age of development: food allergy that starts in adulthood often persists.
- Type of food: allergy to milk, eggs, soy or wheat is more likely to be outgrown than allergy to fish, shellfish, tree nuts or peanuts.
- Level of IgE: patient with high specific IgE level by ImmunoCAP assay (Quest Diagnostics, Madison, NJ, USA) are at risk of persistence (Fiocchi *et al*., 2008).
- Size of skin-prick test (SPT) wheal: but in some cases, SPT responses remain positive long after tolerance has developed.
- IgE patterns: the epitope-binding profile of IgE might help to predict the clinical course of food allergy (Wang *et al*., 2010).

Prevalence determined on the basis of patient self-report is higher than that

Table 1. Food allergy conditions associated with respiratory complaints

	Key features	Common triggers
IgE mediated (acute onset)		
Anaphylaxis	Rapidly progressive, multiple organ system reaction up to cardiovascular collapse Aggravated by co-existing asthma	Peanut Tree nuts Fish Shellfish Milk Egg
Food-dependent, exercise-induced anaphylaxis	Food triggers anaphylaxis only if ingestion followed temporally by exercise May be confused with exercise-induced asthma	Wheat Shellfish Celery Moulds
Combined IgE and cell mediated (delayed/chronic onset)		
Eosinophilic oesophagitis	Symptoms may include feeding disorders, reflux symptoms including cough, vomiting, dysphagia and food impaction.	Multiple
Food-induced asthma	Asthma induced by food ingestion/inhalation (*e.g.* bakers' asthma)	Cow's milk Wheat
Food-induced rhinitis	Rhinitis induced by food ingestion/inhalation	Cow's milk Tree nuts Peanut
Cell mediated (delayed/chronic onset)		
Heiner syndrome	Pulmonary infiltrates Failure to thrive Iron-deficiency anaemia	Cow's milk

determined by clinical testing and medical history. In general, food allergy affects more than 1–2% but <10% of the population (Keil *et al.*, 2010). It seems that prevalence is rising: a large population-based study of challenge-proven food allergy in 12-month-old infants in Australia reported prevalences of 3% for peanut allergy, 8.9% for egg allergy and 0.8% for sesame allergy (Osborne *et al.*, 2011). The prevalence of food allergy appears to have increased in recent years. Self-reported survey data in the USA suggested there has been an 18% increase in food or digestive allergies from 1997 to 2007, and Chinese paediatricians reported an increased rate of challenge-confirmed food allergy from 3.5% in 1999 to 7.7% in 2009 ($p=0.017$) (Chen *et al.*, 2011).

Prevalence rates of admissions for food anaphylaxis in Australia increased by 350% between 1994 to 2005, and rates of increase were greater for children <4 years of age and for peanut and tree nut anaphylaxis, with more modest increases noted for older age groups and other allergies such as cow's milk or egg.

Food allergy symptoms include:

- food refusal in young children,
- skin symptoms (urticaria, angio-oedema, erythema, itching and eczema),
- gastrointestinal tract symptoms (oropharyngeal tingling and burning, oral allergy syndrome, vomiting, and abdominal pain),

Table 2. Symptoms of food-induced allergic reactions

Target organ	Immediate symptoms	Delayed symptoms
Cutaneous	Erythema Pruritus Urticaria Morbilliform eruption Angio-oedema	Erythema Flushing Pruritus Morbilliform eruption Angioedema Eczematous rash
Ocular	Pruritus Conjunctival erythema Tearing Periorbital oedema	Pruritus Conjunctival erythema Tearing Periorbital oedema
Upper respiratory	Nasal congestion Pruritus Rhinorrhoea Sneezing Laryngeal oedema Hoarseness Dry staccato cough	
Lower respiratory	Cough Chest tightness Dyspnoea Wheezing Intercostal retractions Accessory muscle use	Cough Dyspnoea Wheezing
Gastrointestinal (oral)	Lip oedema Tongue swelling Oral pruritus	
Gastrointestinal (lower)	Nausea Reflux Colicky abdominal pain Vomiting Diarrhoea	Nausea Reflux Abdominal pain Haematochezia Vomiting Diarrhoea
Cardiovascular	Tachycardia Hypotension Dizziness Loss of consciousness	

Reproduced and modified from Boyce *et al.* (2010) with permission from the publisher.

- airway symptoms (persistent cough, hoarse voice, wheeze, stridor and respiratory distress), and
- disturbances of the circulatory system (pale and floppy infant or young child, hypotension, or collapse).

IgE-mediated symptoms develop within minutes to an hour of ingesting the food. In contrast, non-IgE-mediated and mixed IgE- and non-IgE-mediated food allergy syndromes present with predominantly abdominal symptoms (vomiting, diarrhoea, pain and haematochezia) that develop several hours after ingestion of the food.

Neither medical history alone not physical examination is diagnostic of food allergy (Boyce *et al.*, 2010). IgE-mediated food allergies require the presence of specific IgE

to confirm a diagnosis. These can be identified by SPT or by immunoassays of serum levels of specific IgE. SPT can be performed using standardised extracts or, in case of fruit and vegetables, fresh products. These tests identify sensitisation to foods that may provoke IgE-mediated reactions but neither is directly diagnostic of food allergy, nor is, despite many attempts, the patch test with foods. The test results must be reviewed against the clinical history (Boyce *et al.*, 2010; Fiocchi *et al.*, 2010b). For non-IgE-mediated or mixed IgE-mediated and non-IgE-mediated food allergies, the situation is even more complex: in these cases, no laboratory tests can assist the clinician, and the diagnosis relies upon an elimination/reintroduction challenge diet with the suspected food.

Although serum concentrations of specific IgE and SPT wheal sizes generally correlate with the likelihood of a clinical reaction, they do not correlate with or predict the severity of allergic reaction to the food (Sampson, 2001). The availability of recombinant allergen-specific IgE tests against the major allergens in a food (*e.g.* Arah2 in peanuts, Bosd8 in cow's milk and Gald2 in eggs) has paved the way for improving the diagnosis of clinical allergy but the exact use of these tests is still to be studied (Fiocchi *et al.*, 2011).

The double-blind, placebo-controlled food challenge (DBPCFC) is the most specific test for identifying a true food allergy. It reliably distinguishes sensitisation from clinical allergy. Ideally, the challenge is performed as a double-blind procedure; however, it is time- and labour-intensive, and many health systems do not reimburse it. For these reasons, single-blind or open-food challenges often replace the DBPCFC in everyday clinical practice and may be considered diagnostic under certain circumstances. They contribute to food allergy diagnosis in young children or in presence of objective (rather than subjective) symptoms. However performed, a food challenge must be done in a medical facility with onsite medical supervision and appropriate resources for emergency management of allergic reactions. The risk of immediate allergic reaction and anaphylaxis is high and cannot be calculated *a priori*. An absolute contraindication to challenge procedures is a recent anaphylactic reaction: if a patient had a reaction to a known food, they should not undergo a challenge with that food.

Food allergy and respiratory disease

Children with food allergy have a four-fold increased likelihood of having asthma and 3.6-fold increased likelihood of respiratory allergies compared with children without food allergy (Branum *et al.*, 2009). Allergic rhinitis, in particular, has been reported in children allergic to peanuts, tree nuts or milk. Food is rarely a trigger for exacerbation of symptoms in asthma (<2% of patients with asthma) but may be an important co-factor in severe asthma (Roberts *et al.*, 2003). Conversely, the presence of asthma is a risk factor for fatal anaphylaxis and longer persistence of food allergy (Fiocchi *et al.*, 2008). It is therefore important to evaluate the possible presence of asthma in patients with food allergy and to keep it under adequate control. It seems that ongoing airway inflammation (increased exhaled nitric oxide levels) may persist in children with food allergy even after asthma is thought to have resolved (Kulkarni *et al.*, 2012). Such persistent airway inflammation might be important in the evolution of respiratory symptoms after food allergen exposure, even in children whose previously clinically relevant asthma has been apparently quiescent recently.

Treatment

For IgE-mediated, non-IgE-mediated, and mixed IgE-mediated and non-IgE-mediated food allergy syndromes, the first-choice therapy is avoiding the causal food(s) (Boyce *et al.*, 2010). Patients should be instructed on the interpretation of ingredient labels to avoid their specific allergens. However, even in children with severe food allergy, avoidance of responsible foods may be difficult to maintain and accidental ingestion may occur. Therefore, patients at risk for anaphylaxis should be provided with an emergency action plan indicating signs

and symptoms of mild-to-moderate and severe reactions. These plans can guide medical personnel in treatment, including how and when to administer adrenaline if an autoinjector is prescribed (Simons *et al.*, 2012).

Adrenaline is the mainstay of the treatment of anaphylaxis (*i.e.* acute, severe, systemic allergic reactions). Antihistamines can be used to manage symptoms of nonsevere allergic reactions (Boyce *et al.*, 2012). As biphasic reactions may occur in up to 20% of cases, patients who receive adrenaline for a food-induced anaphylactic reaction should be immediately admitted to an emergency facility for observation. Systemic corticosteroids are also often recommended to prevent biphasic or protracted anaphylactic reactions but the evidence beyond their use is thin (Simons *et al.*, 2012). For most patients who have experienced anaphylaxis, observation for 4–6 h is in order. Patients with severe or refractory symptoms require prolonged observation or hospital admission.

Food allergy is a quality-of-life disruptor: anxiety can arise from the perceived risk of anaphylaxis and the burden of allergen avoidance. The caregivers of these children are also anxious, and intra- and interfamilial relationships can be heavily influenced by the disease (King *et al.*, 2009). Education related to managing food allergy may improve patient and caregiver self-efficacy, quality of life, and successful allergen avoidance.

Oral immunotherapy

Strict avoidance of allergens is not curative and the patients remain at risk of accidental exposure. For this reason, several new therapeutic approaches are being tested in clinical trials, but none is ready for clinical care (Nowak-Węgrzyn *et al.*, 2011). Systemic, subcutaneous immunotherapy has been investigated in the past but gave severe adverse effects. Newer forms of therapy (*e.g.* immunotherapy) have sought to provide systemic treatment with reduced risk and side-effects. For a variety of food allergens, oral immunotherapy (OIT) is able to reduce clinical reactivity in some patients. Its ability to induce immunological tolerance, however, remains uncertain and the approach is plagued with the risk of severe reactions. Given the overall very low quality of the evidence and very imprecise estimates of the effects, the true effect of OIT in patients with food allergy is unknown. Consequently, today, patients and clinicians willing to avoid possibly serious adverse effects are likely to continue the elimination diet and re-evaluate the possibility of oral immunotherapy when more robust and precise data are available. Those determined to achieve tolerance and who are less worried about possibly serious adverse effects may choose to undergo immunotherapy with foods (Brożek *et al.*, 2012). Thus, OIT is not yet appropriate for widespread use.

Treatments using modified antigens, epicutaneous administration of allergens or Chinese herbal therapy could also represent safe and efficient alternatives in the future. Additionally, treatment with anti-IgE monoclonal antibodies may increase threshold doses needed to stimulate an allergic reaction and provide enhanced safety profiles for patients. Probiotics, widely used for food allergy, deserve further evaluation (Fiocchi *et al.*, 2012). Recent reports about anaphylaxis to galactooligosaccharides cast a shadow on the possibility of use of prebiotic fibres in the prevention and treatment of food allergy (Chiang *et al.*, 2013).

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Allergic bronchopulmonary aspergillosis

Andrew Bush

Unlike in adults and for reasons which are not clear, allergic bronchopulmonary aspergillosis (ABPA) in children is virtually always seen in the context of CF. ABPA complicating paediatric asthma has only been the subject of isolated case reports. Other, even more rarely, reported associations in children include hyper IgE syndrome, chronic granulomatous disease, bronchocentric granulomatosis, previous TB and treatment of sarcoidosis with infliximab. In adults, it has been described in association with COPD. Unsurprisingly, late diagnosis after a prolonged clinical course is common in this rare setting. If ABPA is suspected in the context of another paediatric respiratory illness, three steps are essential.

Key points

- Unlike in adults where asthma with ABPA is common, ABPA is rarely seen in children other than complicating CF.
- In the context of CF, ABPA is difficult to diagnose because it mimics CF lung disease.
- The single most useful diagnostic test is an abrupt, four-fold rise in serum IgE.
- The mainstay of ABPA treatment is systemic corticosteroids, increasingly pulsed methyl prednisolone rather than oral prednisolone.

- Ensure that atypical forms of CF have been excluded. Even if the sweat test is unequivocally normal, genetic testing and measurement of transepithelial potential differences should be considered.
- Consider alternative differential diagnoses, such as mucus plugging and atelectasis, gastro-oesophageal reflux disease, eosinophilic or other noninfective pneumonias, and collagen vascular disease.
- Consider the possibility of the rare associations mentioned above.

Aspergillus fumigatus is ubiquitous in the environment. Two features make it particularly prone to infect the human lower airway.

- The spores have a mass median diameter in the range of 2–5 µm, meaning that they are the ideal size for impacting in the lower airway.
- They grow at 37°C, *i.e.* body temperature.

However, an ABPA-like picture has rarely been reported as being caused by other fungi, for example other strains of *Aspergillus*, and non-*Aspergillus* species such as *Scedosporium apiospermum*. These are not covered further in this chapter. Manifestations of *A. fumigatus* lung disease are summarised in table 1. The rest of this chapter discusses ABPA in the context of CF.

Definition

ABPA is the clinical manifestation of a T-helper (Th)2 driven hypersensitivity response within the airway to *A. fumigatus* and its exoproducts.

Table 1. Manifestations of Aspergillus fumigatus *lung disease*

Disease	Manifestation
CF	ABPA
	Positive sputum culture which may be associated with worse lung function and more pulmonary exacerbations
	Allergen provoking wheeze
	Large airway plugging
	Mycetoma
	Invasive aspergillosis
Asthma	Isolated positive skin test
	Allergen provoking wheeze due to atopic sensitisation
	Severe asthma with fungal sensitisation
Immunocompromised host (congenital or acquired)	Invasive aspergillosis
Lung cavity (congenital thoracic malformation, TB, post pneumonic)	Mycetoma
Interstitial lung disease	Hypersensitivity pneumonitis

Prevalence of ABPA

The prevalence of ABPA is difficult to determine due to the different diagnostic criteria used, and the different indices of suspicion prevailing in the various clinics. The latest European CF Society Registry report (which unfortunately does not yet contain comprehensive information across the whole of Europe), using the diagnostic criteria shown in table 2, reported prevalence that varied from 1.4% (Sweden) to 17.9% (Switzerland). Whether these differences reflect different levels of diagnostic suspicion, differences in diagnostic testing or a genuine geographical variation in disease prevalence is not clear. The UK CF Trust registry report (7937 patients) reported a total of 725 (prevalence 9.1%) cases of ABPA in 2010, of which 156 were new (incidence 2%). Although the incidence of new cases was the same in adults and children, the prevalence, perhaps surprisingly, was higher in those aged >16 years (10.8% *versus* 7.0%).

There are two other older, but still useful, registry studies from the USA and Europe. The US study (281 (2%) ABPA patients out of 14 210 total registered patients, almost certainly an underestimate) reported an increasing prevalence up to 20 years of age, which thereafter declined. 10% of ABPA patients had a normal FEV_1 and >80% did not report wheeze. Infection with *Pseudomonas aeruginosa* was common (~70%). The European registry study (967 ABPA patients out of a total of 12 447 CF patients in the registry) reported a peak between 13–18 years, and ABPA was rare below 6 years of age. There is no convincing sex difference in prevalence when the two databases are combined. ABPA was associated with a poorer general clinical condition (10% lower FEV_1, lower weight Z-score, more commonly infected with *P. aeruginosa, Burkholderia cepacia, Stenotrophomonas maltophilia*, and, surprisingly, *Haemophilus influenzae*, but not with *Staphylococcus aureus* infection) and there was an association with pneumothorax and massive haemoptysis, presumably related to the underlying severe lung disease. There were no associations with particular genotypes or mutation classes.

Pathophysiology

A. fumigatus may provoke an intense allergic response leading to secondary airway

Table 2. Summary of diagnostic criteria for ABPA used in the European registry

Acute or subacute clinical deterioration, no other aetiology found
Total IgE >500 IU·mL^{-1}
Positive skin prick test (>3 mm) or specific IgE for *Aspergillus fumigatus*
Either:
IgG precipitins or *in vitro* demonstration of IgG antibody response to *Aspergillus fumigatus*
New or recent imaging abnormalities (chest radiograph or CT) not clearing with standard therapy

damage, but proteolytic and other enzymes may lead to non-allergic, direct pulmonary toxicity. ABPA is the result of a skewed $CD4^+$, Th2 T-cell response to *A. fumigatus* leading to interleukin (IL)-4 and IL-5 production and, hence, elevation of serum IgE and airway eosinophilia. *A. fumigatus* may directly lead to the production of pro-inflammatory cytokines from bronchial epithelial cells. The importance of genetics has been suggested by the occurrence of familial cases. Important factors include HLA-DR and HLA-DQ (the latter protective), and polymorphisms in the genes for IL-4RA, IL-10, surfactant protein A and Toll-like receptor 9. Recently, elevated levels of the co-stimulatory molecule OX40 ligand (OX40L) have been shown to be important in driving the Th2 response to *A. fumigatus* in peripheral $CD4^+$ T-lymphocytes. Of possible therapeutic interest, OX40L levels fell with *in vitro* addition of vitamin D. However, *A. fumigatus* downregulates the vitamin D receptor, which may affect the response to vitamin D therapy.

Presentation

ABPA should be at least suspected in CF children with increased respiratory symptoms, particularly if there is wheeze, chest tightness or pleuritic chest pain and an audible pleural rub. Exceptionally, pleural effusion and pneumomediastinum have been described in ABPA. There may be a sharp decline in spirometry, and the chest radiograph typically shows one or more new soft fluffy shadows (fig. 1), with a "gloved finger" appearance of mucus impaction in the airways, which are very unusual in a CF pulmonary exacerbation. Less than half the patients will have a positive sputum culture for *A. fumigatus*.

Confirming the diagnosis of ABPA

Making the diagnosis of ABPA in the context of CF may be difficult; there is no single diagnostic test. The classical case is easy to diagnose. However, many of the symptoms and signs of ABPA are common to the underlying CF. Furthermore, markers of sensitisation to *A. fumigatus* and positive sputum cultures are frequently seen in otherwise uncomplicated CF; and true cases of ABPA may be culture negative for *A. fumigatus*. We found that the single most useful test is an abrupt, at least four-fold rise in total IgE to >500 IU·mL^{-1}; IgE may sometimes, but not always, fall with treatment so serial IgE measurements should be used with caution in monitoring response. A high level of IgG precipitating antibodies to *A. fumigatus* may also be suggestive (>90 mg·mL^{-1}; ImmunoCap; Thermo-Fisher Scientific, Uppsala, Sweden); multiple positive precipitins are more suggestive of mycetoma. Major and minor criteria for ABPA have been proposed, but atypical cases may not meet classical criteria yet still require treatment, which should not be delayed if the index of suspicion is high but "classical" criteria are not met. In doubtful cases, many would initially give a trial of intravenous antibiotics and then treat for ABPA if there was no response.

The tables of major and minor criteria are useful guides to the diagnosis of ABPA, but are no more than guides, and atypical cases will continue to be diagnosed on an individual clinical basis. The United States

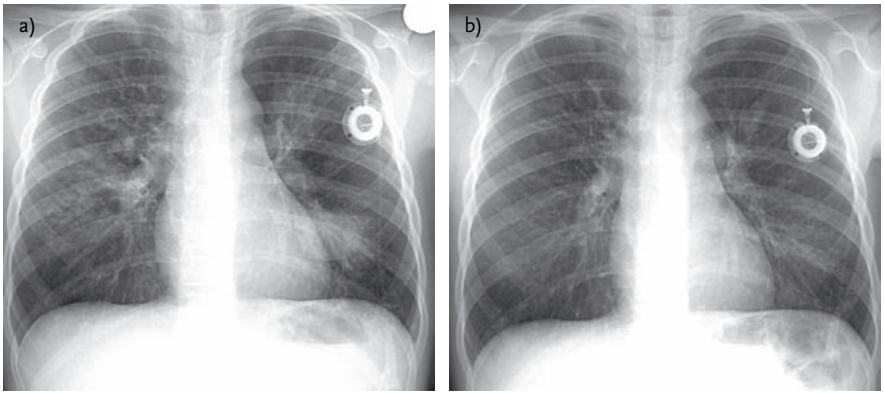

Figure 1. Chest radiograph from a CF patient recently diagnosed with ABPA. a) A combination of widespread indistinct nodular opacities, ring shadows (bronchiectatic airways) in the right mid zone, and consolidation in the left lower lobe can be seen. b) Several months later, most of the shadowing has resolved but there is a new elliptical opacity (a plugged bronchiectatic airway) just above the left hilum.

Cystic Fibrosis Foundation (USCFF) Consensus Conference proposed criteria for classic ABPA, minimal diagnostic criteria and recommendations for screening (table 3). These are a useful guide to the clinician, and very helpful for ensuring uniformity of diagnosis in registries, but cannot be considered definitive under all circumstances.

Novel, more sophisticated, testing has been proposed. Cytoplasmic *A. fumigatus* antigens may be elevated in ABPA. Initial studies using targeted allergy testing to specific purified *A. fumigatus* antigens including Asp f1, f3, f4 and f6, and serum thymus- and activated-regulated chemokine (TARC) levels looked promising. Only TARC has been studied in a second prospective cohort, but its measurement currently remains in the research domain.

Lung function testing in ABPA

There are no changes specific to ABPA. Characteristically, there is an acute

Table 3. Diagnostic criteria for ABPA in the context of CF

Classical ABPA
Acute or subacute clinical deterioration not attributable to another cause
Serum total IgE >1000 IU·mL^{-1} in a patient not receiving oral corticosteroids
Positive skin prick test to *Aspergillus fumigatus*
Positive IgG precipitins to *Aspergillus fumigatus*
New or recent chest radiograph abnormalities not clearing with conventional therapy, such as physiotherapy and antibiotics
Minimal diagnostic criteria for ABPA
Acute or subacute clinical deterioration not attributable to another cause
Serum total IgE >500 IU·mL^{-1} (retest in 1–3 months if 200–500 IU·mL^{-1})
Positive skin prick test to *Aspergillus fumigatus*
Either: positive IgG precipitins to *Aspergillus fumigatus*, or new or recent chest radiograph abnormalities not clearing with conventional therapy, such as physiotherapy and antibiotics

worsening of pre-existing airflow obstruction or its *de novo* development. This is initially, at least partially, reversible, but becomes fixed with low lung volumes if the disease progresses. Diffusing capacity may be low in an acute exacerbation, and remain low in end-stage disease. Spirometry is probably the most useful marker of response to treatment, being better than serum IgE or more sophisticated biomarkers.

Screening

An annual measurement of total IgE is recommended, with further investigation if IgE is >500 IU·mL^{-1} or 200–500 IU·mL^{-1} and the index of suspicion is high. The possibility of ABPA should be considered in all pulmonary exacerbations, in particular if there are fresh chest radiographic infiltrates or response to treatment is poor; an admission measurement of total IgE is routine in our CF unit.

Management

Prevention Playing or working in damp places such as stables where *A. fumigatus* spores are in high concentrations must be discouraged. Although there is less evidence, it would seem sensible to ensure there are no moulds in the house, and to check that that *A. fumigatus* (or indeed other organisms) are not cultured from the nebuliser by maximising hygiene. Recent immunological work suggests that optimising vitamin D levels may be helpful.

Treatment As with much of paediatric respiratory medicine, there are no randomised controlled trials to inform treatment decisions, and no satisfactory evidence base on which to recommend the nature and duration of treatment of ABPA. If there is any doubt about the diagnosis, then intravenous antibiotics should be given first. Treatment is aimed at reducing the inflammatory and tissue-damaging consequences of fungal infection, and also reducing the burden of the fungal infection.

Corticosteroids: Conventionally, the mainstay of treatment is oral prednisolone, which may need to be given in high dose for a prolonged period of time. A typical regimen would be 2 mg·kg^{-1} for 2 weeks (maximum 60 mg), then 1 mg·kg^{-1} for 2 weeks, then 1 mg·kg^{-1} on alternate days for 2 weeks, followed by a slow taper. The alternative to oral corticosteroids is pulsed methyl prednisolone, 500 mg·m^{-2} on three successive days every 4 weeks. It is suggested that there is improved efficacy and fewer side-effects. Certainly, the use of pulsed therapy means that adherence is not an issue, provided the child is brought to the hospital.

Antifungal therapy: The Cochrane review identified only two trials of antifungal therapy in ABPA, neither suitable for inclusion here. Itraconazole in combination with steroid treatment is used for two reasons. First, in ABPA complicating asthma there is clear evidence that this is beneficial, and there is weak retrospective evidence of benefit in CF. Secondly, rare cases of invasive aspergillosis complicating CF have been described and at least, in theory, itraconazole may prevent this. Oral absorption of itraconazole is poor, and serum levels should be measured and the dose adjusted. Furthermore, at least in adults, azole resistance in *A. fumigatus* is common. Itraconazole inhibits the cytochrome p450 enzyme CYP3A, which can lead to Cushing's syndrome and iatrogenic adrenal suppression in patients also taking inhaled budesonide or fluticasone and oral methyl prednisolone (but not prednisolone). Other anti-fungal options include nebulised

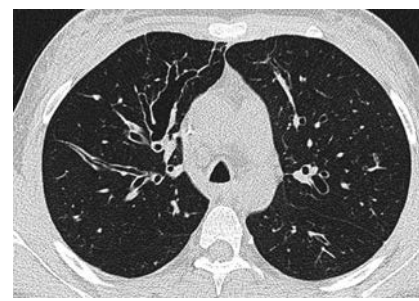

Figure 2. HRCT through the upper lobes showing bilateral bronchiectasis; the varicose pattern of bronchiectasis in the anterior segment of the right upper lobe is typical of APBA.

Table 4. Stages of ABPA

Stage 1: Acute phase
There are acute infiltrates that clear completely with prednisolone
Stage 2: Remission
No prednisone therapy or infiltrates for 6 months
Stage 3:
Recurrent exacerbation similar to stage 1
Stage 4:
Phase of steroid dependent asthma
Stage 5:
Fibrotic disease no longer completely responds to prednisolone therapy
Although frequently described, the clinical utility of this staging is not great.

amphotericin (liposomal if the standard preparation cannot be tolerated) with or without nebulised budesonide, voriconazole, posaconazole and intravenous liposomal amphotericin. The evidence for usage of these agents is minimal.

Other current treatment options: There are small case series reporting the use of the anti-IgE monoclonal antibody omalizumab (xolair) in ABPA. Inhaled corticosteroids are commonly employed, but there is only the most limited evidence that they are beneficial. There are occasional anecdotal reports of bronchoscopic airway toilet in recalcitrant airway plugging.

The future: The evidence of Th2 driven responses suggests that monoclonal antibody-directed signature Th2 cytokines (IL-4, IL-5 and IL-13), which are already researched in asthma, may also be useful in ABPA

Complications of ABPA

These are the complications of the disease itself, and complications of treatment.

Disease-specific complications are severe proximal bronchiectasis (fig. 2) and, in some, but not all series, accelerated decline in lung function. ABPA is a risk factor for infection with atypical *Mycobacteria* infection, although whether because of steroid therapy rather than the underlying disease is not known.

Complications of treatment are generic to the medications used but for CF, loss of bone mineral density and precipitation of CF-related diabetes are particularly important.

Prognosis

Mild cases of ABPA may resolve spontaneously, but the majority relapse after treatment. Accelerated decline in lung function is reported in patients treated for ABPA. ABPA has been divided into five stages with different prognoses (table 4); it is arguable whether these are clinically useful. They are not a chronological progression in clinical practice. Prolonged and recurrent ABPA is common, so prognosis must be guarded.

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Specific immunotherapy, prevention measures and alternative treatment

Susanne Halken and Gunilla Hedlin

The majority of schoolchildren with asthma are allergic to airborne allergens and allergy is a common trigger of asthma symptoms. The allergens associated with allergic airway disease depend on the age, climatic, seasonal and social factors, and housing conditions. In temperate and humid regions, allergy to house dust mites shows the strongest association with asthma followed by allergy to furred pets (especially cats). In arid climates, allergy to the fungus (*Alternaria* spp.) is prevalent.

Allergic asthma is most often associated with indoor inhalant allergens, whereas allergic rhinitis most often is associated with outdoor allergens such as pollen. In children with allergic asthma, persistent allergen exposure is associated with airway inflammation, bronchial hyperresponsiveness, and an increased risk of persistent and severe asthma.

The aerodynamic characteristics of the allergen-carrying particles vary considerably. Thus, most house dust mite and cockroach allergens are carried on relatively large particles, whereas most pet allergens are carried on small particles. Therefore, house dust mite exposure is most commonly associated with chronic inflammation, in contrast to exposure to pet allergens, which may induce acute reactions as well.

Key points

- Immunotherapy with seasonal and perennial airborne allergens has beneficial effects on allergic asthma.
- Anti IgE therapy reduces the risk of asthma exacerbations on children with severe allergic asthma.

Subcutaneous immunotherapy (SCIT) is still questioned as a safe and efficacious way of treating allergic asthma in children. Children with severe allergic asthma are often sensitised to multiple allergens, which makes SCIT both complicated and less safe to administer. In a Cochrane review published in 2010, however, it was concluded that SCIT has significant and beneficial effects on symptoms and medication use in both children and adults with mostly mild asthma. Only a few studies have been performed specifically on SCIT in children with moderate and severe asthma. Sublingual immunotherapy (SLIT) has also been shown to improve asthma symptoms and decrease medication use.

Anti-IgE (omalizumab) is the only monoclonal antibody so far with a documented effect in children with severe allergic asthma. Although this drug could turn out to be very efficacious in children with milder disease, the cost of the treatment is one limitation of the use of this therapy

Allergen avoidance

Avoiding exposure to relevant allergens is a logical way to treat allergic airway diseases, when the offending allergen can be identified and effective avoidance is feasible. In the case of allergy to pollen and foods, it is well recognised that avoidance of these allergens results in less or no symptoms. The case of allergy and exposure to perennial airborne allergens is more complex, as exposure is not restricted to specific situations or environments, but may

occur throughout the community. Moreover, many children with allergic asthma are allergic to a number of allergens (*e.g.* both house dust mites and pets). Pet allergens are, to a high degree, airborne and ubiquitous. Significant concentrations are also found in clothes and places without direct contact with pets, even several years after removal of a pet.

A clinical effect of allergen avoidance was first suggested by studies in which patients were removed from their homes to low-allergen, mountain environments, which resulted in improved lung function and normalised markers of allergic inflammation in children with allergic asthma. Later, several studies on different measures of environmental control in patients' homes indicated a clinical effect of allergen avoidance. Still, much controversy exists over the evaluation of results from these studies and from meta-analyses, mainly due to methodological problems. In order to document a cause–effect relationship, avoidance measures should be capable both of reducing the allergen level sufficiently and of resulting in a clinical effect.

Most of the previous studies on environmental allergen avoidance measures have focused on a single allergen, and the measures for exposure have been concentrations of allergens in dust from mattresses, floors or furniture. This may not represent personal exposure to aeroallergens. Individual differences in sensitivity to exposure may be important. In addition, the level of anti-inflammatory treatment may be important for evaluation of a possible effect of different environmental measures.

House dust mite allergen avoidance House dust mites are an important and widely distributed allergen source. House dust mites require high humidity and a temperature of ~24°C for their life cycle and reproduction, and the best conditions are in temperate, humid regions. House dust mites are mainly in our bedding but may also be detected in, for example, carpets and upholstered furniture, although in lower concentrations. Many different single measures have been recommended for house dust mite allergen avoidance, most of them focusing on the bedding environment (table 1).

Table 1. Recommendations for children with asthma and allergy to house dust mites

Ensure sufficient ventilation
Avoid damp housing conditions
Encase mattresses
Wash pillows, duvets, blankets and bed pads every 3–4 months (>55°C)
Wash soft toys and other mite reservoirs

A recent update of the Cochrane meta-analysis concluded that current chemical and physical methods aimed at reducing exposure to house dust mite allergens cannot be recommended for patients with asthma and house dust mite allergy (table 2). However, this conclusion may have many explanations (*e.g.* heterogeneity in studies, inclusion criteria and the fact that some of the allergen avoidance measures did not sufficiently reduce allergen exposure).

Well performed, controlled, randomised studies with adequate design and methods have demonstrated that some avoidance measures, such as *mattress encasings* with mite allergen-impermeable coverings, have proven effective both in reducing the level of house dust mite allergens and in improving disease control in children.

There is no evidence that *synthetic fillings* of bedding (duvets and pillows) are more beneficial than feather fillings. Some recent studies indicate that feather fillings result in lower exposure to house dust mite allergens.

Table 2. No documented effect of allergen avoidance

Synthetic filling of pillows and duvets
Foam mattresses
Chemical treatment of mattresses
Special vacuum cleaners
Air filters, ionisers, *etc.*

It has also been argued that *foam or water mattresses* should result in lower exposure, as compared with spring mattresses, but the few available data indicate no difference except that using a washable bed pad may reduce exposure from the mattress.

Different *floor coverings* may have different effects. Carpeted floors contain different particles and allergens to which small children playing on the floor are especially exposed. It has been assumed that hard floors have a beneficial effect, but available data suggest a complex and small effect.

Washing of bedding and clothing at >55°C kills house dust mites and effectively removes allergens. Washing at low temperatures also removes allergens. However, it is not known whether washing has any clinical effect.

Vacuum cleaners remove allergens and vacuum cleaning may result in a modest decrease of allergen reservoirs, but it also causes a brief increase in personal aeroallergen exposure while vacuum cleaning and high-efficiency particulate arrest (HEPA) filters make only little difference. Data on the quantity of a possible reduction of personal allergen exposure and its clinical effect are lacking.

The effect of *air filtration* is still debated and there is no good evidence for a possible effect.

Acaricides have been included in some studies but there is no good evidence of clinical benefits, and concerns about human health and environmental toxicity remain.

Recently, a clinical effect of a novel concept with nocturnal temperature *controlled laminar airflow treatment* has been demonstrated, and the results are encouraging, but further studies are needed.

A large trial provided evidence of improvement of asthma control by *multifaceted intervention* that was tailored to the child's sensitisation and exposure status. This included several measures, such as education, encasing of mattresses and pillows, high-filtration vacuum cleaners, and HEPA filters.

Apart from attempts to reduce the reservoirs of allergens, it is obvious to try to remove the conditions for the house dust mites to live and reproduce by *reducing humidity* (to below 45–50% relative humidity), avoiding moisture problems and increasing the ventilation of the home, although clinical data are limited.

Pet allergen avoidance In the case of asthma and allergy to pets, repeated exposure is associated with bronchial hyperreactivity and eosinophil inflammation, even without obvious symptoms. Cat allergens in particular are airborne, and are found at varying levels in houses and public places without cats. Removal of a pet from the home reduces the allergen level but does not abolish exposure (table 3). Washing of bedding and clothes might reduce exposure.

Washing of the pet has been tried in some studies and it has been shown that it may reduce the allergen level but only for a short time. We lack good data on the clinical effectiveness of different measures to reduce pet allergen levels and exposure.

Pest avoidance Particularly in inner-city environments, cockroach allergy is a major cause of allergic asthma. Approaches include pesticides and sanitation (*e.g.*

Table 3. Advice for children with asthma and allergy to pets

The only effective method is removal of the pet
General cleaning and vacuum cleaning is advised, although there is no good evidence for this
Even after removal of a pet, it may take many months before the reservoir of allergens is reduced sufficiently and it may take 6–12 months before the full benefit is seen
Complete avoidance of pet allergens is impossible as the allergens are ubiquitous and can be found in many environments outside the home including schools

avoiding making food available to the cockroaches, control of water leaks and control of entrances). After such elimination procedures, thorough cleaning is necessary for a long period to remove the pesticides and allergens.

Likewise, mouse exposure, particularly in bedrooms, is prevalent, especially in inner-city dwellings, and methods for effective rodent control have been shown to reduce exposure and improve symptoms. However, to date, the evidence is limited.

Mould avoidance Many studies have shown that exposure and allergy to fungi are often associated with severe asthma. Some fungi (often *Aspergillus*) may colonise and even infest the lungs, thereby causing severe disease. Many other fungi, most often *Alternaria* but also others such as *Cladosporium* or *Penicillium*, appear to play an important role in severe asthma. There is limited evidence about the role of fungal allergen avoidance in asthma. Moisture issues cause most instances of fungal growth in the indoor environment, and control of indoor environmental humidity and removal of contaminated material has been recommended. There are no convincing trials of avoidance of *Alternaria*, which is primarily an outdoor allergen, though it can also be found indoors.

In the case of suspicion of significant problems with fungal growth in the indoor environment, it is often necessary to investigate which fungus is present, and to involve experts and technicians with special expertise in this area.

Table 4. Indications for allergen immunotherapy

Allergic asthma triggered by allergen exposure
Confirmed specific allergy
Seasonal allergy to pollens
Perennial allergy to house dust mite, *Alternaria*, cat

Immunotherapy for allergic asthma

Criteria for commencement of immunotherapy Before considering immunotherapy, the allergens triggering asthma symptoms must be identified and the allergic sensitisation confirmed (table 4). While *in vitro* or skin tests are good enough for confirming pollen and animal dander allergy, it may be necessary to perform allergen provocation tests in the eyes and/or the nose to confirm other perennial allergies like dust mite and *Alternaria* allergy. More information on the relevant procedures can be found in the position paper published as a Global Allergy and Asthma European Network (GA^{2}LEN)/European Academy of Allergy and Clinical Immunology (EAACI) pocket guide on allergen-specific immunotherapy for allergic rhinitis and asthma.

Immunotherapy to improve and/or prevent deterioration of asthma The majority of immunotherapy studies in children (and adults) with asthma have been performed in those with mild allergic asthma, usually combined with rhinitis. Most of the studies have been performed using single allergens, the most predominant perennial allergen being dust mite, and the dominant seasonal allergens being birch, olive/*Parietaria*, grass and ragweed (mostly in the USA). The best evidence of efficacy of immunotherapy in children with asthma emanates from studies of children allergic to pollen and house dust mites (table 5).

SCIT with cat allergen extracts has also shown beneficial effects both on allergen sensitivity and bronchial hyperresponsiveness, while so far, dog allergen extracts have been less efficacious. A recent study of treatment with *Alternaria*

Table 5. Documented effects of immunotherapy

Less severe symptoms on allergen exposure
Decreased medications use during the allergy season
Quality of life improvements
Lasting effect after cessation of therapy

extracts in children has been shown to have convincing clinical effects, reducing symptoms of asthma.

Few studies have been carried out in children with both seasonal and perennial allergies. One placebo-controlled American study of multi-allergic children demonstrated no significant effect of SCIT on medication use and symptom control. A few other studies have been more successful; thus, the possibility remains that SCIT may alter the severity of asthma by inducing allergen tolerance. More studies are needed; however, in the mentioned Cochrane report and two recent extensive reviews conclude that there is evidence for efficacy of SCIT and SLIT in both children and adults with asthma.

Dosing schedules for SCIT and side-effects Different up-dosing regimens are used for the stepping up of the dose phase of SCIT treatment. There are "rush" up-dosing schedules, cluster regimens and the conventional "one injection per week" regimen. The advantages and disadvantages of immunotherapy have been discussed (table 6).

The risk of systemic side-effects (SSEs) has to be considered and the highest risk has been reported when a rush regimen is used. However, none of the schedules is without risk of SSEs, which is an important reminder that requires special attention. Implementation of safety measures and standardised procedures are mandatory when the injections are administered. Precautions are important. Lung function should be checked. Injections should not be given if the subject has ongoing allergic symptoms or a current infection; asthma symptoms have to be controlled and recent allergen exposure should be checked. Dose adjustments have to be made if the subject had side-effects like major local swelling and/or any sign of systemic effects. A standard procedure for required dose adjustments should be followed. After the injection, the subject should stay at the clinic for observation for $\geqslant$30 min, as most SSEs occur within that time. At any sign of a SSE – cough, sneezing, itch or signs of anaphylaxis – adrenaline injection(s) should be promptly given. Local side-effects can usually be treated or prevented by oral antihistamines. It is mandatory at any clinic that administers SCIT that there is equipment and trained staff to take immediate action in case of a SSE.

Table 6. Problems with allergen immunotherapy

Mostly an injection therapy
Long-term therapy (>3 years)
Loss of school attendance
Risk of systemic side-effects

The available guidelines serve an important role in providing standards for the indications, use and administration of SCIT and SLIT.

SLIT for asthma SLIT has been shown to improve asthma symptoms and medication use. SLIT is safe, although the efficacy compared to SCIT has been very little studied. In one recent paediatric review, the efficacy of both SCIT and SLIT were reported. In another recent review, SLIT studies in both children and adults were reported. In the paediatric review, it is stated that there is good evidence that SLIT has effects on asthma in children; this is in agreement with the other reviews. However, dose and dosing are still major issues for SLIT. There is, for example, in different SLIT studies, a large variation of the cumulative dose of house dust mite administered, ranging from 0.25 to 12 mg Der p. This is an issue that has been discussed and has caused some concern, in that there are still few dose–response studies that have confirmed the standard doses that should be used for SLIT. The first dose of SLIT should be given at a clinic and followed by $\geqslant$30 min observation time. The best documented SLIT to date is for treatment of pollen and dust mite allergy.

Immunotherapy combined with anti-IgE: safety and efficacy in children with severe allergic asthma Few studies have addressed this question in children. One of the paediatric studies was performed in

polysensitised children with seasonal rhinitis and included children with birch or grass allergy. Results showed that the combination of omalizumab and pollen SCIT had superior effects on symptom load in both birch- and grass-allergic children. Other studies performed in groups of children and adults have shown similar results. Pre-treatment with omalizumab in patients with severe multi-allergic asthma was the subject of another study of combined therapy, although omalizumab treatment only overlapped at the start of immunotherapy in symptomatic patients with asthma. The risk of SSEs was reduced, although severe systemic reactions still occurred in the group pre-treated with omalizumab. There is a need for more studies of this combination before it can be considered an additional therapy in children with asthma and severe allergies. At this stage, SCIT alone or in combination with omalizumab should not be used in children with severe and/or uncontrolled asthma.

Conclusion

A pragmatic approach in clinical practice should involve interventions tailored to the patient's sensitisation and exposure in a multifaceted allergen avoidance regime, based on removal of the accumulating allergens. The extent of such avoidance measures should also be tailored to the severity of the disease, and combined with education and other relevant treatment options.

Environmental avoidance measures have proven effective as a specific treatment of a specific allergy under the right conditions, but it requires defining specific sensitivity, education and an overall plan to reduce exposure in the child's home, and its success depends on the relevance of other allergens and exposure outside home. Thus, in children with allergic asthma, measures to reduce allergen levels significantly should be included in an individual treatment plan as well as an appropriate pharmacological treatment and avoidance of exposure to tobacco smoke.

If allergen avoidance is not possible, the addition of immunotherapy could be the next step, provided it is combined with adequate pharmacotherapy. Studies of SCIT for pollen, house dust mite and cat allergy have shown convincing effects on the specific allergies. A couple of recent reviews have confirmed the utility of SCIT and SLIT for asthma and rhinitis in children. The treatment can improve the quality of life for the allergic child but the overall effect on asthma severity, as demonstrated by a decreased need for pharmacotherapy for asthma control, has been uncertain in children with multiple and perennial allergies.

Anti-IgE is a treatment possibility for severe allergic asthma and, so far, the documented effects on risk of exacerbation have been shown in children needing high-dose inhaled corticosteroids for symptom control. The efficacy increases in those with high exhaled nitric oxide fraction (F_{ENO}) and other signs of ongoing eosinophilic airway inflammation.

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Genetics, pathophysiology and epidemiology of CF

Sabina Gallati

CF has been recognised as a distinct inheritable clinical entity for more than 70 years. It is the most common life-threatening autosomal–recessive disorder among Caucasians with an incidence of approximately one in 2500 and a carrier frequency of 4%. Heterozygotes carry one normal and one mutant CF gene and are therefore healthy, but they have a 50% risk of passing the defective gene on to their offspring. If two partners are carriers they face a 25% risk of having a child with CF, a 50% chance that the child will carry only one of the two parental CF mutations and a 25% chance that the child will inherit two intact genes. Phenotypically healthy siblings of CF patients have a 66% risk of a positive carrier state.

Key points

- CF is the most common life-threatening autosomal-recessive disorder in Caucasian populations with an incidence of 1/2500 and a carrier frequency of 1/25.
- CF is caused by mutations in the CFTR gene on chromosome 7.
- The CF phenotype is very heterogeneous and depends on both nature and localisation of the underlying CFTR mutations, as well as genetic background and environmental influences.
- CFTR analysis is indicated for diagnostic purposes in individuals with clinical suspicion of CF or CFTR-related disorders, fetuses with echogenic bowel or whose parents are proven CF carriers, and for carrier testing in persons with a positive family history or in partners of proven CF carriers.

The CFTR gene and protein

The gene causing CF, identified in 1989, is located on chromosome 7q31.2 spanning ~200 kb of genomic DNA and containing 27 exons. It is transcribed into 6.13 kb messenger ribonucleic acids (mRNAs) encoding a transmembrane protein of 1480 amino acids known as the cystic fibrosis transmembrane conductance regulator (CFTR). The CFTR protein is a member of the ATP-binding cassette (ABC) transporter superfamily whose proteins transport various molecules across extra- and intracellular membranes. The predicted structure of CFTR includes:

- a symmetrical, multi-domain structure consisting of two membrane-spanning domains (MSD1 and MSD2) with six hydrophobic transmembrane helices forming the channel through the membrane;
- two nucleotide binding domains (NBD1 and NBD2) gating the channel through ATP-binding and hydrolysis;
- a central, highly charged regulatory domain with multiple consensus sites for phosphorylation by protein kinase (PK)A and PKC.

The regulatory domain is unique for CFTR as it is not present in the other members of the ABC superfamily. CFTR is mainly located at the apical membrane of polarised epithelial tissues. Its main function is that of a cyclic AMP-regulated chloride channel, which is

expressed in several functionally diverse tissues including the lung, sweat ducts, pancreas, gastrointestinal tract and vas deferens. Moreover, CFTR directly mediates secretion of bicarbonate across the apical membrane linking ion transport and luminal pH with mucin secretion, mucus plugging and retention, the hallmarks of CF pathology. CFTR-mediated chloride secretion across epithelial cells is controlled by both modulating channel activity and regulating the total number of CFTR channels in the membrane.

CFTR mutations

To date, nearly 2000 mutations have been reported to the Cystic Fibrosis Genetic Analysis Consortium. The most common CF causing defect is the F508del mutation (c.1521_1523delCTT; p.Phe508del according to the current standard nomenclature), a 3 bp deletion in exon 10 (current nomenclature: exon 11) causing the loss of the amino acid phenylalanine at position 508 of the protein. There are another 23 relatively common mutations (frequency >0.5%) worldwide and a few mutations with an unusually high frequency in specific populations indicating founder effect genetic drift. The remaining mutations represent rare or even individual sequence changes that are distributed throughout the entire gene. Mutations (missense, nonsense, frame-shift, splice, small and large in-frame deletions, and insertions) contribute to the phenotype by their nature and position in the gene. Therefore, they can be grouped into different classes based on their known or predicted molecular mechanisms of functional consequences for the protein.

Class I mutations include mainly nonsense, frame-shift and splice site mutations resulting in premature termination signals or defective splicing and, as a consequence, producing truncated, deleted or elongated protein variants. Such proteins tend to be unstable and rapidly degraded and cleared from the cell. In effect, virtually no functional CFTR reaches the apical membrane of epithelial cells and, therefore, class I mutations are expected to cause severe phenotypes (fig. 1). The second class of mutations contains many missense mutations as well as in-frame deletions or insertions, including the F508 deletion. The corresponding proteins fail to be properly processed to a mature glycosylated form and will not, or only exceptionally, appear at the apical membrane. Interestingly, some of the class II mutations, *e.g.* F508del, if correctly processed, possess residual chloride channel activity and may lead to a milder phenotype. For this reason, mutations in this group are targets of potential therapies, aimed at correcting the processing and delivery of a mutated CFTR protein to the apical membrane (fig. 1). Mutations of class III affect the regulation of CFTR function by preventing ATP binding and hydrolysis at NBF1 and NBF2 required for channel activation. However, the missense mutation G551D within NBF1 disrupts not only the binding site through which ATP-dependent gating normally occurs, but also allows some ATP-independent chloride transport making it a promising candidate for therapeutic approaches using CFTR potentiators (fig. 1). The fourth class of mutations involves amino acids located within MSD1 and MSD2 and results in a CFTR channel with defective conductive properties. Mutations (*e.g.* R117H, R334W, R347H and R347P) in this class are typically associated with a milder clinical phenotype (fig. 1). Various mutations are associated with reduced biosynthesis of fully active CFTR due to partially aberrant splicing (3849+10kbC->T, T5), promotor mutations or inefficient trafficking (A455E). These mutations, forming class V, result in reduced amounts of functional gene products and, thus, in milder CF phenotypes (fig. 1). Class VI includes nonsense and frame-shift mutations (*e.g.* Q1412X, 4326delTC and 4279insA) causing a 70- to 100-bp truncation of the C-terminus of the CFTR that leads to a marked instability of an otherwise fully processed and functional protein, and as a consequence to a severe CF presentation (fig. 1). Mutations in any of the classes II to V display a broad range of phenotypic effects making prediction of the clinical course of a patient impossible

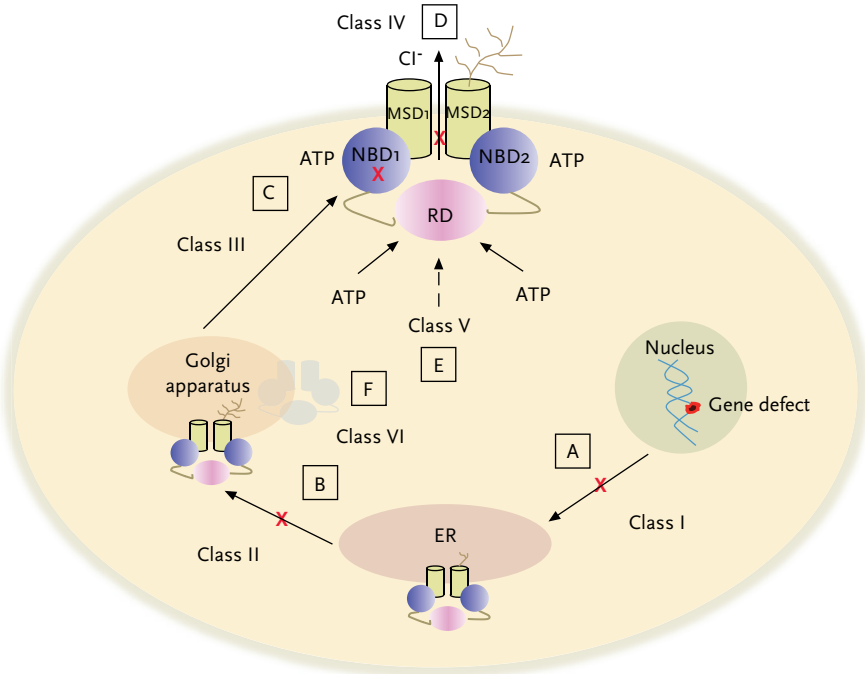

Figure 1. Class I (A): nonsense, frame-shift and splice site mutations resulting in no functional CFTR protein. Class II (B): mutations (e.g. F508del) that lead to abnormal processing and trafficking of proteins. Class III (C): mutations in this group (e.g. G551D) affect the regulation of CFTR and channel gating activity. Class IV (D): mutations (e.g. R117H, R334W, R347P and R347H) within the MSDs reducing CFTR channel conductance. Class V (E): mutations associated with reduced biosynthesis of fully active CFTR due to alternative splicing (e.g. T5). Class VI (F): nonsense and frame-shift mutations causing truncation of the C-terminus of CFTR and leading to highly unstable proteins. ER: endoplasmic reticulum; RD: regulatory domain.

simply based on mutation classification. Moreover, the potential of a mutation to contribute to the phenotype depends not only on its nature, localisation in the gene and molecular mechanism, but also on its interaction with the second mutated CFTR allele, as well as on disease modifiers.

Pathophysiology of the mutated CFTR gene and protein

As mentioned before, pathogenic CFTR gene mutations can disrupt CFTR protein function through a variety of mechanisms ranging from complete loss of protein synthesis to normal apical membrane expression of the protein with, however, reduced chloride conductance. Furthermore, alterations in the synthesis or sequence of the CFTR protein may affect the number of channels in the plasma membrane and/or channel activity and/or intracellular trafficking of CFTR. Reduced or missing CFTR function leads to a failure of chloride and sodium transport across epithelia. The defective ion conductance and the associated water transport abnormalities produce increased viscosity of secretions in a variety of exocrine epithelia, such as the respiratory tract, pancreas, gastrointestinal tract, urogenital tract and sweat glands and result, as a consequence, in the multi-organic disease of classic CF. Moreover, there is growing recognition of atypical CF and CFTR-related disorders including

primary male infertility, isolated idiopathic pancreatitis, chronic rhinosinusitis, nasal polyposis and idiopathic bronchiectasis, presenting in adolescence or adulthood and making diagnosis and prognosis much more complex.

Based on the considerable technical problems in successfully targeting the basic defects of CF on the one hand, and on the major advances in the understanding of CFTR pathophysiology on the other, the focus of treatment strategies has turned toward pharmacotherapy and the development of agents that may increase residual protein synthesis and/or transport to the cell membrane and/or ion conductance. Therefore, mutation-specific ''orphan drug'' therapies are currently the most favoured strategies. However, they represent a symptomatic treatment option rather than a cure and gene therapy may yet provide the best solution.

Genetic testing

Genetic testing should be performed in the context of appropriate genetic counselling, and it is the laboratory technician's responsibility to explain CF testing to the healthcare provider such that meaningful informed consent from the patients may be obtained. Performing a molecular genetic diagnostic test is a complex process requiring internal quality control systems such as good laboratory practice procedures or some form of accreditation. A wide range of mutation testing methods are available and can be divided into two groups: specific mutation detection based on the well-known spectrum of CF mutations in a defined ethnic group or population (*e.g.* using commercial kits), and mutation screening methods (*e.g.* sequencing of the entire coding region of the CFTR gene) with a high detection rate and the ability to identify novel mutations independent from allele frequencies and ethnic origin (table 1).

Genotypic and phenotypic heterogeneity

Although CF is considered a monogenic disorder, studies of clinical phenotype in correlation with the genotype have revealed a very complex relationship. Some phenotypic features are closely determined by the genotype in an essentially monogenic fashion, whereas others are strongly influenced by both modifying genetic factors and the environment. There is a close

Table 1. CFTR analyses indications

CFTR analyses are indicated for:
Diagnostic testing in
Patients with a definite or possible clinical diagnosis of CF
Newborns with positive neonatal screening test
Infants with meconium ileus
Males with proven congenital bilateral absence of vas deferens or suffering from primary infertility
Patients with idiopathic pancreatitis
Patients with idiopathic bronchiectasis or chronic rhinosinusitis or nasal polyposis
Carrier testing in
Individuals with positive family history
Partners of proven CF carriers
Gamete donors
Prenatal and pre-implantation diagnostic testing
If both parents are proven carriers and both mutations have been identified
In fetuses present with an echogenic bowel during the second trimester

Table 2 Incidence and carrier frequency of CF in different countries

Country	Carrier frequency	Incidence
Europe		
Finland	1/79 (1.3)	1/25 000
Turkey	<1/50 (2.0)	<1/10 000
Sweden	1/43 (2.3)	1/7300
Poland	1/39 (2.6)	1/6000
Russia	1/35 (2.9)	1/4900
Denmark	1/34 (2.9)	1/4700
Norway	1/33 (3.0)	1/4500
Netherlands	1/30 (3.3)	1/3600
Greece	1/30 (3.3)	1/3500
Spain	1/30 (3.3)	1/3500
Germany	1/29 (3.4)	1/3300
Czech Republic	1/27 (3.7)	1/2800
UK	1/26 (3.8)	1/2600
Switzerland	1/25 (4.0)	1/2500
Italy	1/25 (4.0)	1/2500
France	1/24 (4.2)	1/2400
Scotland	1/22 (4.5)	1/2000
Republic of Ireland	1/21 (4.8)	1/1800
North America		
USA	1/30 (3.3)	1/3500
Canada	1/27 (3.7)	1/3000
Latin America		
Mexico	1/46 (2.2)	1/8500
Brazil	1/41 (2.4)	1/6900
Chile	1/32 (3.1)	1/4000
Cuba	1/31 (3.2)	1/3900
Middle East		
United Arab Emirates	1/63 (1.6)	1/15 900
Bahrain	1/38 (2.6)	1/5800
Asia		
India	1/100–1/158 (1.0–0.6)	1/40 000–100 000
Japan	1/158–1/296 (0.6–0.3)	1/100 000–350 000
South Africa	1/42 (2.4)	1/7100
Australia	1/25 (4.0)	1/2500

Data are presented as one case per × persons of a population × births.

relationship between the CFTR genotype and the pancreatic phenotype revealing "severe" mutations (*e.g.* F508del, all class 1 mutations) to be associated with pancreatic insufficiency and "mild" mutations with residual function, such as a series of missense and alternative splice mutations, to be associated with pancreatic sufficiency. The development of meconium ileus, diabetes and liver disease is mainly confined to patients with severe mutations without residual function. However, because of its complexity and patient exposure to a multitude of endogenous and exogenous factors, pulmonary outcome is clinically the most variable, as well as the most unpredictable, component of the CF phenotype. Several studies have shown significant correlations between CFTR genotypes and pulmonary status concluding that patients with class I or II mutations on both chromosomes have more rapid deterioration in lung function and lower survival rates than patients with other genotypes. Moreover, F508del homozygous patients were found to present the most considerable variation in severity of pulmonary disease. The broad range of disease severity, even in patients with the same genotype (*e.g.* F508del homozygotes), point to the understanding that a CFTR genotype constitutes only the source or potential for CF disease and that the overall genetic background, as well as environmental factors, may have a major effect on clinical phenotype.

Modifying factors

A multitude of genetic loci and genes have been investigated as modifiers of CF expression at the pulmonary, gastrointestinal and liver levels suggesting that a number of genes could interact in different ways to produce the highly variegate CF phenotype. Some of the most promising potential modifiers of CF include mannose-binding lectin (MBL)2, endothelial receptor type A (EDNRA), transforming growth factor (TGF)-β1, interleukin (IL)-8, transcription factor 7-like 2 (TCF7L2) and α_1-antiprotease (SERPINA1). However, further studies on large numbers of cases with homologous genotypes and well-defined phenotypes, as well as on functional consequences, are required to provide clinical utility.

In complex diseases such as CF, contribution of epigenetic factors such as DNA methylation, chromatin remodelling, histone modification and RNA interference might be substantial. It is well established that polymorphisms in a poly-T tract (c.1210–12T [5_9]) and a TG repeat (c.1242–35_1242–12GT [8_13]) in intron 8 (standard nomenclature: intron 9) of the CFTR gene causes alternative splicing resulting in variable exon 9 (standard nomenclature: exon 10) skipping. Moreover, several polymorphisms have been reported to lead to alterations in transcription factor binding and, therefore, to be involved in the modulation of CFTR transcription. Hence, it is very likely that a significant number of polymorphisms, transcription factors and splicing factors interact to effect the complex tissue-specific regulation of the CFTR gene.

Epidemiology

CF causing mutations have existed for more than 50 000 years and many are strongly associated with specific European populations. The most common CFTR mutation, the F508 deletion, accounts for ~60% of all CF chromosomes worldwide with considerably variable frequencies depending on populations and geographical locations. There is a clear North West to South East gradient in F508del frequency across Europe with a maximum of 100% in the isolated Faroe Islands of Denmark and a minimum of ~20% in Turkey. Caucasians in Canada and North America present with an F508del frequency of 68–71%, whereas Hispanic populations and African–Americans show significantly lower frequencies (42–48%). The overall frequency of non-F508del mutations is low, except for some population-specific mutations such as W1282X, which accounts for ~48% of CF chromosomes in Ashkenazi Jews or 621+1G>T accounting for 23% of French Canadian CF chromosomes. Therefore, it is

the presence of the F508del mutation that increases the frequency of CF in Caucasians compared to other races (table 2).

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Screening and diagnosis of CF

Jürg Barben and Kevin Southern

Diagnosis of CF

A diagnosis of CF is based on one or more typical phenotypic features (table 1): a history of CF in a sibling or a positive newborn screening result, and a laboratory confirmation of cystic fibrosis transmembrane regulator (CFTR) protein dysfunction and/or identification of two CF causing mutations. In most cases, the diagnosis of CF will be confirmed by measurement of sweat chloride concentration using quantitative pilocarpine iontophoresis, which measures chloride transport through the CFTR channel. A positive result (sweat chloride $\geqslant$60 mmol·L^{-1}) should always be confirmed with a second sweat test and CFTR mutation analysis. The 40 most frequent disease-associated CFTR mutations will detect >90% of affected CF patients in most European populations. Up to now, more than 1900 CFTR mutations have been identified, but only a small percentage (<10%) have been shown to definitely cause CF.

Key points

- The gold standard confirmation method for a suspected CF diagnosis is the measurement of sweat chloride using pilocarpine iontophoresis.
- A borderline or positive result should always be confirmed with a second sweat test or by CFTR mutation analysis.
- Until recently, the diagnosis has usually been made based on clinical manifestations, but newborn screening for CF has been implemented in many European countries.
- Once CF diagnosis has been confirmed, other family members should be offered screening for the disease using sweat testing, especially all siblings.

The sweat test comprises three phases:

- stimulation of the sweat glands (pilocarpine iontophoresis),
- sweat collection,
- sweat analysis.

The collection of a sufficient amount of sweat can sometimes be difficult, especially in very young children, but there have been many improvements in the sweat collection method. Newer techniques have reduced the amount of sweat needed, including the macroduct collection system or the nanoduct sweat analysing system (fig. 1). Sweat testing should always be carried out in accordance with the current guidelines and by a trained and experienced professional. Sweat testing is vulnerable to many sources of errors. Table 2 lists some of the common causes of false-negative and false-positive sweat test results.

Sweat chloride concentration increases with age in people without CF, but a sweat chloride concentration of $\geqslant$60 mmol·L^{-1} is usually diagnostic for CF (fig. 2). Values between 30 and 59 mmol·L^{-1} are intermediate. However, undoubted cases of CF with normal sweat electrolytes have been described. The measurement of other

Table 1. Age-related signs and symptoms of CF

Age	Presentation		
	Common respiratory	**Common non-respiratory**	**Less common**
General (any)	Moist cough with sputum production Respiratory infection with typical CF pathogen (*e.g. Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Burkholderia cepacia*)	Salty-tasting skin	
Neonatal		Diagnosis made by newborn screening (elevated immunoreactive trypsinogen) Meconium ileus (10–15% of patients with CF) causing bowel obstruction, partly with perforation and peritonitis Abdominal cramps, fatty stool	Protracted jaundice Intestinal atresia Intestinal atresia Fat soluble vitamin deficiency (*e.g.* bleeding due to vitamin K deficiency)
Infancy and childhood	Recurrent respiratory symptoms (chronic cough, wheeze and pneumonia)	Failure to thrive due to exocrine pancreas insufficiency with steatorrhoea, diarrhoea and abdominal distension	Rectal prolapse Anaemia, oedema and hypoproteinaemia Dehydration and electrolyte disturbance (Pseudo-Bartter's syndrome, hypochloraemic metabolic alkalosis) Cholestasis Chronic sinusitis
Adolescence and adulthood	Recurrent respiratory symptoms (cough and wheeze) Bronchiectasis Clubbing of fingers and toes Chronic pansinusitis and nasal polyps	Azoospermia (secondary to congenital bilateral absence of vas deferens)	Acute pancreatitis Liver disease and portal hypertension Pulmonary infection with atypical mycobacteria Haemoptysis Allergic bronchopulmonary aspergillosis

electrolytes (potassium and sodium) is not recommended as they are not diagnostic for CF, but a ratio of sodium/chloride >1 can be supportive for CF. The measurement of conductivity is approved for screening, but a value $\geqslant$50 mmol·L^{-1} should always be confirmed with a sweat chloride measurement.

For patients with an unclear diagnosis, there are two main methods of further characterisation of the salt transport defect:

- nasal potential difference,
- intestinal current measurement.

Both are challenging and only available in a few centres. In certain cases, however, they can provide valuable further information to help support or refute a diagnosis of CF.

Newborn screening

Newborn screening for CF, using immunoreactive trypsinogen (IRT) in dried blood spots taken from infants at the third/fourth day of life, has been implemented in many European countries (fig. 3). The first newborn screening programmes were based on IRT measurements from a heel prick test with repeat testing for infants with an elevated initial measurement 6 weeks later. With the detection of the CFTR gene in 1989, many countries introduced DNA analysis as the second tier of analysis. To date, more than 30 screening programmes have been developed, with quite marked variation in protocol design. All screening algorithms rely on testing for IRT as the primary screen for CF. Infants who have an

Figure 1. a) A child with a macroduct collection system. After pilocarpine iontophoresis to stimulate sweating, the system is firmly attached to the skin of the forearm. Sweat can be seen entering the tube system (blue rings). Chloride analysis can be performed on as little as 15–30 μL of sweat. b) A child with a nanoduct analysing system. After pilocarpine iontophoresis to stimulate sweating, the system measures sweat conductivity while attached to the patient. Measuring conductivity can be performed on as little as 3–5 μL of sweat

elevated IRT (usually >99th percentile) undergo further assessment either by another IRT measurement (IRT/IRT algorithm), genetic testing for the most common CFTR mutations (IRT/DNA algorithm) or further screening algorithms. Within these two categories, a variety of modifications are used because no single algorithm is perfect. The screening algorithm of each country depends on programme resources, and goals including mechanisms available for sample collection, regional demographics, the spectrum of disease phenotype that is to be detected and acceptable failure rates.

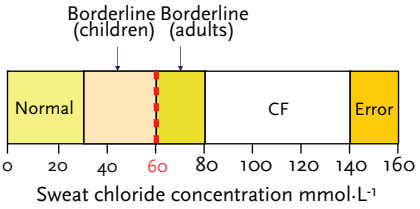

Figure 2. Sweat chloride measurement.

Screen-positive infants are referred to a CF centre for sweat testing, where the suspected CF diagnosis will be confirmed or rejected. The aim of a newborn screening programme is primarily to detect as many children with CF and pancreas insufficiency as possible in order to start treatment as early as possible, whilst avoiding false-positive screening results resulting in unnecessary recalls and sweat tests. The advantages of early diagnosis include nutritional benefits, early substitution of pancreatic enzymes and fat soluble vitamins, treatment of CF specific pathogens, access to specialised care, a reduction in the time of diagnostic uncertainty and the ability to counsel parents for prenatal testing. However, screening programmes also have some negative effects. Newborn screening identifies some healthy heterozygote carriers, which can cause anxiety and depression in affected families. In addition, some CF-affected individuals will be missed even in the best newborn screening programme, depending on the chosen cut-off value of the initial IRT measurement (false negatives in up to 8%). Another negative impact is the unnecessary medicalisation of infants with an equivocal diagnosis who turn out not to have CF.

Once CF diagnosis has been confirmed, other family members may be offered screening. All siblings need to be screened for the disease (sweat test), which may be pre-symptomatic or unrecognised. Asymptomatic adult family members may wish to be screened for carrier status to allow them to make informed choices about prenatal screening.

Table 2. Causes of false-negative and false-positive sweat test results

False-positive results	False-negative results
Evaporation of the sweat sample	Dilution of sweat sample
Severe malnutrition	Oedema
Anorexia nervosa	Dehydration
Atopic dermatitis (eczema)	Hypoproteinaemia
Familial hypoparathyroidism	Mineralocorticosteroid treatment
Pseudohypoaldosteronism	Some CFTR mutations, *e.g.* R117H, A455E, G551S
Adrenal insufficiency	
Glucose-6-phosphatase	
Nephrogenic diabetes insipidus	
Mauriac syndrome	
Fucosidosis	
Klinefelter's syndrome	
Familial cholestatic syndrome	

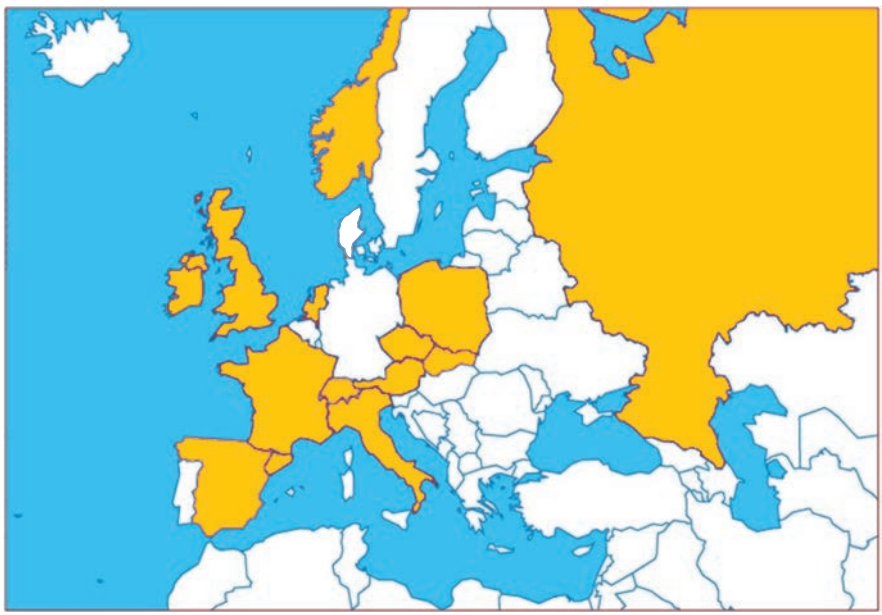

Figure 3. Newborn screening programmes in Europe 2012. Data from Southern (2013).

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CF lung disease

Nicolas Regamey and Jürg Barben

Lung disease accounts for most of the morbidity and mortality in CF. CF lung disease begins early in life. It is characterised by impaired mucociliary clearance and mucus obstruction, as well as chronic pulmonary infection and inflammation, leading to tissue destruction. Early CF lung disease is characterised by small airways obstruction and the development of bronchiectasis. There is a progressive decline of lung function with episodes of acute worsening of respiratory symptoms, often referred to as "pulmonary exacerbations". Tissue damage ultimately results in lung failure and death in most people with CF.

Key points

- CF lung disease begins early in life. It is characterised by impaired mucociliary clearance and mucus obstruction, and chronic pulmonary infection and inflammation.
- There is a progressive decline of lung function with episodes of acute worsening of respiratory symptoms, referred to as pulmonary exacerbations.
- Pulmonary effects of CF typically have the largest impact on morbidity and mortality, and account for over 80% of fatalities due to the disease.
- Current management of CF lung disease is predominantly symptomatic. The cornerstones of CF respiratory care are airway clearance and treatment of pulmonary infections.
- Lung transplantation is the final therapeutic option for patients with end-stage lung disease.

Pathophysiology

The most commonly accepted pathophysiological explanation for airway disease in CF is the "low volume" hypothesis. This hypothesis postulates that cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction leads to a loss of inhibition of airway epithelial sodium channels which, in turn, leads to excess sodium and water reabsorption. This results in dehydration of airway surface liquid. Reduced volume of the airway surface liquid causes failure of mucociliary clearance, which leads to mucus obstruction of the small airways. The lungs are not able to effectively clear inhaled bacteria, viruses, fungi and airborne pollutants. The thickened mucus on the epithelium forms plaques with hypoxic areas that can harbour bacteria and other pathogens.

The lungs of children with CF appear normal at birth but quickly become infected by organisms that are not adequately cleared. Infants with CF develop persistent endobronchial infections early in life due to *Staphylococcus aureus*, nontypable *Haemophilus influenzae* and Gram-negative bacilli. By the end of the second decade of life, *Pseudomonas aeruginosa* is the predominant pathogen. Chronic bacterial endobronchial infection is associated with an intense neutrophilic inflammatory response that damages the airway, impairs local host-defence mechanisms and

facilitates further infection. For a given bacterial load, a person with CF will have up to 10-times more inflammation than a person with a lower respiratory tract infection but without the disease. This vicious cycle of inflammation and infection with airway damage results in progressive bronchiectasis, gas trapping, impaired gas exchange (hypoxaemia and hypercarbia) and ultimately leads to respiratory failure (fig. 1).

Airway disease in CF is present early, even in asymptomatic infants diagnosed through newborn screening. Both infection and inflammation are detected by bronchoalveolar lavage in CF infants as young as a few weeks of age. CT scans in CF infants show the presence of structural airway wall changes including thickened airway walls, narrowed airway lumens, air trapping and bronchiectasis. Once present, bronchiectasis persists and is progressive. Lung function has also been shown to be diminished in infants with CF, and lung function declines over time throughout life. Pulmonary insufficiency is responsible for at least 80% of CF-related deaths.

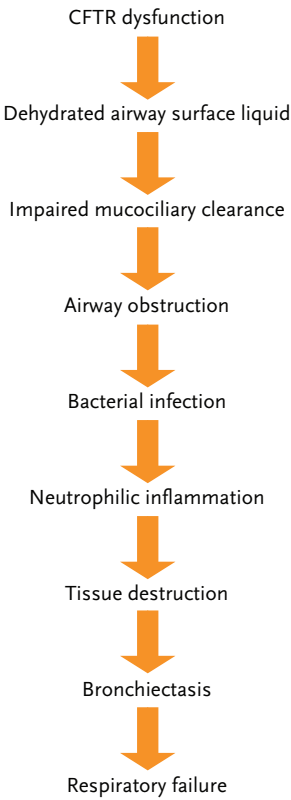

Figure 1. Pathophysiology of CF lung disease. Steps hypothesised to be relevant in the progression of CF lung disease are shown. Note that the steps do not necessarily occur in the order presented, for instance, chronic neutrophilic inflammation leads to further airway obstruction through the accumulation of dead cells and mucus in the airway lumen.

Clinical manifestations

Pulmonary manifestations of the disease appear throughout life with a great variability from patient to patient (table 1; see also table 1 in the Genetics, pathophysiology and epidemiology of CF section in this *Handbook*).

In the first months of life, respiratory symptoms can already be present, but gastrointestinal symptoms (meconium ileus, fatty stools and failure to thrive due to pancreatic insufficiency) are predominant. Infants with CF do not experience more often respiratory virus infections than their healthy peers but the course of viral infections can be severe, especially in the case of an infection with respiratory syncytial virus. Recurrent cough, tachypnoea and wheeze are the main clinical signs of CF lung disease in early stages. At first, the cough may be dry but eventually it becomes loose and productive. Some children remain asymptomatic for long periods or seem to have only prolonged acute respiratory infections. Others acquire a chronic cough within the first weeks of life or have repeated pneumonias. High energy consumption due to an increased work of breathing can aggravate failure to thrive.

Older children present with a persistent moist cough and sputum production. Expectorated mucus is usually purulent. Late clinical findings include increased anteroposterior diameter of the chest, localised or scattered crackles and digital clubbing. Chest radiograph abnormalities

Table 1. Pulmonary manifestations

Stage	Manifestation	Aim of treatment	Management	Comments
Early	Pre-infection: impaired mucociliary clearance, virus infections	Mucus clearance, prevent bacterial infection Maintain good lung function	Airway clearance techniques: physiotherapy and inhalation with hypertonic saline and rhDNase Influenza immunisation	Early start of treatment before onset of symptoms is recommended
	Intermittent isolation of CF pathogens	Eradication of infection	Different protocols with oral, inhaled and systemic antibiotics	Eradication can usually be achieved, but evidence of long-term benefit unclear
Intermediate	Chronic infection with Sa, Hi, Pa	Suppression of bacterial load	Oral, inhaled and systemic antibiotics	Segregation of patients with Pa, Bcc, Sm and Ax to prevent cross infection is important
	Infection with less common CF pathogens: Bcc, Sm, Ax	Eradication if early manifestation; suppression of bacterial load	Individual treatment based on antibiotic susceptibility	Confirmation in a reference laboratory essential
	Allergic bronchopulmonary aspergillosis	Reduce allergic response and fungus load, prevent bronchiectasis	Oral steroids and antifungal agents	Long course over several months required
	Non-tuberculous mycobacterial infection	Eradication	Long-term combination therapy for $\geqslant$12 months	Treatment started after repeated detection of the same isolate with clinical manifestations
End stage	Haemoptysis	Prevent bleeding, which may be fatal	Intravenous antibiotics, pause airway clearance therapy for a few days, bronchial artery embolisation	
	Pneumothorax		Drainage, pleurodesis if recurrent	
	Respiratory failure		Low-flow oxygen therapy, temporarily CPAP, lung transplantation	

rhDNase: recombinant human deoxyribonuclease; Sa: *Staphylococcus aureus*; Hi: *Haemophilus influenzae*; Pa: *Pseudomonas aeruginosa*; Bcc: *Burkholderia cepacia* complex; Sm: *Stenotrophomonas maltophilia*; Ax: *Alcaligenes xylosoxidans*.

(*e.g.* infiltrates, atelectasis, bronchiectasis) are common pulmonary features of CF (figs 2 and 3). As airways disease persists and worsens, exercise intolerance and shortness of breath are noted. Exacerbations of pulmonary symptoms eventually require hospitalisation for effective treatment, but what constitutes a pulmonary exacerbation of CF is not clearly defined. Increased cough, change in sputum colour or quantity, decreased appetite or weight, change in respiratory rate and presence of new wheezes or crackles on auscultation of the chest are particularly important features.

With pulmonary disease progression, there is an increased likelihood of respiratory complications. Lobar atelectasis may be asymptomatic and noted only at the time of a routine chest radiograph. Aggressive antibiotic therapy and increased chest physiotherapy may be effective. Allergic bronchopulmonary aspergillosis (ABPA) may present with wheezing, increased cough and shortness of breath. The presence of new, focal infiltrates on chest radiograph, the recovery of *Aspergillus fumigatus* from sputum, the demonstration of high IgE serum levels or serum antibodies against *A. fumigatus* support the diagnosis. Treatment involves antifungals and steroids to control the inflammatory reaction. Airway infection with *Burkholderia cepacia* may be associated with rapid pulmonary deterioration and death. Nontuberculous mycobacteria, *Stenotrophomonas maltophilia* and *Alcaligenes xylosoxidans* are emerging pathogens in patients with CF. Their clinical impact is not fully understood but infection with *Mycobacterium abscessus* can be a rapidly progressive process.

Haemoptysis and pneumothorax are complications in advanced lung disease. Endobronchial bleeding is the consequence of airway wall erosion secondary to inflammation and infection. Small volume haemoptysis is relatively common and prompts for intensified antimicrobial treatment and chest physiotherapy. Persistent, massive haemoptysis can be controlled by bronchial artery embolisation.

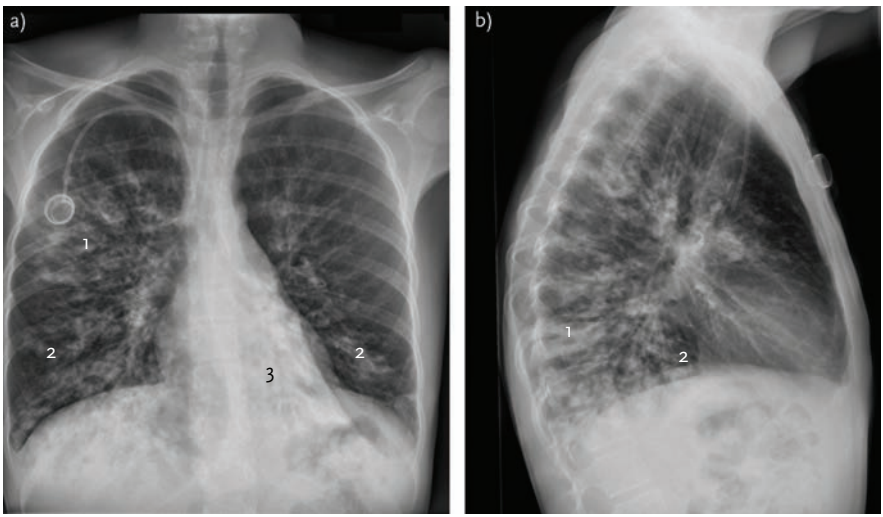

Figure 2. Chest radiograph of a 15-year-old female CF patient with advanced lung disease a) posteroanterior view and b) lateral view. The radiograph shows pronounced pulmonary hyperinflation with sternal bowing, bronchial wall thickening and bilateral bronchiectasis, infiltrates mainly in the right upper lobe (1) and in the lower lobes on both sides (2) as well as atelectasis of the left lower lobe (3). Note the central venous access (Port-a-Cath system; Smiths Medical, St Paul, MN, USA). Image courtesy of E. Stranzinger (Division of Radiology, University Children's Hospital of Bern, Bern, Switzerland).

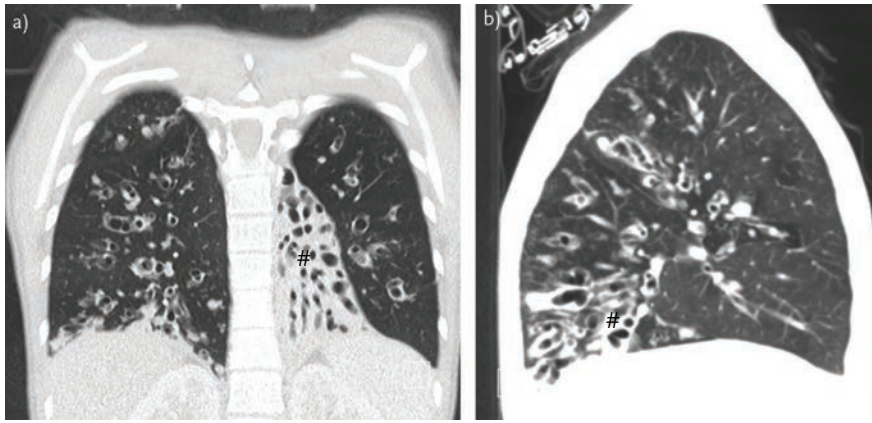

Figure 3. CT scan of a 15-year-old female CF patient (same patient as in fig. 2) a) coronal plane view and b) sagittal plane view of the left lung. Bilateral mucus plugging and bronchiectasis, as well as atelectasis of the left lower lobe (#) is clearly visible. Image courtesy of E. Stranzinger (Division of Radiology, University Children's Hospital of Bern, Bern, Switzerland).

Pneumothorax is rarely encountered in children, but may be a life-threatening complication in older patients. A small pneumothorax is managed conservatively, but a large (distance between the apex and cupola >3 cm) pneumothorax or under tension requires rapid treatment with drainage. If recurrent, pleurodesis or surgical intervention has to be performed.

Acute respiratory failure rarely occurs and is usually the result of a severe viral illness, such as influenza. Patients eventually progress to chronic respiratory failure from slow deterioration of lung function. Chronic right-sided heart failure (cor pulmonale) is a complication seen in CF patients with long-standing, advanced pulmonary disease, especially in those with severe hypoxaemia.

For most patients, lung disease is the major health problem in terms of symptoms and treatment required and because it is the most likely cause of morbidity and death.

Management of lung disease

Nowadays, most CF patients in Europe receive care on a regular basis every 1-3 months, coordinated by a team of trained and experienced health professionals in a tertiary centre. CF centre care is essential for optimal patient management and outcome.

A CF team is usually led by a respiratory physician and includes many other specialists (gastroenterologist, microbiologist, respiratory therapist, dietetician, social worker, psychologist, specialised CF nurse). For patients living a long distance from a CF centre, formalised "assisted" care with local clinics can be considered. However, only when the quality of the assisting team is up to standard.

During follow-up outpatients visits, an interval history should always be taken and a physical examination performed. A sputum sample should be obtained for microbiological analysis, or if not available a lower pharyngeal swab taken during or after a forced cough. Pulmonary function tests should be performed at regular intervals to monitor lung disease progression. Chest radiographs or CT scans are usually included as part of the annual review. Apart from the annual review, chest radiography should be considered when atelectasis or a pneumothorax is considered. In some centres, yearly bronchoscopy with bronchoalveolar lavage is performed for microbiological surveillance in young children unable to expectorate, but it is yet unclear whether this approach results in better outcomes.

Current management of CF is predominantly symptomatic. The cornerstones of CF respiratory care are clearance of lower airway secretions and treatment of pulmonary infections. Annual influenza vaccination is recommended. The goal of therapy is to maintain a stable condition and to prevent any irreversible structural lung changes. Much of the clinical practice has evolved over decades without being subjected to high quality randomised controlled trials, especially in children <6 years.

Knowledge of the basic CF defect has led to the development of new therapeutics aimed at potentiating or even correcting defective CFTR channel function, which also improves lung function. The first such molecule (VX-770, Ivacaftor) which potentiates CFTR function in patients with the G551D mutation, has recently been licensed in the USA and Europe (see the Emerging treatment strategies in CF section in this *Handbook*).

Treatment modalities

Treatment aims and modalities for CF lung disease vary according to the disease stage (table 1).

Early disease stages So far there have been hardly any randomised controlled trials on chronic pulmonary therapies in young children with CF. This is, in part, because appropriate end-points are difficult to identify, but also because federal regulations make inclusion of young in children in research studies complicated. Therefore, current recommendations for therapies in the pre-school age are mainly based on studies in older children. Studies including very young patients must be designed and undertaken, because it is likely that early therapy, before lung disease is established, will provide the most significant and long-term benefits for children with CF.

Preventive therapy with chest physical therapy is recommended. The goal of physiotherapy is to clear secretions from airways. There are many techniques available to augment clearance of tenacious airway secretions. These include postural drainage, vibration and percussion, airway-oscillating devices positive expiratory pressure (PEP) devices, active cycles of breathing techniques and autogenic drainage (series of respiratory huffs and coughs designed to move mucus from distal to proximal airways so it can be coughed out). Close supervision by an experienced physiotherapist and continuity of care is essential. There is a divergence of opinion about specific aspects of therapy, but the consensus is that this form of therapy is highly effective in older subjects, as it favours clearance of secretions that accumulate in small airways, even before the onset of symptoms. Its role is far less clear in younger children diagnosed through newborn screening, and some forms of physical therapy might even be detrimental (*e.g.* by inducing gastro-oesophageal reflux).

Hypertonic saline acts as an hyperosmolar agent and presumably rehydrates the airway surface liquid layer, thus improving mucociliary clearance. It is delivered using a small compressor that drives a hand-held nebuliser. It has been shown to be effective in older subjects, but its role in young children aged <5 years is unknown. Saline at a concentration of 6–7% is usually applied. Whether lower strength saline (3% or even 0.9%) is also efficacious has not yet been systematically studied. In general, hypertonic saline is well tolerated. In patients with reactive airways, salbutamol or other bronchodilators can be added. In the light of the current knowledge about the pathophysiology of the disease, early start with a trial and error approach of inhalation with normal or hypertonic saline seems reasonable.

Early antibiotic treatment of typical CF pathogens is recommended. Antibiotics are the mainstay of therapy against pulmonary infection. Their goal is to control progression of lung infection and to delay progressive lung damage. Antibiotic treatment varies from intermittent short courses of oral antibiotics to continuous treatment with one or more oral or inhaled antibiotics. Dosages of oral antibiotics for CF patients are often two to three times the amount recommended for minor infections

in order to achieve effective drug levels in sticky respiratory tract secretions, and because CF patients have proportionately more lean body mass and higher clearance rates for many antibiotics than do other individuals. Whenever possible, *in vitro* sensitivity testing should be performed to guide the choice of antibiotics, although it does not always reflect bacterial susceptibility to antimicrobial agents *in vivo*.

Infection with *S. aureus* and *H. influenzae* is usually treated with oral antibiotics, but despite this, chronic infection persist in many patients. Anti-staphylococcal prophylaxis with oral antibiotics is performed in some countries but this approach is subject to debate.

P. aeruginosa initially grows in a non-mucoid form that can be eradicated by aggressive antibiotic treatment. Over time, it builds colonies that synthesise an alginate coat and forms biofilms, which are difficult, if not impossible, to clear with antibiotic treatment. Patients infected with *P. aeruginosa* have more rapid lung function decline and diminished survival compared to non-infected subjects. Therefore heightened surveillance and aggressive treatment of *P. aeruginosa* is warranted.

First infection with *P. aeruginosa* is always treated with antibiotics with the goal to eradicate the germ. Treatment with 1 month of tobramycin nebulisation is currently the first line of treatment, and eradication can be achieved in most cases. Other treatment protocols have been shown to be of similar effectiveness and include oral, inhalation and intravenous antibiotics but there are only few comparative studies available and, therefore, the optimal antibiotic regimen is not known. In cases of eradication failure, repeating antibiotic eradication treatment is recommended. If there is chronic airway infection with *P. aeruginosa*, maintenance treatment with chronic suppressive antibiotics should be initiated. Often used regimens are intermittent one month on one month off inhalation of tobramycin or continuous administration of inhaled colistin. These treatment strategies have proven successful in the maintenance of lung health.

Intermediate disease stages In school-aged children, treatment with inhaled hypertonic saline, dornase alfa (recombinant human deoxyribonuclease (rhDNase)) and intensive airway clearance is recommended. Exercise is beneficial for CF patients, as it improves sense of wellbeing, improves quality of life and might stabilise lung function to some degree. Exercise alone should however not be used as an alternative to airway clearance.

Continuous oral azithromycin treatment, which has both antibacterial and anti-inflammatory effects, is often added to improve lung function and to reduce exacerbations. Oral high-dose ibuprofen has been shown to slow disease progression, but it use is hampered by the necessity of monitoring serum concentrations and unfavorable side-effects. Systemic corticosteroids are useful for the treatment of ABPA but side-effects (growth retardation, cataracts, abnormalities of glucose tolerance) have limited their use as a standard therapy. Inhaled corticosteroids show no significant benefits in CF lung disease, unless the patient has concomitant asthma. Systemic expectorants such as iodides and guaifenesin are not effective in assisting with the removal of secretions from the respiratory tract.

For CF patients with chronic *P. aeruginosa* infection, long-term treatment with inhaled antibiotics (tobramycin, colistin or aztreonam) is recommended, with the goal of reducing the frequency of pulmonary exacerbations and slowing the disease progression.

Intravenous antibiotics are indicated for patients who have progressive or unrelenting symptoms (pulmonary exacerbation) or a decline in lung function despite intensive home therapy. Intravenous antibiotic therapy is usually initiated in the hospital but is often completed on an ambulatory basis. The usual duration of intravenous antibiotic therapy is 14 days, but this can be extended to several weeks.

In general, a combination therapy is applied. Since most patients with pulmonary exacerbations have *P. aeruginosa* in their airways, the usual in-hospital treatment is a combination of a β-lactam and an aminoglycoside. *In vitro* antibiotic sensitivity tests do unfortunately not predict clinical outcome in patients with chronic infection and routine testing of the susceptibility of bacteria to combinations of antibiotics (synergy testing) is not recommended. In some centres, intravenous antibiotics are given on a routine basis independent of pulmonary exacerbations.

Late disease stages Low-flow oxygen therapy at home, especially with sleep, is applied in case of chronic respiratory failure. Lung transplantation is the final therapeutic option for patients with endstage lung disease. Transplantation has the potential to extend and substantially improve quality of life in properly selected patients. How to select patients (especially children) in an optimal way for this high-risk procedure, is still the subject to debate (see the Prognosis, management of end-stage lung disease and indications for lung transplantation in CF section in this *Handbook*). CF patients with chronic respiratory failure who are on a lung transplant waiting list may be candidates for nocturnal non-invasive ventilatory assistance.

Respiratory treatments represent the greatest challenge to patients and families; proper physiotherapy and inhaling hypertonic saline, antibiotics and/or rhDNase is very time consuming and takes 1–2 h per day during periods of good health and much longer during a respiratory exacerbation.

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Extrapulmonary manifestations of CF

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Nutritional approach in patients with CF

Maintaining adequate nutritional status in terms of lung health and survival is a cornerstone of the CF multidisciplinary approach. Consensus-based nutritional guidelines provide an invaluable tool in daily care management. Neonatal screening programmes enabling very early follow-up care, prior to clinical pulmonary involvement, offer a unique opportunity for nutritional assessment at a crucial period of rapid growth.

Key points

- Nutritional status is strongly associated with pulmonary function and survival in CF.
- Nutritional management should be started as soon as possible after diagnosis.
- Patients' height and weight should be measured at each clinical visit and BMI calculated (percentile or z-score in children, absolute BMI in adults).
- EPI should be confirmed by a biological test (steatorrhoea or faecal elastase-1) and PERT should be started as soon as possible.
- Fat-soluble vitamins need to be given in association with pancreatic enzymes in EPI patients.
- The gastrointestinal tract is a major source of comorbidity in CF patients.
- Entities such as fibrosing colonopathy, appendiceal mucocoele and DIOS are specific to CF.
- In the case of acute abdominal pain, surgical conditions need to be sought; all surgical aetiologies may take on the appearance of recurrent pain with mild symptoms.

Nutrition When providing nutritional intake to achieve normal growth in children and maintain adequate weight in adults, sex, age (rapid growth rate in infants and adolescents), specific needs during pregnancy, nutritional and pancreatic status, family circumstances, cultural dietary beliefs, and patient food preferences all must be taken into account.

Energy requirements of newly diagnosed infants with CF may range from 110% to 150% of the recommended daily allowance (RDA) (Borowitz *et al.*, 2002; Sinaasappel *et al.*, 2002; Stallings *et al.*, 2008; Munck, 2010). Infants with CF can be safely breastfed. Additional calories (carbohydrate content up to 10–12 g per 100 mL and fat density 5 g per 100 mL) can be added to expressed breast milk and/or infant formula can be concentrated (1.2–1.5 cal·mL^{-1}) if weight gain is poor, rather than increasing milk volumes, due to the enhanced risk of gastro-oesophageal reflux (GOR). There is no evidence to support the use of protein hydrolysate formulas with the exception of infants undergoing small bowel resection for meconium ileus, severe failure to thrive or with co-existing cows' milk protein intolerance. Solid food can gradually be introduced between 4 and 6 months; parents should seek the dietician's advice on the most suitable foods and pancreatic enzyme dosage. Young children should later

eat three regular meals and two snacks of high nutrient and calorie density.

Protein needs are unknown but may be higher than normal. Dietary fat intake is considered adequate at 50% of total energy intake at <6 months, and between 40% and 50% in older patients.

Sodium supplementation is recommended for all infants, in hot climates, and in the case of fever or sport activities.

Adolescence is another crucial period, with increased energy requirements related to rapid physical growth.

Maintaining optimal nutritional status in adulthood is a challenge, as the prevalence of malnutrition increases with age-related CF complications. Patients' height and weight should be measured at each clinical visit and BMI calculated (percentile or z-score in children, absolute BMI in adults).

Patients who develop CF-related diabetes are encouraged to continue eating a diet rich in energy and fat (Moran *et al.*, 2010a). A minimal change in the quantity of carbohydrates is generally advised but distribution may need to be adapted.

Pregnancy is possible in women with CF but the risk of a negative impact on survival may increase with more severe disease and, therefore, it is not recommended in these patients. Additional recommended energy requirements for pregnancy vary from 200 to 300 kcal·day^{-1} (Edenborough *et al.*, 2008). Nutritional status before and during pregnancy influences the evolution of pregnancy and newborn outcome.

Careful monitoring of the growth chart at each consultation is mandatory to prevent malnutrition. Dietary diary intake with the help of a dietician and evaluation of treatment compliance are part of multidisciplinary assessment, and are needed for early nutritional intervention. If the principal cause of poor nutritional status is insufficient food intake despite a high-energy diet, the use of oral nutritional supplements may be of some use at an individual level; a large variety of flavours and textures may help in preventing lassitude. In children, behavioural interventions have been shown to improve nutritional outcome.

Nocturnal enteral feeding through a nasogastric tube or gastrostomy, according to the patient's preference, has to be considered to provide long-term nutritional support in patients not gaining (children) or keeping (adults) weight. The majority of patients tolerate high-energy polymeric feed but a semielemental feed may be beneficial for some. All feeds need pancreatic enzyme replacement therapy (PERT). Patients may need up to 70% of RDA by enteral feeding to improve their weight and are encouraged to continue with a high-energy diet during the day. It is important to monitor for glucose intolerance and GOR symptoms.

Pancreatic enzyme replacement therapy

Exocrine pancreatic insufficiency (EPI) (Munck, 2010) is present in 85–90% of patients. Symptoms include: pale, oily stools; abdominal pain; and poor weight gain. Even if the patients show these symptoms, a biological confirmatory test is required to define pancreatic status. The faecal elastase-1 test is now widely used and a level of <200 μg·g^{-1} is diagnostic of EPI. Once EPI is confirmed, PERT should start as soon as possible. Currently available preparations are derived from porcine pancreas. Enteric-coated preparations dramatically decrease enzyme degradation by stomach acidity and improve the release of enzymes in the duodenum.

For some patients with poor response to PERT needing high doses, H2-receptor antagonists or proton pump inhibitors may be beneficial.

Following the occurrence of fibrosing colonopathy in the early 1990s in young children receiving very high doses of daily PERT and despite the rareness of this complication, the severity of the condition led to consensus guidelines for PERT in 2002 recommending not exceeding a daily dose of 10 000 IU lipase per kilogram per day (2500–3000 IU lipase per 120 mL breast milk or formula, 500–2500 IU lipase per

kilogram per meal or 500–4000 IU lipase per gram of fat) of "standard" or "high–strength" enzyme preparations. Enzymes should be given with all fat-containing foods at the beginning and middle of the meal, with the dose gradually increased.

Capsules can be opened for infants and toddlers. In infants, micro- or mini-microspheres can be mixed with a small amount of breast milk, formula or fruit puree. Microspheres should not be crushed, chewed or mixed with the meal.

There is insufficient evidence to establish a dose–response association between PERT and weight gain. Usually, adequacy of PERT is evaluated clinically by growth, weight, stool pattern and abdominal pain. In some cases, it may be helpful to assess the coefficient of fat absorption (3-day stool collection and diet intake).

Fat-soluble vitamin supplementation Patients with EPI should be supplemented with fat-soluble vitamins (table 1) (Maqbool *et al.*, 2008) from the time of diagnosis and serum levels measured annually. Pancreatic-sufficient patients should have their serum fat-soluble vitamin levels checked annually, with doses adjusted accordingly.

To ensure satisfactory oral bioavailability, all fat-soluble vitamin (A, E, D and K) formulations need to be ingested concomitantly with pancreatic enzymes during the meal. Vitamin A is stored in the liver. Plasma retinol measurements should be taken during clinical stability. β-carotene, a pro-vitamin A antioxidant, is subject to regulation in its conversion to vitamin A, potentially decreasing the risk of hypervitaminosis A. Vitamin E represents an important, powerful antioxidant. Vitamin E status can be evaluated by serum level concentration or serum concentration/lipid ratio. Vitamin K deficiency is common in pancreatic-insufficient patients with additional risk factors: first year of life, frequent antibiotic use (reduced production of menaquinones by the modified gut flora) and cholestasis. Prothrombin time is monitored annually. Routine supplementation for all patients might be beneficial.

Low plasma 25-hydroxyvitamin D levels have often been reported and suboptimal status after adjusting for season remains common. Cholecalciferol (vitamin D_3) supplementation is more effective than ergocalciferol (vitamin D_2). Recent improvement in our knowledge of the different roles of fat-soluble vitamins emphasises the need for optimal supplementation. Water-miscible multivitamins formulations with satisfactory bioavailability profiles have been developed. Current guidelines (Sinaasappel *et al.*, 2002; Maqbool *et al.*, 2008) on fat-soluble vitamin prescriptions are old and may require updating.

Gastrointestinal complications in CF

Digestion, absorption and motility In CF, the three main gastrointestinal functions are impaired (Borowitz *et al.*, 2005). Maldigestion and malabsorption are secondary, and the main cause is abnormal pancreatic function with reduced bicarbonate secretion (thus impairing pancreatic enzyme lipase activity and precipitating bile acids, inhibiting lipid emulsification) and a dramatic decrease in enzyme secretion. Other luminal factors are excessive mucus production with abnormal composition, impaired gut motility, small intestine bacterial overgrowth, chronic gut inflammation and gut lumen dehydration closely related to a CF transmembrane conductance regulator (CFTR) basic ion transport defect (*i.e.* decreased chloride secretion, and enhanced sodium and water absorption from the lumen).

Physiological and pathological abnormalities A variety of abnormalities have been identified in the gastrointestinal tract but their role in clinical syndromes remains poorly understood. Gut histology shows dilated mucus glands with inspissated mucus and a normal enterocyte brush border. Ultrasonography identifies a marked increase in small and large bowel wall thickness (Wilschanski *et al.*, 1999). Recently, duodenal pH studies with wireless

Table 1. Fat-soluble vitamins: current daily intake

Vitamin	Age group	Intake recommendations µg (IU)	Monitoring recommendations
A	0–12 months	510 (1500)	Serum retinol (deficiency $<20\ \mu g \cdot dL^{-1}$) (RBP zinc level)
	1–3 years	1700 (5000)	
	4–8 years	1700–3400 (5000–10 000)	
	>8 years/adults	3400 (10 000)	
E	0–12 months	40–50 (40–50)	Serum α-tocopherol
	1–3 years	80–150 (80–150)	
	4–8 years	100–200 (100–200)	
	>8 years/adults	200–400 (200–400)	
K	0–12 months	0.3–0.5	Serum prothrombin time
	1–8 years	0.3–0.5	
	Adults	2.5–5 per week	
D	0–12 months	10 (400)	Serum 25(OH)D in late autumn or winter
	>1 year	10–20 (400–800)	

RBP: retinol binding protein; 25(OH)D: 25-hydroxyvitamin D. Reproduced and modified from Maqbool *et al.* (2008).

capsules demonstrated low pH as a consequence of decreased pancreatic bicarbonate secretion. Transit time was also evaluated with this technique and identified delayed small bowel transit without a compensatory increase in whole-gut transit (Gelfond *et al.*, 2012). Chronic gut inflammation has been identified in duodenal biopsies and by increased calprotectin levels in stools and pro-inflammatory cytokines in gut lavage (Werlin *et al.*, 2010).

Pancreatic exocrine and extrahepatic biliary complications Pancreatitis (De Boeck *et al.*, 2005; Ooi *et al.*, 2012) occurs in up to 20% of pancreatic-sufficient patients carrying at least one mild *CFTR* mutation (class IV or V). It is more common in adolescents and adults. Patients are at risk of recurrent acute or chronic pancreatitis. Progression to EPI with acinar destruction – which may take years – contributes to the resolution of the pancreatitis. Possible triggering factors include alcohol, gallstones, abnormalities of the pancreaticobiliary junction, dehydration, modifier genes and specific non-*CFTR* mutations (Ooi *et al.*, 2012). The typical presentation includes recurrent acute abdominal pain, vomiting, increased amylase and lipase levels, and pancreatic ultrasonography or CT abnormalities. Amylase and lipase levels may also be normal or only slightly elevated. Management consists of pain relief, fasting, intravascular hydration, use of proton pomp inhibitors and progressive diet reintroduction (initially lipid-free diet). Because pancreatitis may be a presenting feature of CF or CFTR-related disorder (Munck, 2004), sweat testing and *CFTR* genetic testing are recommended in pancreatitis of unknown cause.

Extrahepatic biliary manifestation with undetectable gallbladder in CF fetuses is common. Later, gallstones with cholesterol or calcium bilirubinate are frequent and are a consequence of chronic bile salt loss and enhanced unconjugated bilirubin in the colon impairing colonic reabsorption. Medical treatment with ursodeoxycholic acid (UDCA) is ineffective. In the case of complications (pain and jaundice), which occur in 4–10% of patients, surgery is required.

Gut manifestations GOR is very frequent in CF, even in infants (Vic *et al.*, 1995). It has been postulated that GOR is a consequence of respiratory disease but there is no correlation between GOR and lung disease severity. The underlying mechanisms are not completely understood and appear to be multifactorial: the majority of reflux episodes are caused by transient lower oesophageal relaxation rather than decreased lower oesophageal sphincter pressure (Pauwels *et al.*, 2012). Other factors are involved such as thoracic distension, coughing, malnutrition, delayed gastric emptying, postural drainage head-down and certain drugs. The most common symptoms are heartburn (pyrosis), nocturnal cough, vomiting, abdominal epigastric pain, dysphagia and unexplained pulmonary deterioration, but GOR may also remain asymptomatic. GOR may affect both respiratory function and nutritional status. It is reasonable to start a trial of medical therapy based on clinical symptoms. An upper endoscopy is indicated in case of dysphagia, haematemesis or suspicion of peptic ulceration; a 24-h ambulatory oesophageal pH probe is useful when there is doubt as to whether GOR is the cause of symptoms, prior to starting enteral feeding and when lung transplant is considered. Standard management combines thickening food in infants, raising the head of the bed and acid suppression with proton pump inhibitors. Prokinetic drugs are no longer available in many countries. For patients who fail to respond, a surgical fundoplication can be discussed and may slow pulmonary decline, reduce the number of exacerbations and improve weight gain (Sheikh *et al.*, 2012).

Meconium ileus is the earliest CF clinical manifestation occurring in up to 20% of CF newborns. Diagnosis can be made through ultrasonography *in utero* during the second trimester revealing polyhydramnios with a dilated, hyperechogenic fetal bowel. The distal intestinal obstruction is caused by accumulation of abnormal viscous meconium in the lumen. Careful diagnostic evaluation and a consultation with a genetic counsellor are recommended, including *CFTR* gene analysis if pregnancy termination is discussed. Meconium ileus is not exclusive to CF patients (although the majority have CF) and thus diagnostic tests should be performed as soon as possible to confirm or refute CF diagnosis. The tendency to express the meconium ileus phenotype might also be related to non-*CFTR* genetic factors called modifier genes (Dorfman *et al.*, 2009). The clinical presentation of this distal bowel obstruction combines distension, bilious vomiting and failure to pass the meconium within 48 h of birth. Radiography identifies abdominal distension and dilated loops. Barium enema shows a microcolon with a "soap bubble" aspect in the right iliac fossa corresponding to meconium pellets in the distal ileum. Management of uncomplicated meconium ileum relies on enema with diluted Gastrografin, a hyperosmolar, water-soluble, radio-opaque meglumine diatrizoate solution containing 0.1% polysorbate 80 (Tween 80) slowly infused at low pressure under fluoroscopy control to relieve obstruction. Enema can be repeated and the success rate is close to 40%. In case of failure, surgery is required. Complicated meconium ileus (40%) with peritonitis, volvulus and intestinal atresia requires immediate surgery. Depending on the severity of the newborn's clinical condition, different surgical approaches can be considered: enterostomy irrigating the distal bowel through the stoma, resection of the compromised bowel with complete proximal and distal meconium evacuation, and either a primary anastomosis or a temporary enterostomy (Carlyle *et al.*, 2012). Post-operative care and nutritional support by a gastroenterology team is part of meconium ileus management. With early detection, appropriate therapy and nutritional support, death is now uncommon, and long-term nutritional and pulmonary outcomes are equivalent to those of other CF patients.

Meconium plug syndrome consists of abnormal meconium accumulation located in the colon that produces mild abdominal distension and failure to pass meconium. Management relies on contrast enema. About 25% of patients present underlying CF.

Distal intestinal obstruction syndrome (DIOS) is specific to CF and is a common complication in adolescents and adults (five to 12 cases per 1000 patients per year) (Houwen *et al.*, 2010; Colombo *et al.*, 2011). It is characterised by the accumulation of viscid faecal material in the terminal ileum and/or the right colon. Patients are at high risk of recurrence (50%). The physiopathology is not fully understood and probably multifactorial, involving gastrointestinal lumen dehydration, impaired motility and abnormal bile acid absorption. Reported risk factors include a severe genotype, pancreatic insufficiency (but it does not play a central role because DIOS does not occur in pancreatic insufficiency out of CF and may occur in pancreatic-sufficient CF patients), dehydration, poorly controlled fat malabsorption, intestinal dysmotility, history of myocardial infarction and surgery. DIOS typically has an acute onset of symptoms. Complete DIOS is defined as the combination of 1) complete intestinal obstruction with bilious vomiting or fluid levels on radiography with 2) a faecal mass in the right iliac fossa and 3) abdominal pain and/or distension. Incomplete DIOS gathers the two latter symptoms. A surgical aetiology has to be ruled out (appendicitis, intussusception, volvulus adhesions, *etc.*), thus an ultrasonography or an abdominal CT may be needed. Treatment of DIOS relies on a stepwise approach depending on the severity of the syndrome. Complete DIOS with moderate obstruction can be treated with polyethylene glycol (PEG) lavage; in the case of more severe presentation with bilious vomiting, hospitalisation with fasting, intravascular hydration and diluted sodium meglumine diatrizoate (Gastrografin) enema under direct vision until the terminal ileum is reached may achieve resolution of obstruction. Close monitoring of the patient is recommended because Gastrografin enema may cause major ion and water shifts. In the case of failure, because surgery is a high-risk intervention, a colonoscopy with local instillation of Gastrografin in the caecum and ileum lavage may be an alternative. If it fails an attempt of washout, enterostomy may be tried before considering resection of the ileocaecum. Patients presenting incomplete DIOS usually respond to oral rehydration combined with osmotic laxative lavage containing PEG. Maintenance therapy with oral PEG for a few months is recommended and, in cases of a decline in the frequency of bowel movements, this has been shown to decrease the risk of recurrence of DIOS episodes in up to 50%. Bowel preparation before surgery (transplantation) has been suggested to prevent DIOS post-operatively.

Fibrosing colonopathy was first described in the 1990s (Smyth *et al.*, 1995) in four young children thought to have DIOS. They presented acute abdominal pain, diarrhoea and partial to complete abdominal obstruction. Investigation with contrast enema showed loss of haustral folds and mild to complete occlusion, mainly in the right colon. In most cases, a laparotomy had to be performed with a right hemicolectomy. Histology identified submucosal thickness due to fibrous connective tissue and an intact epithelium border. A case–control study confirmed a strong association between fibrosing colonopathy and excessive PERT supplementation (>50 000 IU lipase per kilogram per day). Thus, European and American guidelines (Sinaasappel *et al.*, 2002; Borowitz *et al.*, 2002) published in 2002 agreed to recommend restrictions on PERT doses to $\leqslant$10 000 IU·kg^{-1}·day^{-1}; since then, cases have virtually disappeared.

Acute appendicitis is less common in CF patients (1.5–5% compared with 7% in healthy peers). Surveys have shown a high rate of perforation and abscesses related to subacute presentation and delayed diagnosis probably as a consequence of frequent antibiotic prescriptions for pulmonary exacerbations (Coughlin *et al.*, 1990). Appendiceal mucocoele is a mucoid distension of the appendix that can remain asymptomatic, or cause chronic pain or mimic appendicitis. It can occur at all ages. Clinical examination of the right iliac fossa identifies a small ovoid mass. Ultrasonography focusing in the right iliac

fossa shows a multilayer mass with an enlarged appendix (>6 mm) filled with echogenic material. To rule out other aetiologies, CT or contrast enema may be indicated and may reveal the caecal defect. In the case of symptoms, appendectomy with resection of the appendix edges and resection of the caecal tip will avoid the risk of recurrence (Munck *et al.*, 2000). At histology, the appendix is distended with inspissated mucus.

The incidence of intussusception is 1%, and it occurs mainly in children and adolescents. It is usually ileocolic, but can also be ileoileal; it may resolve spontaneously. It is a consequence of dehydrated mucus and impaired intestinal motility but a starting point is frequent, such as inspissated secretions, lymphoid follicles, the appendix or polyps (with a malignancy risk in adults). Clinical presentation combines severe colicky abdominal pain, vomiting, bloody stools and a palpable mass in the right iliac fossa. Abdominal radiography may show obstruction, ultrasonography may reveal the characteristic "bull's eye" and abdominal CT can confirm the diagnosis if there is a doubt concerning the differential diagnosis. Intussusception reduction in children is the first choice unless complicated (perforation). If it fails or is complicated, immediate surgery is required (Nash *et al.*, 2011).

Rectal prolapse occurs mainly at preschool age and usually resolves after adjustment of PERT, an adequate-fibre diet, stool softeners and advice concerning voiding. Rectal prolapse may be also be a presenting feature of CF.

Comorbid gastrointestinal conditions Milk protein intolerance occurs more often in CF. Infants present nonspecific symptoms such as diarrhoea, constipation, vomiting, failure to thrive and eczema. Abnormal biological tests, including IgE levels, specific antibodies and prick tests, are helpful for indicating a semielemental diet.

Coeliac disease has a prevalence of 1.2% in CF, which is higher than in the general population (Pohl *et al.*, 2011). It should be considered in any CF patient presenting with chronic diarrhoea or abdominal pain despite adequate PERT replacement. The presence of anti-endomysium and anti-transglutaminase antibodies has good sensitivity but a duodenal biopsy is required to confirm diagnosis and start the patient on a lifelong, strict gluten-free diet.

Crohn's disease has been reported in CF. Symptoms are difficult to differentiate from symptoms in CF, including diarrhoea, abdominal pain, weight loss and inflammatory parameters. A colonoscopy with multiple biopsies is essential to confirm diagnosis.

There is an increased risk of digestive tract cancer, mainly colon, bowel, biliary tract, liver and pancreas, but these remain rare conditions. However, patients with CF have earlier onset with a markedly increased risk between 20 and 29 years of age (Alexander *et al.*, 2008).

CF-related liver disease

CF-related liver disease (CFLD) accounts for ~2.5% of overall mortality in CF. 27–35% of patients will develop some sort of liver involvement while about 5–10% will develop multilobular cirrhosis (MLC) with portal hypertension (PHT) (Flass *et al.*, 2012; Debray *et al.*, 2011). In patients developing severe liver disease, liver involvement commonly starts during the first decade of life and develops to MLC with PHT during the second decade of life. Often, the PHT is complicated by variceal bleeding before liver failure develops. The variceal bleeding demands treatment with variceal banding/sclerosing and, sometimes, nonselective β-blockers. The final option is often orthotopic liver transplantation.

Pathophysiology CFTR is expressed on the apical surface of the cholangiocytes, and the current belief is that missing CFTR results in obstruction of the small intrahepatic bile ducts and retention of toxic substances, leading to the most common histological feature in CFLD, focal biliary cirrhosis. The reason for its focality is unknown. The focal biliary cirrhosis slowly develops into MLC without any symptoms (Debray *et al.*, 2011).

Most commonly, only patients with two severe mutations (class I–III) and pancreatic insufficiency develop MCL (Colombo *et al.*, 2002). No CF mutations have been related to more severe liver disease and the liver phenotype in patients with the same genotype varies. Modifying genes have been sought but, so far, only the *SERPINA1* Z-allele shows an association with MLC and PHT (Bartlett *et al.*, 2009).

Other liver involvement Neonatal hyperbilirubinaemia can be associated with CF but normally resolves spontaneously (Shapira *et al.*, 1999). Liver enzymes are often raised during the first year after diagnosis and not related to later severe liver disease. Up to 75% have steatosis of differing degrees, most probably related to nutritional deficiencies. Massive steatosis in the early years has become less common, probably due to improved care and nutrition. Currently, steatosis in CF is considered a benign condition not related to the development of MLC.

Screening for liver disease Since the development of MLC with or without PHT is asymptomatic, screening for CFLD is necessary. At the annual review, liver enzymes and other biochemical markers of liver disease, including alanine transaminase (ALT), aspartate transaminase (AST), serum alkaline phosphatase, γ-glutamyl transpeptidase (GGT), albumin and prothrombin time, and a thorough physical examination must be included. Regular ultrasound of the liver and the biliary tract are often performed, at least during childhood and adolescence, and are suggested if the liver enzymes are raised at the annual review. The presence of CFLD should be suspected when the liver enzymes (ALT, AST and GGT) are raised three times over a 12-month period after excluding other causes of liver disease, and ultrasonography shows hepatomegaly/splenomegaly, increased/irregular echogenicity or irregular margins. Signs of PHT are leukopenia, thrombocytopenia and splenomegaly. It is important to emphasise that not all patients developing CFLD display pathologically increased liver enzymes and ultrasonography may be even more sensitive than clinical or biochemical abnormalities. In some situations, liver biopsy can be indicated (Debray *et al.*, 2011).

Treatment The liver disease in CF develops slowly, and may remain stable for years and maybe decades. In many cases, liver transplantation is not needed. Based on the hypothesis that the starting event of CFLD is bile duct obstruction, UDCA, a bile acid that has hydrophilic and choleretic properties and may act as a cytoprotective agent, is used for treatment of CFLD, mostly in Europe. Although evidence of an effect on the level of liver enzymes, biliary drainage, ultrasound changes and possibly liver histology exist, there is no information about long-term effects of halting the progression of CFLD. It has been suggested that patients would gain from early treatment when there are less severe pathological changes, although there is no evidence to support this. The recommended starting dose is 20 $mg \cdot kg^{-1} \cdot day^{-1}$ (Debray *et al.*, 2011). Common recommendations include contraindication of salicylic acid and nonsteroidal anti-inflammatory drugs, vaccination against hepatitis A and B, and special attention to nutritional status to ensure adequate caloric intake (increase energy intake, and enteral nasogastric feeding when awaiting a liver transplant).

All patients with signs of CFLD should be evaluated by a paediatric gastroenterologist with knowledge of liver disease in CF.

CF-related diabetes

CF-related diabetes (CFRD) is the most frequent comorbidity in CF. Starting with a prevalence of <3% at the age of 10 years, the prevalence increases and peaks at 25–30% at 35–40 years. CFRD mimics some aspects of type 1 and other aspects of type 2 diabetes (Moran *et al.*, 2010a): it is an insulin-deficient status but with some remaining insulin secretion. CFRD is associated with a faster decrease in lung function, weight loss and reduced survival compared with age- and sex-matched nondiabetic CF patients. It is difficult to diagnose CFRD at an early

stage because typical clinical symptoms are often absent. There is no simple laboratory test to screen for CFRD. Glycated haemoglobin (HbA1c), as a single laboratory marker, will miss ~30% of all CF patients with CFRD. The oral glucose tolerance test (OGTT) is the "gold standard" for diagnosing CFRD (Moran *et al.*, 2009a). Some specialised centres use continuous glucose monitoring, a more sophisticated method for early identification of CF patients with CFRD. Annual OGTTs starting at the age of 10 years are a recommended screening procedure for CFRD. Screening for CFRD is especially important for patients who are on nocturnal feeding, pregnant, experiencing a severe acute exacerbation or on systemic steroids.

It is well accepted to start treatment of CFRD independent of fasting hyperglycaemia (Moran *et al.*, 2009b). Clinical studies in the last 15 years have shown positive clinical effects of insulin treatment of CFRD, with an increase in lung function and nutrition, and decreasing risk of exacerbation. The recommendation is initially single insulin doses with main meals and adding long-acting insulin as soon as fasting hyperglycaemia is observed (Moran *et al.*, 2009a; UK Cystic Fibrosis Trust Diabetes Working Group, 2004). In general, nutritional advice differs significantly between diabetes treatment in general and in the case of CFRD. CF patients have to maintain a high caloric intake not to lose weight. Management of CFRD must be individualized (UK Cystic Fibrosis Trust Diabetes Working Group, 2004). Oral antidiabetic drugs have been used in the treatment of CFRD. Up to now, prospective randomised controlled clinical studies demonstrating a positive clinical effect of these drugs in the treatment of CFRD are lacking. The use of oral antidiabetic drugs is therefore not recommended outside clinical trials. Late complications of CFRD are well described for microvascular (retinopathy, neuropathy and nephropathy) but not for macrovascular diseases (van den Berg *et al.*, 2008). CF patients on insulin should participate in CFRD education programmes and follow their treatment like other diabetic patients, including self-managed glucose measurements, blood pressure control and 3-monthly HbA1c measurements. The aim is HbA1c <7% and no hyper- or hypoglycaemic situations. The risk of hypoglycaemia is real and must be addressed with education of the patient and monitoring of blood glucose levels. Since ketoacidosis is untypical in CFRD, in these rare cases, type 1 diabetes must be excluded. In CF centres, treatment of CFRD is by a team approach including pulmonologists, diabetologists, dieticians and psychologists.

Sinus disease in CF

Sinus abnormalities are prevalent in CF and chronic rhinosinusitis has been shown in up to 74–100% of the patients, increasing with age, but is not always symptomatic. The pathophysiology is unclear but is believed to be a combination of increased viscosity of mucus, decreased clearance and chronic infection (Schraven *et al.*, 2011). Problems from the upper airways should be handled in close cooperation with an otolaryngologist with experience of CF sinus disease.

Common radiological findings are frontal sinus agenesis/hypoplasia and opacification of the maxilla ethmoid sinus. There is no or only low correlation of CT findings with symptoms. Nasal polyps are common from childhood, increasing with age. Symptoms of the upper airways, like nasal obstruction, chronic or recurrent headache due to sinusitis and anosmia/hyposmia, are frequently found when the patient is asked and it is important to include these symptoms in the annual assessment.

Medical management includes nasal steroids, saline irrigation and antibiotics (adapted to local sampling). The type of bacterial colonisation of the upper airways may differ from the colonisation of the lower airways. Up to 25% of cases undergo sinus surgery, where endoscopic sinus surgery has been more successful than polypectomy alone or Caldwell Luc procedures (Haworth, 2010).

CF-associated osteoporosis

Osteoporosis is a common medical problem in adults with CF. Although osteoporosis is

seldom symptomatic in the paediatric age group, osteopenia/osteoporosis starts during childhood/adolescence. It is therefore of vital importance that this problem is addressed during these age periods, with special attention to the risk factors mentioned below, to be able to decrease the prevalence of osteopenia/osteoporosis in adults.

The pathogenesis is a combination of factors: malnutrition/malabsorption, delayed puberty and hypogonadism, vitamin D and K deficiency, systemic inflammation due to pulmonary infections, use of oral glucocorticosteroids, low activity level and possibly a direct effect of CFTR dysfunction on bone cells (Aris *et al.*, 2005).

For the recommended frequency of performing dual-energy X-ray absorptiometry (DEXA), refer to the Further reading list. At all ages, the frequency of DEXA should be increased if there are significant risk factors or before prescribing bone protective therapy.

Preventive measures rely on normal nutritional status, weight-bearing exercise, supplementation with cholecalciferol to achieve optimal plasma 25-hydroxyvitamin D levels, high dietary intake of calcium and possibly supplementation with vitamin K_1 (Aris *et al.*, 2005; Sermet-Gaudelus *et al.*, 2011).

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Emerging treatment strategies in CF

Melinda Solomon and Felix Ratjen

Traditionally, treatment has included airway clearance therapies, and inhaled and systemic antibiotics, as well as strategies to improve nutritional status. More recent therapeutic interventions have focused on correcting the protein defect or the abnormal ion composition in the CF airway. The hope is that this form of therapy/intervention could change the prognosis of CF patients by altering the disease progression.

Key points

- Despite the successes of CFTR modulation, treatment of infection and inflammation remain important targets.
- Therapeutic options in CF are increasing rapidly.
- CFTR directed pharmacotherapy is moving into the clinic.

CFTR pharmacotherapy

Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations result in protein dysfunction by affecting a variety of different steps in CFTR protein production and function, including synthesis, maturation, intracellular transport, epithelial expression and gating function (fig. 1). CF drugs are currently being evaluated to improve CFTR protein expression at the cell surface and/or CFTR function. CFTR pharmacotherapy affects aspects of disturbed intracellular function including protein trafficking, CFTR expression or function of CFTR at the cell membrane. Therapies currently being evaluated target class I to III mutations, but it is important to recognise that these therapies could potentially also benefit patients with class IV and V mutations as well.

CFTR potentiators Class III mutations are characterised by a reduced opening probability of the CFTR channel, but the CFTR expression at the cell surface is not altered. Potentiators are pharmaceuticals that increase the probability of the CFTR channel opening.

Ivacaftor (previously VX-770) is an orally bioavailable CFTR potentiator with impressive clinical efficacy and a good safety profile. Studies have focused on CF patients carrying the most common gating mutation (G551D), but clinical trials for other mutations in this class are currently under way. In patients carrying at least one allele of G551D, ivacaftor was found to improve ion transport as illustrated by nasal potential difference measurements and to reduce sweat chloride concentrations after oral administration of the drug in CF patients. The mean sweat chloride concentrations in treated patients fell below 60 $mmol \cdot L^{-1}$; the diagnostic threshold for making a CF diagnosis. This effect has not been observed for any other treatment in CF care. Significant clinical effects included a more than 10% absolute change in FEV_1, reductions in pulmonary exacerbations and improvements in symptom scores. This medication was approved by the US Food and Drug Administration in 2012 for patients older than 6 years of age with a G551D mutation and has recently received approval in Canada and Europe as well.

Defect classification	Normal	I	II	III	IV	V
						
Defect result		No synthesis	Block in processing	Block in regulation	Altered conductance	Reduced synthesis
Types of mutation		Nonsense; frameshift premature stop codon (G542X)	Missense; amino acid deletion (ΔF508)	Missense; amino acid change (G551D)	Missense; amino acid change (R117H) (R347P)	Missense; amino acid change (A445E) alternative splicing
Potential therapy		Ataluren	CFTR corrector (VX-809)	Ivacaftor (Kalydeco)	Ivacaftor? (Kalydeco)	Ivacaftor? (Kalydeco)

Figure 1. Potential options of CFTR directed therapies. Reproduced from Welsh (2001) with permission from the publisher.

While these gating mutations are relatively rare, this has proven the concept that CFTR directed pharmacotherapy can have significant beneficial effects in patients that exceed the efficacy of any other treatment previously studied in this disease.

CFTR correctors Class II mutations, such as the most common mutation, F508del, result in misfolded CFTR protein which, when expressed at the apical membrane, has some chloride conducting ability, but with a much shorter half-life than wild-type CFTR. Most of this misfolded protein will be recognised as abnormal by the intracellular quality control machinery and degraded prior to leaving the endoplasmic reticulum. Thus, a potential treatment strategy is rescue of CFTR (rescue from endoplasmic degradation). Compounds that result in CFTR rescue are called 'correctors' referring to their effect on correcting the intracellular trafficking defect. A number of drugs have been identified to potentially improve mutated CFTR processing using high-throughput assays to screen libraries of known therapeutics. The lead compound is currently called VX-809 and has recently shown some promising results in early phase clinical studies. In CF patients homozygous for the F508del mutation, oral application of the compound VX-809 was well tolerated and there was a dose-dependent effect on sweat chloride levels at higher doses, suggesting an effect of this drug on F508del activity. However, no change in lung function was observed.

It is important to appreciate that CFTR corrector therapy alone may not be sufficient to induce a clinically meaningful response and for this reason VX-809 is currently being studied in combination with a CFTR potentiator to enhance activity (described below).

Combining potentiator and corrector While VX-809 is designed to move CFTR to the cell surface, ivacaftor is intended to improve the protein's function once it has reached the cell surface. A recently completed phase II clinical trial studying multiple dose

combinations of ivacaftor with VX-809 showed improvements in lung function in CF patients with two copies of the F508del mutation at higher doses of the drug combination; VX-809 alone did not have any effect on lung function and no effect was seen in a group of patients heterozygeous for this mutation. The effect size for this drug combination in F508del patients was much smaller than the one observed for ivacaftor alone in G551D patients indicating that CFTR pharmacotherapy addressing intracellular trafficking is a much more difficult target. This is not surprising as intracellular trafficking involves multiple steps; each of which could be a potential target for therapy. Other correctors are currently in development and future therapy may require the combination of more than one corrector plus a potentiator, such as ivacaftor.

Suppressors of premature stop codons Premature termination codons (PTCs) are the cause of CF in only 5% of cases in countries other than Israel, where class I mutations are more frequent. This potential treatment strategy will be an option for only a small fraction of the CF patient population. Aminoglycosides have been shown to induce read through of PTCs (class I mutations) in CF. The first drug to have shown this effect is gentamicin. Ataluren, previously called PTC 124, has been developed as a compound sharing the action on stop codons, but lacking both aminoglycoside antibiotic function and toxicity. It is an oral medication. *In vitro* studies have shown that ataluren improves read through of stop codons without affecting nonsense mediated decay, which is an important cellular mechanism that is needed to protect the cell from dysfunctional proteins. So far, data from phase II clinical studies in CF patients have been variable in terms of treatment response suggesting that it may not be equally effective in all CF patients within a given class of mutations.

Recently a phase III clinical trial of ataluren has been completed. Study participants who received ataluren showed a trend towards a lower decline in lung function and a lower rate of pulmonary exacerbations compared with the placebo group. A stronger effect was seen in patients not receiving inhaled antibiotics as inhaled tobramycin may potentially interfere with the effect of this drug. Therefore, the current evidence for its efficacy is not convincing and it may be that only a subgroup of patients will respond.

Many patients carrying stop mutations in one allele are also compound heterozygotes for F508del and potentially a combination of drug therapy directed toward a PTC could be combined with CFTR corrector therapy in the future. Alternatively, an effective therapy for stop mutations could be combined with a potentiatior such as ivacaftor thereby maximising the function of any CFTR protein expressed at the cell surface.

Gene therapy: CFTR replacement therapy The goal of gene therapy in CF is that delivery of a normal CFTR gene to the lung would result in expression and restored function of CFTR in the CF airway epithelium. There are several challenges, including: which vector to use for gene delivery and the problem of short-term gene expression, which would require repeated dosing. Viral vectors like adenovirus seem more efficacious, but more likely to cause side-effects compared to liposomal vectors which demonstrate lower transfection efficacy. Gene therapy is currently not close to clinical use, but a multi-dose clinical trial conducted by the UK Gene Therapy Consortium using a liposome vector is currently on its way.

Mucus hydrators

Inhaled hypertonic saline Dysfunction of the CFTR protein results in an imbalance of ion homeostasis and consequently dehydration of airway secretions. This leads to disruption of ciliary function and mucociliary clearance. A treatment option addressing the depletion of airway surface liquid in CF is the inhalation of hypertonic saline solution. A study in Australia showed that inhaled hypertonic saline improves mucociliary clearance in a dose-dependent fashion up to 7% hypertonic saline. A double-blind parallel group (7% hypertonic saline *versus* 0.9%

normal saline) treatment trial showed a small absolute difference in lung function between the two groups, and significantly fewer pulmonary exacerbations for the group treated with 7% hypertonic saline. Inhaled hypertonic saline is now part of standard of care in most centres. The beneficial effects are probably multi-factorial including:

- effect on mucus hydration,
- improved mucociliary clearance,
- increase of airway-surface liquid height,
- cough induction.

Inhaled hypertonic saline is known to be safe to use in infants with CF. However, a recent study did not show clear effect of treatment on pulmonary exacerbation in infants and young children and the role of hyertonic saline in this age group is still unclear.

As hypertonic saline is an irritant for the airways, it is recommended to test tolerability in patients in the clinic before initiating long-term therapy. It should be used only after pre-treatment with a bronchodilator, such as salbutamol.

Mannitol Mannitol was developed as a dry powder formulation as an alternative treatment to hypertonic saline. It has been used as a hyperosmolar agent used to encourage the flux of water across the lung surface to improve mucociliary clearance. Phase II and III trials show promising evidence that long-term inhalation of mannitol improves lung function in patients with CF and decreases the frequency of pulmonary exacerbations. The main side-effect is bronchoconstriction and associated cough. At the present time mannitol is only approved for treatment in CF in Australia and for adults in Europe, but additional studies in children are under way.

Sodium channel blockers

Decreased CFTR-related chloride secretion, in association with increased sodium and water absorption, results in depletion of airway surface liquid. Theoretically, amiloride improves mucociliary clearance by blocking airway epithelial sodium channels (ENaC) and expanding airway surface liquid. Unfortunately, trials of topical administration of this short-acting sodium channel blocker in CF patients did not show any evidence that it improves lung function and one study showed that it may even deteriorate lung function. Newer studies are looking at novel ENaC blockers that are more potent and less reversible than amiloride.

Modulators of ion channel function

Chloride channels other than CFTR exist and a calcium dependent chloride channel has been shown to secrete chloride in epithelial cells. Therefore, increasing the activity of alternative chloride channels in CF airways could potentially be therapeutic. Two drugs have been in clinical trials. Lancovutide, previously known as Moli 1901, is a chloride transport activator that was studied and, initially, showed some early promising results. A large trial was completed in Europe, but did not show clear evidence of efficacy.

Denufosol, a $P2Y_2$ agonist designed to restore chloride transport and to increase mucocilicary clearance, also yielded promising results in early phase studies but ultimately showed nonsignificant results compared with placebo in a large confirmatory trial. Therefore, there is currently no ion channel modulator that is close to clinical use.

Modulation of airway inflammation

The beneficial effects in anti-inflammatory treatments, such as systemic steroids, have been outweighed by the risks, which are related to the side-effect profile. In addition, the use of non-steroidals has also been studied, but the side-effects of gastrointestinal bleeds and potential nephrotoxicity has prevented more extensive use.

Oral N-acetylcysteine Oral *N*-acetylcysteine has also been studied and although it is well tolerated and does not cause significant adverse effects, the trials have not shown significant pulmonary function test improvements or significant clinical benefit. However, in one study there was marked

post-treatment decrease in elastase activity, which needs to be confirmed before treatment can be recommended.

Inhaled glutathione Reduced glutathione is known to be decreased in the bronchoalveolar lavage fluid in CF patients. Glutathione is a major antioxidant and mediator of cell proliferation. Inhaled glutathione has been used as a means to modify CF respiratory tract oxidative processes. A few small studies have shown mild improvements in the pulmonary function in CF patients but larger, longer studies are required. At this time there is inadequate evidence to recommend inhaled glutathione as a treatment for CF patients.

Anti-protease therapy is currently being evaluated, but the studies are still in early stages. The most convincing effect to date has been seen with drugs that target both infection and inflammation, such as azithromycin.

Azithromycin Azithromycin has both anti-infective and anti-inflammatory properties. In CF, recurrent airway infections and chronic inflammation result in progressive airway damage. Treatment with azithromycin in subtherapeutic doses for an antibiotic effect has been shown to improve lung function and decrease exacerbation rates in CF patients who are chronically infected with *Pseudomonas aeruginosa*. Furthermore, a randomised, placebo-controlled trial of azithromycin in CF patients with *P. aeruginosa* showed a significant reduction in both oral and parenteral antibiotic use and significant weight gain in the treatment group. The mechanism of action is still not completely clear. Azithromycin is also used to treat bronchiolitis obliterans, a condition not associated with chronic infection. This would support the idea that a major factor of its effect is its anti-inflammatory properties.

A more recent study showed no improvement in pulmonary function in children and adolescents with CF uninfected with *P. aeruginosa*, who were treated with azithromycin for 24 weeks. However, the treatment group had a significant decrease in the frequency of pulmonary exacerbations and an increase in body weight.

It is important to assess patients for atypical mycobacterial infections by sputum culture prior to starting azithromycin, as this could be subtherapeutic/partial treatment for these organisms. In addition, there is some recent evidence suggesting that azithromycin may predispose patients to mycobacterial infection.

Antibiotics

Chronic infection continues to be a significant challenge in CF care. *Pseudomonas aeruginosa* is one of the major pathogens in CF lung disease and has been a major target for antibiotic therapy. The reasons for failure of antibiotics to eradicate mucoid *P. aeruginosa* are multiple and may include:

- high bacterial loads,
- bioflims,
- poor penetration of antibiotics into the mucus,
- antibiotic resistance.

Recent anti-infective tactics have utilised currently available antibiotics in inhaled forms. Inhalation of antibiotics allows higher concentrations at the location of the infection, while decreasing the potential systemic side-effects that could occur with oral or parenteral treatment. Early eradication of *P. aeruginosa* to delay the establishment of chronic infection is also very important and the use of tobramycin inhalation solution alone has been shown to be highly effective.

Chronic maintenance therapy for *P. aeruginosa* consists of the inhalation of antibiotics such as tobramycin and colistin. Tobramycin can be administered as a nebulised solution and more recently has been introduced as a dry powder formulation (tobramycin inhalation powder), allowing shorter administration time and greater portability. Aztreonam lysinate for inhalation is currently available and is being utilised as an alternative to inhaled tobramycin by either adding it during the off months of cycled tobramycin

or as a replacement for tobramycin inhalation.

Other inhaled antibiotics being developed and studied include inhaled liposomal amikacin, ciprofloxacin inhaled powder, inhaled levofloxacin and fosfomycin.

Conclusion

Many new therapies are currently in development and will probably change our therapeutic approach in the near future. The goal for emerging therapies is to find treatments that slow down the progressive decline in lung function, decrease hospital admissions, and improve quality of life. The success of ivacaftor, a CFTR potentiator, demonstrates that this approach is feasible, but not yet available for many patients. As we learn more about CFTR mutation-specific abnormalities we can hopefully decrease symptoms, decrease treatment burden, and improve the outcome for CF patients. While treatment strategies targeting the basic defect have the highest likelihood of changing patients' outcomes, it is important to explore new therapies for other targets including infection and inflammation.

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Prognosis, management and indications for lung transplantation in CF

Helen Spencer and Andrew Bush

The CF patient with end-stage or rapidly deteriorating lung disease will usually have been followed up in a specialist centre for many years, with intensive therapeutic attempts to improve lung function. Part of the management should be a detailed re-evaluation of all aspects of care to ensure that nothing has been missed.

The nature of the problem

The combined Royal Brompton Hospital/ Great Ormond Street Hospital (both London, UK) experience of death and transplantation in CF in the decade 2000–2009 was of 1022 children cared for, there were 11 deaths (median age 14.2 years) and eight transplantations (median age 13 years), with a female predominance for both. Of note, spirometry 5 years before death was not predictive. This is in agreement with an adult study which showed that median survival for patients with an FEV_1 <30% predicted had increased from 1.2 years in the 1991 cohort to 5.3 years in the 2003–2004 cohort. In the paediatric series all but one of the children had severe obstructive lung disease, and most were being actively managed at the time of death; most deaths were in the paediatric intensive care unit (PICU). A key message from these two studies and other data is that spirometry is a poor predictor of prognosis, although frequently used clinically as such.

Key points

- Every effort should be made to optimise standard therapy in patients with apparently end-stage CF lung disease.
- Prediction of prognosis in end-stage CF lung disease is difficult, and more prolonged survival than previously expected can be anticipated.
- Timely referral for lung transplant assessment is essential to maximise chances of benefit.

Lessons from problematic severe asthma: are the basics right?

More than half of all children referred to the Royal Brompton Hospital quaternary referral severe asthma service for consideration of "beyond guidelines" therapy in fact do not have severe asthma at all, but merely need to get the basics right for good asthma control to be restored. No comparable study has been performed in CF, but it seems likely that similar issues are present in what we term "challenging CF" (table 1). The definition is somewhat arbitrary; it should be noted that children may become challenging very quickly (*e.g.* failure to improve after two or more courses of intravenous antibiotics in quick succession) or gradually, with a series of small, almost subclinical, deteriorations.

Experience from asthma has identified four key areas often needing attention as:

- medication adherence and administration;
- adverse environmental circumstances, particularly environmental tobacco smoke;
- allergen exposure;
- psychosocial factors.

Table 1. Definition of challenging CF

Lung function is ⩾2 Z-scores below normal from the CF-specific charts
At least three courses of *i.v.* antibiotics annually (whether planned electively or unplanned)
Requirement for home oxygen or nasal mask ventilation
Nutritional failure: BMI ⩽2 Z-scores below the mean; drop in weight or BMI centiles by 10% over 1 year
Any severe CF pulmonary complication, such as massive haemoptysis, pneumothorax, therapy-resistant ABPA or other causes of oral severe steroid dependency
Any child whose self- or parent-reported symptoms are significantly different to those expected by a clinician (either overestimated or underestimated)
Any child in whom there is refusal or extreme reluctance to give prescribed treatment by the carers
Note, that these are arbitrary and not evidence based.

In the context of asthma, a nurse-led home visit is often enlightening, and perhaps this should be used more in CF. Adherence is notoriously difficult to judge in the clinic; doctors obtain prescription records (acknowledging that collecting a prescription does not mean that the medication has been administered, but failure to collect prescriptions does guarantee non-adherence) and the nurses assess the availability and accessibility of medications in the home, and whether they are in date. Obviously inhaler and nebuliser techniques are also checked. More objective data about nebuliser usage can be downloaded from the microchips in some modern nebulisers. Active and passive tobacco smoke exposure is checked by measuring urinary or salivary cotinine. Allergic sensitisation and allergen exposure is less important in CF than in really severe asthma, but should at least be considered in the atopic CF patient. Finally, psychosocial factors are explored. Most referrals in the asthma context are made after discussions in the home, where families are much more ready to discuss personal matters. It is suggested that adaptations of this sort of approach may be beneficial in challenging CF. This should include ensuring that all standard therapies have been trialled, or discarded as having not been beneficial, including nebulised antibiotics, rhDNAse, hypertonic saline and azithromycin, certainly before deploying some of the experimental therapies described below.

Is the diagnosis really CF?

This may seem an odd question, but it is important for two reasons. First, if the diagnosis is wrong it is important to determine whether there is a disease-specific treatment for what is actually the problem, for example bone marrow transplantation for certain immunodeficiencies. Secondly, innovative therapies are increasingly being discovered that are CF gene mutation or mutation class specific. It would be ludicrous to try to apply these therapies to a patient who did not have CF! So, it is essential to make every effort to establish the genotype of the patient with whole gene sequencing if this has not already been done, to check eligibility for these potential treatments. The Clinical and Functional Translation of CFTR website (www.cftr2.org) provides current knowledge of the probable disease causing status of rare mutations and should be consulted in cases of doubt.

Management of end stage lung disease: pulmonary aspects

Our experience is that there are two main types of end-stage lung disease: the more common is characterised by severe bronchiectasis, chronic infection and

copious purulent secretions. Less usually, a so-called "dry and distal" lung disease is seen, characterised by distal airway obstruction and air trapping with no or minimal bronchiectasis, and little or no sputum production. The evidence for the existence of the dry and distal phenotype is based on personal experience and case reports, although we suspect most experienced CF physicians will have seen cases. There is little or no evidence base for the treatment of either phenotype, but suggested lines of management differ. The evidence for most is so scanty that the right approach is to discuss options with the patient and family, and form an individualised plan on the basis of those discussions.

Are resistant or unusual microorganisms present? Standard sputum culture, if available, will identify most of the common pathogens, but other samples should be considered. Bronchoscopy and bronchoalveolar lavage is considered the gold standard, but there are regional variations in culture results and not all lobes are usually sampled. Induced sputum may have a greater yield than spontaneously expectorated. Both techniques should be used with caution in patients with severe airway obstruction. Infection with nontuberculous mycobacteria appears to be becoming increasingly common and *Mycobacterium abscessus*, in particular, may be associated with decline in lung function. A HRCT scan should be considered to look for suggestive features, such as the presence of extensive tree-in-bud. If re-evaluation results in the detection of new microorganisms, then energetic attempts should be made to eradicate them.

Recent molecular microbiology studies have shown that CF is a far more polymicrobial disease than was previously thought and, in particular, anaerobes may be as prevalent as *Pseudomonas aeruginosa*. End-stage CF seems to be characterised by loss of bacterial diversity, but it is not known whether this is as a reflection of disease progression or as a consequence of multiple courses of antibiotics. The interpretation of these very sensitive molecular techniques is unclear, and how (if at all) they should be used to guide treatment at any stage of disease is unknown. In the context of end-stage lung disease, it might be worth considering molecular studies and intensive treatment of any dominant organism, particularly if frequently detected. Certainly, an empirical trial of anti-anaerobic antibiotics should be considered, in particular if there is severe bronchiectasis.

Use of antibiotics in end-stage CF lung disease Any isolated Gram-negative rods should have extended sensitivities performed; occasionally they may be sensitive to unlikely oral antibiotics such as minocycline. While accepting that the link between *in vitro* sensitivity and clinical efficacy is at best weak, there would seem to be little to be lost by prescribing an oral antibiotic to which the organism appears to be sensitive, at least in the laboratory.

Most, if not all, patients with end-stage lung disease, especially those with severe bronchiectasis, will have been prescribed either inhaled tobramycin or colistin because of chronic infection with *P. aeruginosa*. Particularly in those patients with severe bronchiectasis, a trial of nebulised aztreonam lysine should be considered, also rotating combinations of nebulised antibiotics, such as tobramycin, with alternate months of aztreonam. There is some evidence that combined nebulised tobramycin and amiloride may be effective against some genomovars of *Burkholderia cepacia*. Combinations of nebulised fosfomycin and tobramycin have also shown efficacy against some antibiotic-resistant organisms.

Intravenous antibiotics should be used liberally. Most would use planned regular (usually 3-monthly) courses, with interval courses as needed. The optimal duration of such courses is not known, but it is likely that longer than the conventional 10–14 days will be beneficial. Anecdotally, we have used intravenous colistin for many consecutive weeks in this situation. Here, as elsewhere, there are no randomised

controlled trial data to guide the paediatrician.

Antibiotic allergy is a frequent problem in CF. A history of possible allergic reactions should be taken and cautious challenge testing should be performed in conjunction with an experienced allergist to determine which antibiotics truly cannot be used without desensitisation. The transplant centre should be contacted to discuss whether desensitisation to particular antibiotics would be helpful.

Optimising airway clearance A very experienced physiotherapist should assess the patient. There are numerous aids to sputum clearance, including positive airway pressure and external oscillation, and all options should be reviewed. Anecdotally, cough-assist devices have been beneficial in some patients, despite fears that the negative pressure phase might lead to airway collapse if there is significant bronchomalacia.

Clinically significant expiratory muscle dysfunction is rarely, if ever, seen in CF, so cough strength should be normal. However, stress incontinence is common in both sexes in CF, even in children, and this may lead to reluctance to cough forcefully. Tactful questioning should elicit whether this is a problem and, if so, referral for treatment is mandated.

Pharmacological adjuncts to mucus clearance include rhDNase, hypertonic saline and inhaled mannitol. There is marked and unpredictable individual variation in response to these agents, and all should be trialled. Combinations should be considered, with two caveats. The first is adherence; it is all too easy to overburden the patient with excessive numbers of nebulised therapies, in particular. The second is the theoretical possibility that therapies may be antagonistic, as was found in one study when mannitol and rhDNAse were combined.

Anti-fungal therapies It used to be thought that *Aspergillus fumigatus* was only a significant problem in CF if it caused allergic bronchopulmonary aspergillosis (ABPA). However, there is increasing evidence that airway infection *per se* is associated with worse lung function and an increased rate of exacerbation. In the setting of end-stage lung disease, we recommend intensive anti-fungal treatment if *A. fumigatus* is isolated. Itraconazole is poorly absorbed, and in this setting we would use prolonged courses of voriconazole, posaconazole or even intravenous liposomal amphotericin B. Anecdotally, nebulised amphotericin (standard or liposomal) has been used, but again the question of not over-burdening the child with multiple treatments must be considered.

Corticosteroids and other standard treatments We know that the inflammatory response is protective, and indeed in CF anti-inflammatory therapy with a leukotriene (LT)B_4 antagonist actually led to more infective exacerbations. Conversely, we know that at some stages of CF (those patients chronically infected with *P. aeruginosa*) prednisolone improves spirometry, albeit at the cost of unacceptable side-effects. Various anti-inflammatory strategies may be tried especially in dry and distal disease. A trial of systemic corticosteroids is the first to be considered, balancing the risks of worsening CF-related diabetes and reducing bone mineral density against possible benefit. Dry and distal disease is treated with pulsed intravenous methyl prednisolone (500 $mg \cdot m^{-2}$) on 3 successive days every 4 weeks, to try to reverse the airflow obstruction, combining this with high-dose inhaled corticosteroids. A trial of oral prednisolone is indicated in CF patients with severe bronchiectasis but only in those who are atopic and have acute bronchodilator reversibility. If neither of these features is present, we would be reluctant to risk the side-effects of prolonged steroid therapy.

Should oxygen therapy and NIV be initiated? Whereas in hypoxaemic COPD patients there is clear evidence of benefit with oxygen supplementation in terms of survival, there are no such data in CF. Nonetheless, most paediatricians would actively screen for overnight hypoxaemia with saturation

studies, and correct it if present. Assessment by a skilled occupational therapist is mandatory if daytime oxygen is prescribed, to allow mobility to be maintained as far as possible by using lightweight portable systems.

There is no general consensus as to when and how to initiate NIV. Positive-pressure devices may be used to assist daytime sputum clearance by a skilled physiotherapist, with due regard to the risk of a pneumothorax. In terms of use during sleep, polysomnography should be part of the work-up of these patients. If there is clear cut evidence of nocturnal hypercapnia then we would offer NIV, having excluded any upper airway obstruction (*e.g.* due to nasal polyps) as a potential cause of hypoxaemia. If gas exchange is adequate, but work of breathing is high (usually assessed clinically outside a research context), then we would still consider NIV in the hope of improving nutritional status. However, as stated elsewhere in this chapter, more work is needed.

Innovative therapies are mostly used in the dry and distal form of end-stage CF lung disease, and none are evidence based. There are anecdotal reports of success. These include monthly infusions of intravenous Ig, methotrexate and cyclosporine A. In all cases, careful monitoring of response and alertness for side-effects is mandated. In the case of cyclosporine, special care should be taken to monitor renal function, which may already be impaired by repeated courses of intravenous aminoglycosides and CF-related diabetes.

Compassionate ground therapies Kalydeco (ivacaftor, VX-770) has burst on the scene as a paradigm-shifting molecule addressing the basic defect in the class III mutation G551D, rather than the downstream consequences of the cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction, as is the case with the more conventional therapies described above. Although only licensed for G551D, compassionate use could be considered if the funding obstacles can be overcome in the other nine known gating mutations, hence the importance of determining the patient's genotype (some of these nine mutations are not detected on routine testing). CFTR channel opening is a function of the number of apical channels, their open probability and channel conductivity. VX-770 may increase channel opening time in non-gating mutations, and there is interest in combining this agent with potentiators such as VX-809 in class II mutations such as ΔF508. Undoubtedly in these days of internet-based knowledge, families will want to discuss compassionate ground use of some of these and other novel molecular therapies, such as Ataluren (PTC_{124}). This is unexplored territory, but one that paediatricians will need to tackle in the very near future.

Management of end-stage lung disease: extrapulmonary aspects

Optimising nutrition/other diagnoses A full dietetic review is mandatory, because most with end-stage lung disease will be malnourished. Obviously, additional diagnoses which may contribute to malnutrition, such as coeliac disease, should be excluded, and insulin deficiency evaluated. Calorie intake must be maximised, usually *via* a gastrostomy, and overnight and daytime bolus high-energy feeds, if not already instituted, will be required. If a gastrostomy is inserted for the first time consideration should be given to performing a laparoscopic or even an endoscopic fundoplication at the same time if gastro-oesophageal reflux is present.

Insulin deficiency Many patients will already have been diagnosed with CF-related diabetes and will be using insulin; in these patients, diabetic control must be optimised. For others, CF-related insulin deficiency should be excluded by oral glucose tolerance testing, random blood glucose measurements and continuous subcutaneous monitoring. There is evidence that even in those with only occasional peaks of blood glucose, insulin therapy can improve nutrition and lung function.

Gastro-oesophageal reflux This has been realised to be increasingly common in end-stage CF lung disease, and should actively

Table 2. Referral for lung transplant assessment

Referral for lung transplantation should be made when the patient has:
Rapidly declining FEV_1 despite maximal medical therapy (particularly females)
FEV_1 approaching <30%
Frequent hospitalisations for exacerbations
Oxygen dependency
Desaturation with exercise
Requirement for NIV
Recurrent or problematic pneumothorax
Recurrent haemoptysis despite embolisation

be excluded. Bile acids can frequently be found in CF sputum and are associated with increased inflammatory markers, suggesting that we are underdiagnosing this complication. There is no gold standard test, but at the very least 24-h oesophageal pH monitoring should be performed. An isotope milk scan is less invasive, but probably a less accurate way of determining if reflux is present. The role of impedance monitoring is not clear pre-transplant but should be completed post-transplant. Gastro-oesophageal reflux, including non-acid reflux, may be an important factor in the development of post-transplant bronchiolitis obliterans syndrome (BOS).

Bone mineral density Severe osteopenia is a relative contraindication to transplantation, so DEXA scanning and appropriate treatment (calcium supplements, vitamin D and bisphosphonates) should be instituted early if bone mineral density is decreased.

Lung transplant Lung transplant is an accepted therapeutic option for patients with end-stage CF lung disease who are failing maximal medical therapy. Paediatric recipients from the International Society for Heart and Lung Transplantation (ISHLT) international registry had a 5-year survival of 54% for the era 2002–2010.

As previously noted there is no one specific clinical or physiological measurement that portends poor prognosis signifying referral for transplant assessment. Most paediatric centres welcome early referral of patients who are becoming difficult to manage. Early referral before a patient becomes critically unwell facilitates a number of processes:

- careful assessment by a multidisciplinary transplant team,
- suggestions for further clinical optimisation,
- information gathering for the patient, family and medical team and education about the complications,
- intense follow-up required after transplant.

Timely referral allows the patient time to reflect on the risks and benefits of both transplant and the alternative of non-transplant, and also allows the transplant physician to monitor an individual's clinical trajectory over a period of time (table 2).

When to list for transplant? Deciding when to list a patient for transplant is one of the most difficult decisions. A transplant physician's aim is to list a patient early enough that they can survive the possible wait for an organ but not so early that a transplant does not offer a survival benefit. Most centres aim to list for transplant when the predicted chance of surviving 2 years is <50%, although this is an increasingly difficult time-point to identify.

Various survival models have been proposed for CF, all of which are imprecise and not particularly useful for an individual. In practice many clinical, physiological, functional and quality of life factors are

taken into account when deciding when to list.

A controversial paper in 2007 suggested that only five paediatric CF patients had a survival benefit with transplant in their US cohort of 514 patients listed for transplant. One of the main criticisms of this study was that the 5-year waiting list survival was 57% and that there was a significantly lower post-transplant survival than in other studies of a similar population. The higher waiting list survival reflected the fact that USA priority listing used to be based on a time accrual basis rather than clinical urgency, suggesting patients were listed too early. Despite its controversial conclusions the paper raises important questions about how we measure the success of transplant, and whether survival benefit is the only valid measure of success or whether quality of life is just as important.

It is important for the CF centre to have an understanding of how the local transplant centre makes decisions about listing and organ allocation. In the UK each transplant centre manages their own waiting list and will have local knowledge of clinical urgency of patients and their own average waiting list times. Other countries have adopted a national waiting list and have used various lung allocation scores (LAS) incorporating factors predicting clinical urgency and probable post-transplant outcome to try and make the best use of available organs.

Unfortunately, lack of donor organs continues to be a major problem, leading to a waiting list mortality of 30–40% in the UK. Expansion of the donor pool is likely in the coming years with the increasing use of non-heart beating donors as well the more conventional heart-beating donors. EVLP programmes (*Ex vivo* Lung Perfusion; a system for reconditioning cadaveric lungs deemed untransplantable) are also likely to boost the number of donors available, with possible use of upper lobes for children when the whole lung cannot be used for adult recipients because of lower lobe consolidation.

What are the contraindications to transplant?

To make the best use of the limited and precious organ resource it is incumbent on the transplant community to transplant patients only if there is a good chance of a successful outcome. It is essential to ensure that there are no major or not too many relative contraindications. Although centre-specific decisions are made in some grey clinical areas there are a number of agreed major contraindications.

- Malignancy in the last 2 years (excluding certain skin cancers).
- Untreatable dysfunction of another major organ system (although lung/another organ transplant can be offered at some centres).
- Infectious diseases: chronic hepatitis B, chronic hepatitis C (biopsy proven), human immunodeficiency virus.
- Active pulmonary TB.
- Refractory non-adherence.
- Significant chest wall/spinal deformity.
- *Burkholderia cenocepacia* (previously BCC genomovar III) is a contraindication in all UK centres.
- Absent or unreliable social support system.

The relative contraindications are:

- critical condition, *e.g.* mechanical ventilation, sepsis, extracorporal membrane oxygenation (ECMO) and shock;
- colonisation with highly resistant bacteria, nontuberculous mycobacterium and fungi;
- severe osteoporosis;
- grossly abnormal BMI (high and low).

Although invasive ventilation or ECMO were previously felt to be absolute contraindications to transplant because of poor outcomes, recently there have been a number of reports of good short-term outcomes in adults in these scenarios. Transplant will only be considered in patients already known to the transplant centre if they have no other significant organ dysfunction. Invasive support systems should only be instigated in end-stage irreversible CF lung disease if the transplant centre feels that the patient has a realistic chance of receiving a suitable organ quickly. This caveat is likely to rule out most

paediatric patients who have much longer organ wait times.

Care of the patient referred and waiting for transplant Adequate preparation, including discussions about prognosis prior to assessment is crucial to give patients and families a realistic picture of transplant. The transplant journey is stressful and the patient and family will need support. Maximal medical therapy should continue once listed for transplant with particular attention to nutrition, bone health, diabetic control and psychological input to address issues such as adherence and needle phobia. Unfortunately, not all patients will receive a transplant and involvement of palliative care should not be delayed because a patient is on a transplant waiting list. A parallel approach of palliation while waiting for transplant is possible and desirable. Some patients may become too sick to transplant and some families prefer to come off the list to focus on end of life care. A sensitive and individualised approach to these difficult issues is essential.

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Airway malformations

Ernst Eber and Andreas Pfleger

This chapter cannot cover the complete spectrum of congenital airway malformations but rather gives an overview of important anomalies (table 1).

Most children with airway malformations are already symptomatic in the neonatal period or in infancy; only rarely are airway malformations discovered incidentally. Early and accurate diagnosis as well as appropriate management is particularly important in children with severe central airway stenoses. Flexible airway endoscopy is the most important diagnostic procedure. In many instances, essential diagnostic techniques are MRI and CT, frequently including angiography (especially preoperatively and in children with associated cardiovascular anomalies).

Depending on the type and severity of the malformation, conservative or surgical management options may be chosen. With airway growth, in particular mild to moderate stenoses in the first years of life frequently become less prominent. Thus, conservative symptomatic treatment and support is often the preferred approach. With adequate management, in most patients the long-term prognosis is favourable.

Key points

- Many children with airway malformations are already symptomatic in the neonatal period or in infancy.
- Airway anomalies are important differential diagnoses in children with many respiratory abnormalities.
- Airway abnormalities may be part of complex syndromes, and in many cases are associated with other congenital anomalies.
- Early, accurate diagnosis and appropriate management is particularly important in severe central airway stenosis.
- With airway growth, mild-to-moderate stenoses in the first years of life frequently become less prominent.
- Depending on the type and extent of the malformation, conservative or surgical management options have to be chosen on an individual basis.
- With adequate management, in most patients the long-term prognosis is favourable.

Nasopharyngeal airway

Choanal stenosis and atresia This malformation represents one of the most common congenital upper airway anomalies (1 in 8000 births). Most cases are due to bony occlusion of the airway; some children show membranous obstruction. About two-thirds of patients with choanal atresia have associated congenital anomalies (*e.g.* CHARGE association). Unilateral lesions are twice as common as bilateral ones.

Bilateral choanal atresia causes immediate respiratory distress at birth; unilateral lesions are often not detected until later in childhood. Some children present with feeding difficulties and persistent

Table 1. Important congenital airway malformations

Nasopharyngeal airway
Choanal stenosis and atresia
Pierre–Robin sequence
Craniofacial malformations
Larynx
Laryngeal atresia
Laryngeal web
Subglottic stenosis
Laryngomalacia (infantile larynx)
Laryngeal cyst
Laryngeal (laryngo-tracheo-oesophageal) cleft
Trachea and bronchial tree
Tracheal agenesis and atresia
Tracheo-oesophageal fistula and oesophageal atresia
Isolated tracheo-oesophageal fistula (H-type fistula)
Tracheomalacia
Tracheal stenosis
Tracheal bronchus and other topographic anomalies
Bronchial atresia
Bronchomalacia
Bronchial stenosis

rhinorrhoea, especially if the patent nostril is occluded during respiratory infections.

Flexible nasal endoscopy and CT can confirm the diagnosis and delineate the exact site of obstruction and also whether it is bony or membranous.

A nasal airway should be established as soon as possible. This can be achieved by a transnasal approach with a dilating instrument and passing airway stents through the nasal passage to ensure continued patency for several weeks. Alternatively, repeated choanal dilatation may be performed at weekly intervals. In severe cases, transpalatal surgery may be required.

Pierre–Robin sequence This anomaly is characterised by micrognathia, glossoptosis, and resultant (pharyngeal) airway obstruction. More than half of affected infants have an associated syndrome, most commonly Stickler syndrome or 22q11.2 deletion syndrome. The severity of airway obstruction is variable. As the mandible grows forward with age, particularly during the first 6 months of life, airway and feeding problems may gradually resolve.

In severe cases, the anomaly can necessitate intubation, especially when associated airway pathologies (*e.g.* laryngomalacia, tracheomalacia) exist. Prone positional therapy has proved to be efficient in mild cases. Airway obstruction may be relieved by a nasopharyngeal airway. Noninvasive respiratory support can relieve upper airway obstruction, with CPAP ventilation in mild and moderate cases, or with noninvasive positive pressure ventilation in severe cases. Surgical procedures include tongue–lip adhesion, mandibular distraction osteogenesis and tracheostomy. Feeding difficulties can be alleviated by upright feeding techniques, modification of the nipple for bottle feeding, temporary use of feeding tubes and the placement of a gastrostomy. Palatal plates such as the pre-epiglottic baton plate with a velar extension pull the base of the tongue forward. This can be helpful in the relief of airway obstruction, facilitates the swallowing mechanism during feeds and accelerates mandibular growth.

Other craniofacial anomalies A number of syndromic craniofacial anomalies can affect the patency of the upper airways. These dysmorphic syndromes are typically characterised by mandibular or maxillary hypoplasia and include Crouzon, Treacher Collins, Apert, Pfeiffer, and Goldenhar syndromes. 36 syndromes with craniofacial anomalies have been found to be associated with one or more of 14 laryngotracheal malformations. Several anomalies such as a narrowed nasopharynx with associated adenotonsillar hypertrophy, midface hypoplasia and hypertrophy of the tongue can cause airway compromise in children with Down syndrome.

Larynx

Laryngeal atresia Laryngeal atresia is a life-threatening malformation, and in the past virtually all affected newborns died. Nowadays, antenatal ultrasound examinations allow diagnosis of the

so-called congenital high airway obstruction syndrome (CHAOS), which may be related to intrinsic causes such as atresia of the larynx or upper trachea or extrinsic laryngotracheal obstruction caused by large masses (*e.g.* cervical teratoma). Identification of the condition by sonography and MRI helps facilitate management, including the *ex utero* intrapartum treatment (EXIT) procedure.

Without antenatal diagnosis, newborns with isolated laryngeal atresia may only survive when emergency tracheostomy is performed immediately after birth. Bag-mask ventilation may save the lives of children with incomplete laryngeal atresia. Laryngeal function in survivors is usually abnormal, and surgical reconstruction is required later in life. The prognosis also depends on the presence of associated malformations (*e.g.* VACTERL association) or syndromic anomalies (*e.g.* Fraser syndrome). Long-term follow-up data after successful EXIT procedure are not yet available.

Laryngeal web Laryngeal webs usually are located at the level of the glottis; supraglottic and subglottic webs may also occur. The webs may be complete or incomplete, and vary in thickness. Incomplete laryngeal webs, usually located anteriorly with posterior openings, are strongly associated with the velocardiofacial syndrome. Complete laryngeal webs present like a laryngeal atresia; symptoms with incomplete webs range from (biphasic) stridor and hoarseness to aphonia and varying degrees of respiratory distress. The diagnosis is established by endoscopy. Treatment options include (laser) excision and dilatation. Sometimes endotracheal intubation solves the problem, but re-stenoses are relatively common. The prognosis mainly depends on the extent of the malformation.

Subglottic stenosis Congenital subglottic stenosis is the second-commonest laryngeal malformation. The more common membranous form is characterised by symmetrical thickening of the soft tissues in the subglottic area. Cartilaginous subglottic stenosis is due to a malformation of the cricoid cartilage, resulting in circumferential stenosis of variable appearance. Myer *et al.* (1994) proposed a grading system for subglottic stenosis based on endotracheal tube sizes (table 2).

The presentation of affected children ranges from severe respiratory distress at birth to the development of inspiratory or biphasic stridor within the first months of life (recurrent or atypical croup). Signs and symptoms clearly depend on the grade of the stenosis. Children with congenital subglottic stenosis are at risk of developing additional acquired subglottic stenosis due to airway trauma (mostly iatrogenic such as prolonged endotracheal intubation or tracheostomy).

Endoscopy is the procedure of choice to establish the diagnosis and to differentiate subglottic stenosis from subglottic haemangioma. Sonography and MRI may be helpful.

As congenital subglottic stenosis generally improves with airway growth, a conservative supportive approach is recommended whenever possible. Surgery should be reserved for severe forms; treatment options include cricoid split, laryngotracheoplasty, and long-term tracheostomy.

Laryngomalacia (infantile larynx) Laryngomalacia is the most common congenital laryngeal anomaly (50–75%) and the most common cause of persistent stridor in children (approximately 60%). The term laryngomalacia suggests that laryngeal cartilage is abnormally soft. However, whether laryngomalacia is primarily an anatomic anomaly or is due to delayed neuromuscular development, is controversial.

Table 2. Grading system for subglottic stenoses

Grade	Degree of obstruction of lumen
I	⩽50%
II	51–70%
III	⩾71% (any detectable lumen)
IV	No detectable lumen

Adapted from Myer *et al.* (1994).

Table 3. Types of laryngomalacia

Type	Characteristics
1	Inward collapse of aryepiglottic folds, primarily the cuneiform cartilages which are often enlarged
2	Long, tubular epiglottis (pathologic exaggeration of the normal omega shape)
3	Anterior, medial collapse of arytenoid cartilages
4	Posterior inspiratory displacement of epiglottis against the posterior pharyngeal wall or inferior collapse to the vocal cords
5	Short aryepiglottic folds

Adapted from Holinger *et al.* (1997).

According to Holinger *et al.* (1997), five types of laryngomalacia can be distinguished (two or more may occur simultaneously) (table 3). Laryngomalacia is frequently associated with other airway lesions and with gastro-oesophageal reflux.

The natural history is characterised by onset of inspiratory stridor usually within the first 4–6 weeks of life; cry and cough are normal. Stridor varies considerably with posture and airflow, is loudest with increased ventilation (e.g. crying, agitation, feeding) and worsens during respiratory tract infections. Some patients will have increasing symptoms during the first few months of life; thereafter, stridor tends to resolve with time. In the very rare severe cases with significant airway obstruction, serious complications such as failure to thrive, pulmonary hypertension and cor pulmonale may develop.

The diagnosis is suspected based on history and physical examination, and confirmed by flexible airway endoscopy. Laryngoscopy demonstrates supraglottic collapse during inspiration (fig.1). Topical anaesthesia can potentially exaggerate the findings; thus, the larynx should be examined before applying topical anaesthesia.

In most cases, apart from parental reassurance and support, no specific therapeutic measures are needed. In severe cases (failure to thrive and/or obstructive apnoeas) surgical treatment (various forms of supraglottoplasty, rarely tracheostomy) is needed. In isolated forms prognosis is excellent, with associated malformations prognosis usually depends on the latter.

Laryngeal cyst Supraglottic cysts, commonly located at the aryepiglottic folds or at the epiglottis, are usually congenital. In contrast,

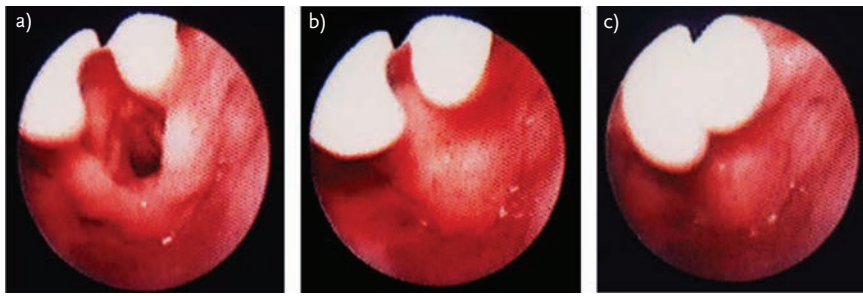

Figure 1. Laryngomalacia (infantile larynx). a) Patent airway during expiration; b) prolapse of arytenoids and aryepiglottic folds into the glottis during mid-inspiration; c) prolapse of arytenoids and aryepiglottic folds and folding of epiglottis along its long axis (''floppy epiglottis'') at end-inspiration, resulting in complete obstruction of the larynx. Reproduced from Eber (2010) with permission from the publisher.

Table 4. Classification system for laryngeal clefts

Type	Characteristics
1	Supraglottic interarytenoid cleft extending inferiorly no further than vocal cord level
2	Cleft with extension below vocal cord level (cricoid cartilage partially involved)
3	Cleft extending through the cricoid cartilage, with or without extension into cervical trachea
4	Cleft with extension into thoracic trachea (may extend as far as the carina)

Adapted from Benjamin *et al.* (1989).

subglottic cysts are usually acquired as a result of airway trauma (*e.g.* endotracheal intubation). The appearance of cysts varies widely; while some are covered by thin mucosa and are easy to recognise, others appear as a submucosal mass. A laryngocele is a rare special form of a laryngeal cyst, which originates from the laryngeal ventricle, consists of an air-filled saccule and may be difficult to diagnose. Infants commonly present with stridor, hoarseness, weak cry or aphonia, and sometimes feeding difficulties. Endoscopy confirms the diagnosis. The treatment of choice is resection of the cyst.

Laryngeal (laryngo-tracheo-oesophageal) cleft

A congenital posterior laryngeal cleft is a rare lesion. Laryngeal clefts may be familial, and may be associated with other anomalies of the trachea or the oesophagus (*e.g.* tracheo-oesophageal fistula) and with multiple congenital anomalies of other organ systems. Several types of clefts are distinguished (table 4); the most common (approximately 50%) is type 1 cleft which should be suspected in infants with laryngomalacia. Anterior laryngeal clefts (*e.g.* bifid epiglottis) are very rare congenital anomalies. While a bifid epiglottis often is associated with other malformations, other anterior clefts appear to be isolated defects.

Aspiration of saliva and food is most likely, and causes coughing, choking, cyanosis, respiratory distress and recurrent pneumonia; stridor results from laryngeal collapse. While infants with type 1 clefts may be asymptomatic, newborns with more extensive clefts may show severe respiratory distress. Diagnosis is often delayed in patients with minor clefts.

A contrast swallow and oesophagogram may be helpful, but airway endoscopy is the diagnostic gold standard (fig. 2). A cleft may be difficult to diagnose with a flexible instrument, as manipulation of the posterior commissure may be necessary to detect the cleft. Rigid bronchoscopy is the ideal technique for the documentation of pathology of the posterior glottis, subglottis, and trachea.

In the absence of complicating factors, treatment is not required for many type 1 clefts. Treatment of gastro-oesophageal reflux, if existing in parallel, is of importance in all patients. Early repair should be sought in children with stable respiratory and nutritional status. Minor clefts (types 1 and 2) may be corrected endoscopically. Surgical repair of type 2, 3 and 4 clefts may be performed through anterior and lateral approaches, often with cardiopulmonary bypass or extracorporeal membrane

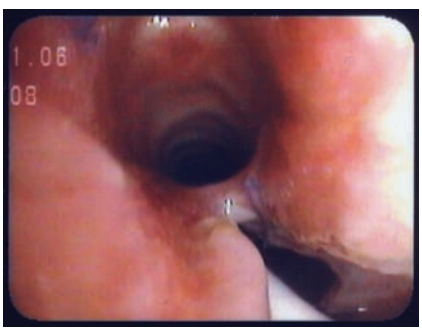

Figure 2. Type 2 laryngeal cleft extending inferiorly to, but not through, the cricoid plate; nasogastric tube in the oesophagus. Reproduced from Eber (2010) with permission from the publisher.

oxygenation (ECMO). Post-operative complications are not uncommon and include tracheo-oesophageal fistula formation and swallowing difficulties. Prognosis depends on the type of the cleft, gestational age, and potentially associated anomalies. For patients with type 1–3 clefts it is favourable.

Trachea and bronchial tree

Tracheal agenesis and atresia Tracheal agenesis and atresia are rare malformations ranging from complete tracheal agenesis to short-segmental atresia, commonly associated with a broncho- or tracheo-oesophageal fistula or other anomalies in various organ systems (*e.g.* VACTERL association). Similar to laryngeal atresia, these malformations are usually lethal. Without antenatal diagnosis affected newborns with short-segment atresia of the proximal trachea may only survive when emergency tracheostomy is performed immediately after birth; in the presence of a fistula or a cleft, intubation of the oesophagus may allow temporary ventilation. After antenatal diagnosis an EXIT procedure may save the life of the affected baby. In those who survive, the short-term prognosis mainly depends on the presence of associated malformations. Long-term follow up data after successful EXIT procedure are not yet available.

Tracheo-oesophageal fistula and oesophageal atresia A tracheo-oesophageal fistula results from a defective separation of the developing oesophagus from the developing lung. Oesophageal atresia is quite common, with an incidence of 1 in 3000 (–4000) births. About 30% of affected children are born prematurely, and more than 50% have associated anomalies (*e.g.* VACTERL association). Various types of oesophageal atresia can be distinguished. The most common type (approximately 85%) is characterised by an upper blind pouch and a fistula between the lower trachea and the lower oesophagus. Structural anomalies of the tracheal wall such as abnormally shaped or hypoplastic tracheal cartilages or a widened pars membranacea (*i.e.* tracheomalacia) are common.

The newborn is commonly tachypnoeic, cyanotic, frothing, and choking despite oral suction. An attempt to pass an orogastric tube should be performed. A chest and abdomen radiograph will show the tube in the upper pouch and may identify pulmonary anomalies, vertebral and/or rib anomalies, and the presence or absence of gas in the stomach, indicating the presence or absence of a tracheo-oesophageal fistula.

Depending on the anatomical situation, associated anomalies and the clinical status of the patient various surgical techniques are recommended. A detailed discussion of surgical aspects is beyond the scope of this chapter.

The postoperative course may be critical due to various complications, such as oesophageal stenosis at the site of anastomosis and recurrence of the tracheo-oesophageal fistula. Gastro-oesophageal reflux and dysphagia are very common and contribute to respiratory morbidity. Tracheomalacia may be severe, sometimes even life-threatening (''blue spells'', ''dying spells''). Many children show the typical brassy ''tracheo-oesophageal fistula (TOF)-cough'', which has been reported to be still present in up to 40% of adults. Recurrent aspiration is frequent and causes bronchitis and pneumonia, causing considerable respiratory morbidity. A missed diagnosis of laryngeal (laryngo-tracheo-oesophageal) cleft or second fistula, or a recurrent fistula should be considered in children with pronounced respiratory symptoms.

Survival largely depends on birth weight, associated malformations, and pulmonary complications. The mortality in children with a birth weight above 2500 g and without other anomalies today is close to zero. In surviving children, the long-term outcome is good.

Isolated tracheo-oesophageal fistula (H-type fistula) This malformation is much rarer than a tracheo-oesophageal fistula in association with oesophageal atresia, and commonly is not associated with other anomalies. Usually, the fistula is located in the extrathoracic part of the trachea and has a narrow lumen.

Children present with recurrent coughing and choking, in particular during feedings. The chest x-ray may show pulmonary infiltrates or atelectases and a distended stomach or bowel. Contrast injection into the oesophagus *via* a tube may show the fistula, but may also (repeatedly) be false-negative. Rigid airway endoscopy is superior to flexible endoscopy in establishing the diagnosis as the posterior tracheal wall can be partly distended and visualised better than with the flexible bronchoscope. Injection of contrast or dye (*e.g.* methylene blue) into a suspected fistula with subsequent detection of the material in the oesophagus may be useful for establishing the diagnosis. Airway endoscopy may also facilitate intraoperative identification by cannulating the fistula.

Treatment is surgical and consists of ligation and division of the fistula, in most cases through a cervical approach. In selected cases, particularly patients with recurrent fistula, glue injection may be used for closure of the fistula. Long-term prognosis is excellent, unless diagnosis is delayed until late child- or even adulthood, which may result in considerable respiratory morbidity due to recurrent aspiration and infection.

Tracheomalacia This anomaly is caused by congenital absence, deficiency, malformation or softness of tracheal cartilage. Congenital tracheomalacia has to be distinguished from acquired forms; the latter may develop as a result of prolonged intubation and mechanical ventilation, tracheostomy or severe tracheobronchitis. Tracheomalacia can be primary or secondary, and may be localised or generalised. Primary tracheomalacia is found in association with oesophageal atresia, Down syndrome, Ehlers–Danlos syndrome, and with laryngomalacia or bronchomalacia. Its incidence has been reported to be at least 1 in 2100. Localised secondary tracheomalacia occurs as a consequence of compression from a vascular malformation (*e.g.* double aortic arch, right aortic arch variants, left pulmonary artery sling, ''anomalous'' innominate artery) or a mediastinal tumour. After surgical repair (*e.g.* division of a vascular ring), the tracheomalacia very often continues to cause symptoms. The prognosis of these anomalies is determined by the respiratory tract. Tracheomalacia is frequently misdiagnosed as bronchial asthma or other respiratory conditions. Thus, patients may be treated unnecessarily with inhaled corticosteroids for long periods of time, and may be undertreated for recurrent or chronic lower airway infections.

Intrathoracic tracheomalacia leads to dynamic airway compression on expiration, in particular during increased respiratory effort (*e.g.* crying) and coughing, or during respiratory infections. Tracheal collapse may result in retention of secretions from the lower airways, which in turn may cause bronchopulmonary infections. In contrast, malacia of the extrathoracic part of the trachea may result in partial or complete airway collapse on inspiration. Signs and symptoms include a ''barking'' cough, tachy- and dyspnoea, retractions, cyanosis, localised monophonic (expiratory) wheezing, and possibly (inspiratory) stridor. Feeding may cause ''dying spells'' (food in the oesophagus may compress the malacic trachea).

With intrathoracic tracheomalacia, a chest X-ray typically reveals bilateral hyperinflation; lateral inspiratory and expiratory radiographs may show marked changes in airway calibre of the malacic part of the trachea. The registration of (tidal and) maximal flow–volume curves allows distinction between extra- and intrathoracic airway obstruction and between variable (tracheomalacia) and fixed (tracheal stenosis) obstruction. Flexible airway endoscopy is the diagnostic procedure of choice; it can be done with only minimal mechanical distortion of the airway anatomy and dynamics, while rigid instruments inevitably distort the airways. It is mandatory that evaluation of airway dynamics is performed during spontaneous breathing. CT and MRI with angiography are complementary techniques, in particular in patients with localised tracheomalacia

where compression by an extrinsic lesion is suspected.

Generally, in patients with isolated tracheomalacia airway function improves with increasing age, as the airway grows and the airway wall stiffens. Thus, most patients can be managed conservatively, with chest physiotherapy and antibiotics for secondary infections. In particular, infants with generalised tracheo- and/or bronchomalacia and significant airway obstruction may benefit from long-term application of CPAP or ventilation with positive end-expiratory pressure (PEEP) *via* tracheal cannula to splint the airway. In most of these patients, gradual reduction of positive airway pressures and eventual decannulation is possible. Clinical and radiological parameters as well as flexible airway endoscopy and pulmonary function testing enable determination of the individual optimal airway pressure. One advantage of this approach is the avoidance of major surgery; disadvantages include long-term tracheostomy and technology dependency. Surgical treatment is indicated in children with life-threatening tracheomalacia. Aortopexy is usually effective in localised tracheomalacia, but is of limited value in generalised forms. Stents may be effective in patients with diffuse tracheomalacia but severe complications including death have been reported in a significant proportion of children. Thus, today most authors agree that stents should only be employed in selected patients when there are no good alternatives. Treatment and prognosis depend on the type and severity of the malacia and on associated anomalies.

Tracheal stenosis Tracheal stenosis occurs more infrequently than tracheomalacia. Membraneous stenoses (webs) are less common than anomalies of the tracheal cartilages. Complete cartilaginous tracheal rings (''napkin ring cartilages'') mainly occur in the intrathoracic part of the trachea along a variable length; sometimes the whole trachea is affected. Stenoses can occur in an hourglass- or funnel-shape (carrot-shape, ''rat-tail'' trachea). They are frequently associated with other anomalies such as a left pulmonary artery sling, abnormal bronchial arborisation (*e.g.* tracheal bronchus), or a single right or left lung. In the past 50 years, various classifications have been proposed, based on the length of stenosis, the severity of symptoms, and recently according to bronchial involvement.

Congenital tracheal stenosis may be life-threatening or may only be detected incidentally. Signs and symptoms depend on the severity and the site of the stenosis, and include localised monophonic (expiratory or biphasic) wheezing or (inspiratory or biphasic) stridor, tachy- and dyspnoea, retractions, cyanosis, and respiratory distress.

Usually, CT or MRI (with three-dimensional reconstruction) is necessary to define the extent of the lesion, and to confirm or rule out compression by an extrinsic lesion (fig. 3). Unless a severe stenosis precludes a complete endoscopic examination, flexible bronchoscopy with an ultrathin instrument is helpful in defining airway anatomy including bronchial arborisation, in detecting possibly associated tracheomalacia, and in planning treatment. Pulmonary function testing shows evidence of fixed airway obstruction with plateaus in both the inspiratory and expiratory limb of the flow–volume loop.

As tracheal stenosis may improve with airway growth, conservative and symptomatic treatment (including chest

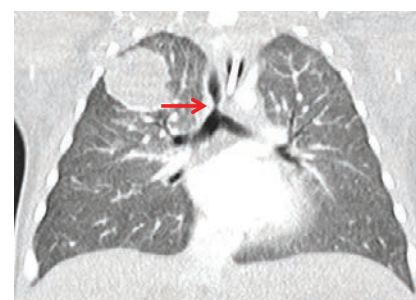

Figure 3. Severe, short segment tracheal stenosis (red arrow), and parenchymal lung malformation in the right upper lobe.

physiotherapy and antibiotics) should be recommended whenever possible. Surgical options for more severe stenoses include tracheostomy to bypass stenosis of the cervical trachea, resection and primary anastomosis for short segment stenosis, and, among others, slide tracheoplasty (including repeated balloon dilation to prevent subsequent recurrence of the stenosis) for long-segment stenosis. Tracheal surgery should only be exercised in specialised referral centres. In the future, tissue-engineered tracheal replacement is expected to play an increasingly important role. Treatment and prognosis depend on the type and severity of the stenosis and on associated anomalies.

Tracheal bronchus and other topographic anomalies Topographic anomalies, representing the most common malformations of the tracheobronchial tree, are mostly observed on the right side. A tracheal bronchus (''pig bronchus'') may be associated with other anomalies in the tracheobronchial tree or in other organ systems. It supplies either the apical segment of the right upper lobe (in this case a normal right upper lobe bronchus supplies the other segments), an accessory segment within or separated from the right upper lobe, or the whole right upper lobe (in this case the normal right upper lobe bronchus is absent). The tracheal bronchus may also originate from the trachea at the level of the carina (''trifurcation''). For a detailed description of the so called ''bridging bronchus'' in patients with a tracheal bronchus and a left pulmonary artery sling, the reader is referred to relevant literature.

These and other lobar or segmental bronchial anomalies are often asymptomatic and thus only incidentally detected. However, if structural anomalies (stenosis, malacia) are present the malformation may result in recurrent or persistent pneumonia or atelectasis, and later bronchiectasis in the respective segment or lobe. Diagnosis is established by bronchoscopy and CT or MRI. Chest physiotherapy and antibiotics are the treatment of choice in symptomatic patients. In patients with persisting problems despite conservative measures, resection of the affected segment or lobe may be necessary.

Topographic anomalies of the whole lung (situs inversus; bronchial isomerism – bilateral right or bilateral left lung) are usually associated with topographic anomalies of the heart and/or abdominal organs (*e.g.* Ivemark syndrome with asplenia).

Bronchial atresia This malformation is frequently associated with congenital lung malformations and is seen by many authors as the underlying cause of the latter. In this rare anomaly, a lobar or (sub)segmental bronchus ends blindly, separated by a short gap from the distally located bronchial tree supplying the lobe or (sub)segment. The clinical picture varies widely, from the neonate with respiratory distress to the asymptomatic adult. CT or MRI is used to confirm the diagnosis. Most authors recommend resection of the lesion.

Bronchomalacia Bronchomalacia is characterised by abnormal weakness of the airway wall. Localised forms are distinguished from generalised (*e.g.* Williams–Campbell syndrome), and primary forms from secondary ones; the latter are usually caused by vascular compression. Bronchomalacia is frequently associated with tracheomalacia, and the left main bronchus is predominantly affected.

Signs and symptoms depend on severity and include cough, localised monophonic wheezing and decreased breath sounds. Some children only develop symptoms during respiratory infections. Flexible bronchoscopy is the diagnostic procedure of choice; echocardiography, CT and MRI are complementary techniques, in particular for localised bronchomalacia.

Gradual improvement may be expected with age and thus airway growth. Only a minority of patients with significant respiratory problems requires treatment apart from the usual conservative measures (chest physiotherapy, antibiotics). Prognosis mainly depends on associated anomalies.

Bronchial stenosis Bronchial stenosis is rare and predominantly occurs in mainstem (left > right) and lobar bronchi. Retention of secretions may lead to bronchopulmonary infections and the development of bronchiectases. Signs and symptoms are the same as with bronchomalacia. Diagnosis is confirmed by flexible bronchoscopy, CT or MRI. As patients tend to show improvement with age, conservative management is recommended. Resection and primary anastomosis may be necessary for severe short segment stenosis; localised bronchiectasis may necessitate resection of the affected segment or lobe.

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Thoracic malformations

Ashok Daya Ram, Jennifer Calvert and Sailesh Kotecha

Congenital thoracic malformations (CTMs) are a heterogeneous group of rare congenital developmental anomalies and disorders of the lung parenchyma and airways with an incidence of approximately 3.5 per 10 000 live births. The use of routine antenatal ultrasound scans, post-natal CT and MRI imaging, and advances in neonatal surgery and intensive care have widened our knowledge of the pathophysiology of CTMs but at the same time have also introduced complexities, especially to the management of asymptomatic lesions. Many excellent recent studies and textbooks of paediatric respiratory medicine cover all CTMs in detail (table 1); however, we will only cover congenital cystic adenomatoid malformations (CCAMs) and relative bronchopulmonary sequestrations (BPS). Close multidisciplinary cooperation between fetal medicine experts, neonatologists, paediatric surgeons, geneticists, paediatricians and/or paediatric pulmonologists is crucial to the overall management and outcome of children with CTMs.

Key points

- The routine introduction of antenatal ultrasound scanning has not only increased our knowledge of CTMs but has resulted in improved antenatal counselling and management of these conditions.
- Antenatal "resolution" of CCAMs is reported in up to 20% cases but in most cases there is evidence of their persistence on post-natal CT images.
- Management of asymptomatic CCAMs is controversial with some physicians opting for regular follow-up and imaging to gauge progress whilst others opt for surgical removal.
- Long-term follow-up studies to assess the natural history, including respiratory and neurodevelopmental outcomes, especially after fetal intervention, are required.

Embryology

The lungs develop as an out pouching from the developing foregut at 3 weeks of gestation. The respiratory diverticulum begins to grow caudally and divides at 4 weeks and further subdivides in a dichotomous fashion. Further lung growth occurs in tightly regulated stages of lung development, namely the embryonic, pseudoglandular, cannalicular, saccular and alveolar phases. By the end of the sixth month of gestation, 17 generations of subdivisions have formed. Lung growth and development continues post-natally until at least 2 years of age or beyond. The exact aetiology for most CTMs remains unknown but for CCAMs the embryological insults are speculated to occur during the pseudoglandular stages of lung development for Types I to III CCAMs and during the late saccular phase of lung development for Type IV lesions. It is postulated that transcription and growth factors, such as homeobox protein Hox-B5 (HOXb5), thyroid transcription factor 1 (TTF) and platelet-derived growth factor (PDGF-BB), may play a role in the pathogenesis of CCAMs.

Table 1. Differential diagnosis of CTMs

Tracheobronchial malformations
Tracheal agenesis/atresia/stenosis
Tracheal bronchus
Oesophageal bronchus/lung
Tracheomalacia/bronchomalacia
Enteric duplication cyst
Neuroenteric cyst
Bronchogenic cyst
Bronchial cyst
Bronchiolar cyst
Pulmonary parenchymal malformations
Agenesis/aplasia/hypoplasia of the lungs
Congenital lobar emphysema
CCAM
Bronchopulmonary sequestration
Vascular malformations
Haemangioma
Arterio-venous malformations
Scimitar syndrome (congenital venolobar syndrome)
Congenital pulmonary lymphangiectasia
Lymphangioma
Congenital chylothorax

Antenatal diagnosis

The routine introduction of antenatal ultrasound scanning (fig. 1a) has not only increased our knowledge of CTMs but has resulted in improved antenatal counselling and management of these conditions. Improved detection may have resulted in increased reporting of CTMs. While antenatal scanning has improved detection, it has also led to some unique challenges, namely the management of lesions with a presumed diagnosis and lesions that may resolve. A pathological diagnosis would clearly require tissue for examination, thus, it is important to describe the lesion in detail and formulate a differential diagnoses (table 1). Important differential diagnoses include congenital diaphragmatic hernia and bronchogenic cysts, which are congenital cysts derived from the primitive foregut containing viscid, milky mucus and occasionally communicate with the airway. They present in several ways:

- on antenatal ultrasound scan,
- respiratory distress in infancy,
- recurrent/persistent pneumonia,
- an incidental finding of a smooth mediastinal mass on chest radiography.

Treatment is by surgical excision.

Modalities such as antenatal MRI (fig. 1b) can accurately delineate and quantify the CTMs providing an excellent method for morphological and volumetric evaluation of the fetal lung, but should be used as an adjunct to routine antenatal ultrasound rather than as a primary investigation.

CCAM of the lungs

CCAM (also termed congenital pulmonary airway malformation (CPAM)) is a congenital lung anomaly in which abnormal development appears to occur in part of the lung, usually at the lower lobe of either lung. The lesion grows fastest between 20 and 26 weeks of gestation, and then plateaus before decrease in volume relative to foetal size towards term. The abnormal lung consists of terminal bronchiolar or acinar structures that can act as space occupying lesions, although it is connected to the tracheobronchial tree. The lesions usually draw their blood supply from the pulmonary circulation but in hybrid lesions, *i.e.* lesions showing elements of both CCAM and BPS, they may have a systemic blood supply. CCAMs can vary in size and consistency, and their continued growth can cause pressure effects on the remainder of the lungs, oesophagus, the mediastinum or the great vessels. CCAMs are usually isolated but Type 2 CCAMs are often associated with other systemic abnormalities.

The incidence of CCAM is 0.94 per 10 000 live births. Some, but not all, studies report a slight male preponderance with no known genetic or familial association (although these are increasingly described for specific lesions).

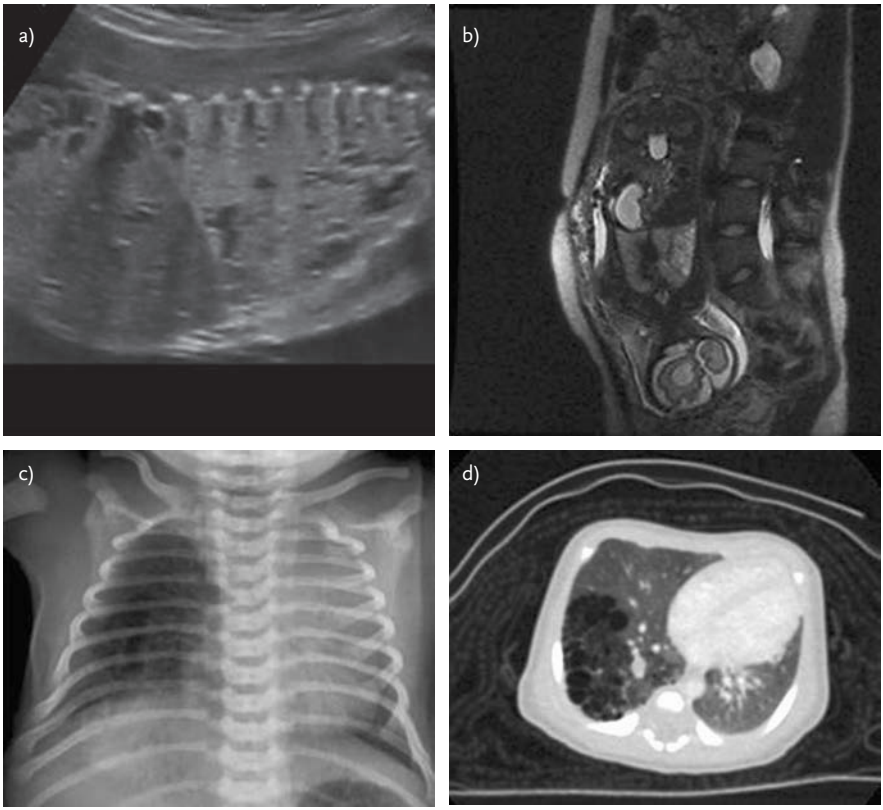

Figure 1. a) Antenatal ultrasound and b) MRI scan of an extensive right sided CCAM, which was symptomatic at birth, with respiratory distress and mediastinal shift as confirmed by c) a chest radiograph and d) a CT scan. It was surgically removed successfully at 3 days of age.

There have been many classifications for CCAMs but the two by Stocker (2002) and Langston (2003) are most commonly used with significant overlap between the two. The Langston classification includes lesions other than CCAMs, including bronchial atresia and pulmonary hyperplasia. The Stocker classification, which focuses on CCAMs, is based on histology and the size of the lesions as follows.

- Type 1 where individual cysts are >2 cm in diameter and are lined by pseudostratified epithelium.
- Type 2 where individual cysts are <2 cm in diameter with the cysts resembling dilated bronchioles; they are lined by ciliated cuboidal or columnar epithelial cells.
- Type 3 are solid lesions without cystic components with an excess of acinar structures.

Other types have subsequently been added to this classification including Type 0, which is best viewed as describing congenital acinar dysplasia, and Type 4, which overlaps with type 1 pleuropulmonary blastoma. Type 1 is the commonest lesion forming ~50–70% of all CCAMs and has the best prognosis. Type 2 CCAMs are often associated with other malformations, which should be looked for at antenatal ultrasound screening.

Since Stocker's classification is based on histological observation, Adzick *et al.* (1998) suggested a more clinical classification based on antenatal ultrasound measurements of the cysts to classify CCAMs into two types:

- macrocystic, where the cyst or cysts are >5 mm in diameter and constitute 75% of all lesions;
- microcystic, where the cyst or cysts are <5 mm in diameter and constitute 25% of the lesions.

CCAMs act as space occupying lesions with pressure effects on the:

- lungs, which can lead to lung hypoplasia,
- oesophagus resulting in polyhydramnios,
- heart, vessels and mediastinum resulting in pleural effusions or hydrops fetalis.

Antenatal ultrasound scanning can detect these lesions as hyperechoic pulmonary masses (fig. 1a), as well as features of associated complications (*e.g.* polyhydramnios or hydrops) in >80% of the cases. Systemic abnormalities including the cardiovascular, abdominal and mediastinal structures should also be investigated. Antenatal "resolution" of CCAMs is reported in up to 20% cases but in most cases there is evidence of their persistence on post-natal CT images. 5–10% of these lesions can lead to the development of hydrops, which is associated with markedly increased fetal demise; thus, this association has received great attention for antenatal fetal surgical intervention.

Currently the best available indicator of prognosis for CCAM is the CCAM volume ratio (CVR). This is the ratio of the lesion volume compared to the head circumference. CVR values >1.6 are associated with increased risk of between 15% and 75% for developing fetal hydrops, *i.e.* poor prognosis. Due to the increased risk of developing a complicated course, the CVR is often used to guide antenatal fetal surgical intervention but has limited sensitivity and specificity. Antenatal interventions include steroid administration, thoracentesis, thoracoamniotic shunt, laser ablation, fetal surgery or injection of a sclerosing agent into any feeding vessel. Hedrick *et al.* (2005) reported an 89% overall survival in nine patients who underwent the *ex utero* intrapartum treatment (EXIT) procedure for fetal hydrops, extensive mediastinal shift or persistently elevated CVR. Ultrasound-guided intrauterine thoracoamniotic shunting for a macrocystic CCAM with a large cyst has the best outcome with the lowest fetal and maternal risk. Out of 23 such patients treated with this approach in one series, the volume reduction of the CCAM was 70% and survival throughout the neonatal period was 74%. Open maternal–fetal surgery with pulmonary resection of a large CCAM yields a 50% probability of survival to discharge from the neonatal intensive care unit, but given the technical complexity this should only be performed in a centre with experience.

However, most studies report a small number of patients and report success although publication bias suggests that those that resulted in failure are unlikely to reach the wider literature. Furthermore, most of these interventions have not been formally assessed, thus, results need to be interpreted with caution. Longer term outcomes after fetal intervention have not been reported in any detail but will clearly need careful follow-up, especially for neurodevelopmental outcomes. Clearly it is important to counsel the parents with a multidisciplinary team offering all available options.

Post-natally, most CCAMs will have been identified antenatally and infants with large lesions may need supportive therapy for stabilisation prior to surgical intervention. Planning to deliver in appropriate centres with the required expertise is a must for these babies. The majority of CCAMs, however, are asymptomatic but some may present with acute (fig. 1c and d) or chronic respiratory distress, recurrent pulmonary infections, bronchiectasis, lung abscesses, haemoptysis, pneumothorax, air embolism, haemothorax, pyopneumothorax, steroid-resistant asthma or high output cardiac failure (if there is a large systemic arterial

blood supply). They may present asymptomatically on chest radiographs obtained for other reasons.

There is little controversy that surgical resection of symptomatic lesions is appropriate in most cases and is relatively straightforward with minimal morbidity and mortality in experienced paediatric/neonatal surgical centres.

Management of asymptomatic lesions is more controversial. Possible reasons for surgical removal of asymptomatic lesions include prevention of chest infections, and other rarer complications such as:

- bleeding and pneumothorax;
- prevention of future malignancy risk;
- encourage compensatory lung growth if performed within 2 years of age;
- decrease post-operative complications.

In most cases surgery is performed between 2 and 12 months. With advances in surgical skills, elective surgery is considered relatively safe in expert surgical hands with few complications involving a short hospital stay but may be associated with poorly delineated longer term outcomes such as scoliosis. Complete excision of the lesion is usually achieved by lobectomy but segmentectomy may be used to preserve parenchyma for small lesions or if there is multiple lobe involvement. If elective surgery is performed during infancy, there may be potential for compensatory lung growth but definitive evidence is lacking. Thoracoscopic surgery may potentially decrease the risks of traditional open thoracotomy such as scoliosis, rib crowding, injury to nerves and vessels, *etc.*, thus may be preferable but needs further evaluation.

However, there are proponents of a ''wait and see'' approach, favouring a conservative approach citing many counter-arguments to surgical intervention. For asymptomatic lesions, a recent meta-analysis of 41 series with 1070 patients suggests that the rate of infection among asymptomatic infants beyond the neonatal period is 3.2% occurring at a median age of 7 months, thus it is claimed that the risks of post-natal infection for asymptomatic lesions are exaggerated. Furthermore, these advocates suggest that the risks of future malignancy are small, there is no evidence for lung physiological improvement after early surgery and the post-operative risks for surgery after respiratory infection in a few children do not justify exposing those children who may never develop symptoms to unnecessary surgery.

Whichever route is taken for management of asymptomatic CCAMs, it is important to ensure appropriate counselling of the parents by a multidisciplinary team and for full risk assessment of any surgical interventions to be balanced against the need for repeated CT scans and risk of loss to follow-up of patients. For an asymptomatic child who develops infection, the surgical risks and complications are marginally higher than those who undergo elective surgery but the absolute risk for development of infection in an asymptomatic child has been poorly reported. Newer interventions, such as thoracoscopic surgery, are being introduced but need to be fully assessed before they become routine, especially for asymptomatic CCAMs.

The natural history of CCAMs is not well defined. It is unclear what proportion of children with asymptomatic CCAM develop symptoms in the future. Although some reports of limited numbers of children suggests symptoms in up to 10%, the duration of follow-up is often short, thus the true value is likely to be higher. Although tumours such as pleuropulmonary blastoma, rhabdomyosarcoma and bronchoalveolar carcinoma are reported to occur with CCAMs, the true risk is unclear and one report has suggested that risk may not be reduced after surgery. Studies reporting physiological lung function in surgical survivors of symptomatic CCAMs are also conflicting with some reporting normal values whilst others report deficits. There is a clear need for further studies to evaluate the natural history of CCAMs.

Bronchopulmonary sequestration

BPS can be extralobar or intralobar with the lesions comprising of lung tissue with its own blood supply *via* an aberrant blood vessel. They lack continuity with the rest of the respiratory tract. Intralobar BPS predominantly occurs in the posterior basal lateral segment of the left lower lobe. It has single or multiple systemic arterial supplies arising from the abdominal aorta in 75% of the cases and venous drainage is usually into the pulmonary vein. Extralobar sequestrations are completely separated from the normal lung, invested by an individual pleura. The commonest site is the left lower lobe but it can occur anywhere in the lungs and even in sub-diaphragmatic areas. In as many as 50% of cases, there are other associated abnormalities including CCAM, congenital cardiac anomalies, pericardial defects, pectus excavatum, bronchogenic cysts and vertebral anomalies. The blood supply is usually from the systemic circulation. BPS is the commonest differential diagnosis of CCAM; they both have distinct radiological, pathological and clinical characteristics. The main distinct characteristics are lack of communication to the tracheobronchial tree and the aberrant blood supply from systemic circulation. In some cases, features of both CCAM and BPS coexist in the same lesion, often termed hybrid lesions.

The treatment for both intralobar and extralobar BPS is surgical resection because of risks of haemorrhage, infection, arteriovenous shuntings and late malignancy but smaller lesions may be left alone or selectively embolised. The most essential step in surgery of these lesions is identification and control of systemic blood vessels. Unrecognised or uncontrolled bleeding from these vessels can be associated with serious morbidity or even mortality.

Conclusion

Although CTMs are rare, they are important causes of respiratory distress in newborns and children. They are increasingly diagnosed antenatally which allows for planning of intervention, delivery, *etc.*, but also introduce newer problems particularly the management of asymptomatic lesions. Whilst symptomatic lesions are amenable to surgical excision, the management of asymptomatic lesions remains controversial and both medical and surgical management needs to be balanced against the risks for each approach. New interventions are being increasingly introduced but need careful evaluation not only in the short term but also for long-term outcomes. However CTMs are dealt with, appropriate counselling of the parents with a multidisciplinary team is essential.

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Vascular malformations

Oliviero Sacco, Serena Panigada, Nicoletta Solari, Elena Ribera, Chiara Gardella, Silvia Rosina, Michele Ghezzi and Francesca Rizzo

A wide spectrum of congenital anomalies can occur during the formation of the aortic arch, brachiocephalic arteries, pulmonary arteries and ductus arteriosus, due to the failure of embryonic structures to fuse and regress regularly. Knowledge of the normal embryonic development of the aortic arch and related structures is important to understand and classify the various form of vascular malformation.

Key points

- The incidence of vascular malformations is ~1% but the true incidence is difficult to assess if less severe abnormalities are included.
- The most severe forms of vascular rings can be detected during the neonatal diagnostic work-up, cause serious symptoms in the newborn period and require surgery within the first year of life.
- The less severe abnormalities are detected in later life, when unexplained recurrent respiratory symptoms or occasional mild dysphagia leads to radiographic or endoscopic evaluation. Symptoms such as dyspnoea, wheezing and cough are often misdiagnosed as asthma, particularly if they occur in older children.
- The vascular malformations that most frequently cause symptoms are: double aortic arch; right aortic arch with a left ligament arising from the descending aorta; aberrant subclavian artery; pulmonary sling; and aberrant innominate artery.

During fetal development, six pairs of primitive aortic arches are sequentially formed and, as successive arches develop, the previous arches regress. The major persistent arches in humans are the fourth and sixth. The fourth arches contribute to a portion of the left aortic arch and of the right subclavian artery; the proximal portions of the sixth arches become the mediastinal segment of the pulmonary arteries, while their distal portions form the ductus arteriosus (Kellemberg, 2010). Abnormal development of the aortic arch complex may represent an uncommon but potentially serious cause of variable degrees of compression of the trachea, bronchi and/or oesophagus, due to the formation of vascular "ring" or "sling". Some of these anomalies, such as the double aortic arch and the right arch/left ligament, are anatomically complete rings, while others, *i.e.* anatomically incomplete or partial rings, are called slings, such as the pulmonary sling.

Clinical presentation and classification

In children with vascular abnormalities, the severity of the resulting respiratory disorder does not appear to correlate tightly with the degree of anatomical obstruction of the airways. Signs and symptoms at presentation are variable, including apnoeic spells, recurrent apnoeas, stridor/noisy breathing, chronic or recurrent cough, a brassy cough similar to a seal's bark,

recurrent respiratory infections and dysphagia for solid foods.

The most severe forms of vascular rings can be detected during the neonatal diagnostic work-up, particularly if associated with congenital cardiac malformations; they cause serious symptoms in the newborn period and require surgery within the first year of life. Less severe abnormalities are detected in later life, when unexplained recurrent respiratory symptoms or occasional mild dysphagia require radiographic or endoscopic evaluation. Symptoms such as dyspnoea, wheezing and cough are often misdiagnosed as asthma, particularly if they occur in older children.

The true incidence is difficult to assess if we include less severe abnormalities/compression. Autopsy studies suggest that 3% of people have a congenital malformation of the aortic arch but about two-thirds of cases remain undiagnosed (McLaren *et al.*, 2009). In this section, we will focus on the vascular malformations that most frequently cause symptoms:

- double aortic arch,
- right aortic arch with a left ligament arising from the descending aorta,
- aberrant subclavian artery,
- pulmonary sling, and
- aberrant innominate artery.

Double aortic arch, the most common and serious complete type of vascular ring, is usually an isolated anomaly without associated cardiac malformation; it is associated with congenital cardiac malformations, such as ventricular septal defect or tetralogy of Fallot, in 20% of cases. It is due to the persistence of both fourth aortic arches encircling the trachea and oesophagus in a tight ring. In 75% of affected infants, the right-sided arch is dominant (larger and positioned higher than the left arch), in 20% the left arch is dominant and in 5% the arches are equal in size (fig. 1a and b). A portion of the left aortic arch can be atretic and persist only as a fibrous band. Each aortic arch passes over the ipsilateral principal bronchus and fuses behind into a common descending aorta, which is more commonly located on the left side of the spine. The ligamentum arteriosum is usually located between the distal part of the left arch and the left pulmonary artery, but may be present on both sides when the aortic arches are both patent (Kellemberg, 2010). Children with this anomaly usually present with severe respiratory symptoms and some swallowing difficulty early in life. Surgical interruption of the smaller or atretic aortic arch and of the ligament is usually required. The most severe case of tight vascular ring can interfere with normal tracheal development; the tracheal lumen can show segmental stenosis with complete cartilaginous rings (fig. 1e).

Right aortic arch, comprising 12–25% of cases of vascular rings, is usually associated with congenital cardiac malformations such as persistent truncus arteriosus, pulmonary atresia with ventricular septal defect, and tetralogy of Fallot. In this group of abnormalities, the regression of the embryonic structures involves the left aortic arch, resulting in the right arch lying to the right side of the trachea, passing over the right principal bronchus and generally continuing as the right descending aorta, located to the right of the spine (fig. 2a and c). A combination of a right aortic arch and a persisting left descending aorta results in a circumflex right aortic arch with an horizontal retro-oesophageal portion of the dorsal aortic arch, which contributes to the compression of trachea and oesophagus from behind (fig. 3). The brachiocephalic vessels may originate as a mirror image of a normal left aortic arch, but many variants are possible. The association of a right aortic arch with a left ligament that passes from the left pulmonary artery to the descending aorta or to the left subclavian artery, coursing to the left of the trachea and oesophagus, describes a complete vascular ring around these structures. If the left fourth aortic arch regresses proximal to the left subclavian artery, a right aortic arch with an aberrant left subclavian artery as the last branch results. The artery passes behind the oesophagus and forms a complete vascular ring together with the left-sided ligamentum arteriosum (Russell *et al.*, 2010).

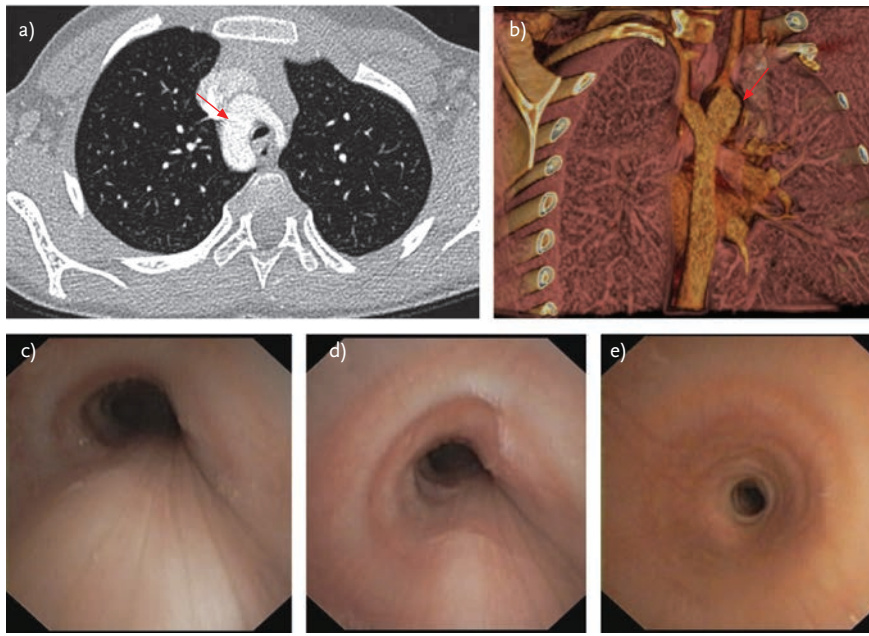

Figure 1. a) Right-sided dominant double aortic arch (arrow); MDCT axial view. b) Same patient, MDCT three-dimensional imaging; posterior view. c–e) Endoscopic images of double aortic arch compression of trachea, increasing severity. e) The tracheal rings are complete or circumferential.

The origin of the left subclavian artery from the descending aorta is frequently dilated, forming the so-called Kommerell diverticulum (fig. 2a and c). In patients with a right aortic arch, the airway compression can be due to different mechanisms: vascular ring due to a left ligamentum arteriosum (fig. 2b), enlargement of the Kommerell diverticulum and/or a midline/ left descending aorta.

Aberrant subclavian artery, the most common among the aortic arch anomalies, occurs in nearly 1% of the population and in 25% of Down syndrome patients. Originally described by Bayford in the 18th century as "*dysphagia lusus naturae*" (dysphagia "freak of nature"), this anomaly most commonly involves the right subclavian artery or, rarely, the left subclavian artery when there is a right-sided aortic arch, as previously described. The aberrant subclavian artery originates as the last vessel of the aortic arch and has an oblique course toward the other side, across the superior mediastinum, passing behind the oesophagus on its way to the upper extremity. An aberrant right subclavian artery as single malformation is rarely symptomatic, although in older children and in adults, mild dysphagia may be present due to compression of the oesophagus. However, an aberrant left subclavian artery, crossing behind the oesophagus as the last branch of a right aortic arch, forms a complete vascular ring together with a left-sided ligamentum arteriosum, as previously described, and commonly causes symptoms due to compression of both the trachea and oesophagus (Kellemberg, 2010).

Pulmonary sling The embryonic origin of pulmonary artery sling occurs when the developing left lung captures its arterial supply from the right sixth arch through capillaries caudal, rather than cephalad, to

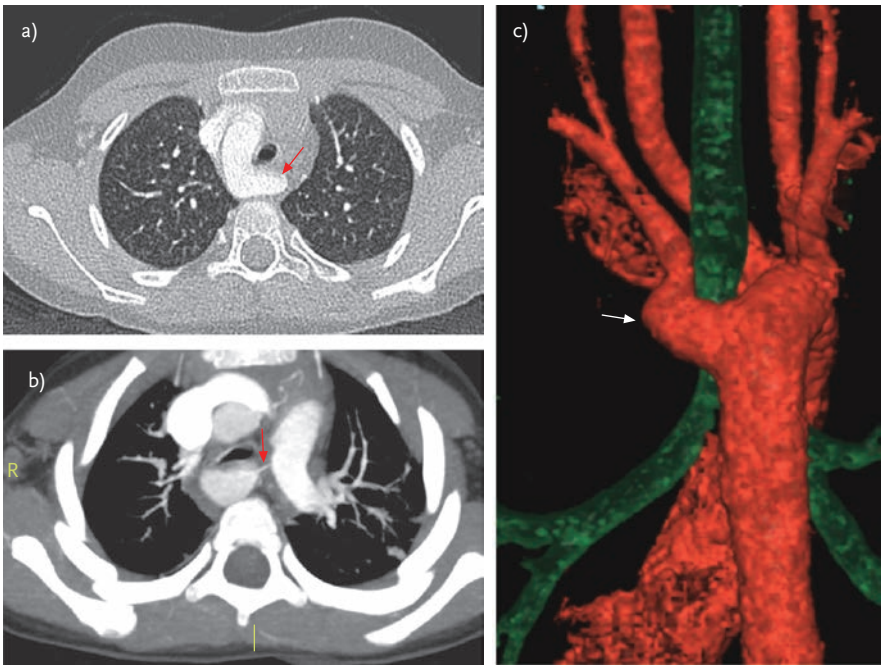

Figure 2. a) Right aortic arch, Kommerel diverticulum (arrow); MDCT axial view. b) Right aortic arch, a rare MDCT imaging of ligamentum arteriosum; axial view. c) Kommerel diverticulum and aberrant left subclavian artery (arrow), MDCT three-dimensional imaging; posterior view.

the developing tracheobronchial tree. As consequence, the anomalous left pulmonary artery arises from an elongated right pulmonary artery, turns dorsally encircling the right main bronchus, and passes to the left between the trachea and oesophagus before entering the hilum of the left lung (fig. 4a).

The airway may also be compromised by associated complete cartilage rings, the so called ring-sling complex present in 40–50% of cases, where the membranous portion of the trachea is absent and the tracheal cartilages are circumferential or ''O-shaped''. Associated tracheobronchial abnormalities may occur, including tracheomalacia, hypoplasia and stenosis of long tracheal segments (fig. 4b and c) (Elliot *et al.*, 2003). Both the right main bronchus and the trachea are affected and compression by the sling can result in hyperinflation or atelectasis of the right lung. Congenital heart defects are found in 50% of pulmonary artery sling cases, most commonly atrial septal defect, patent ductus arteriosus, ventricular septal defect and left superior vena cava.

Aberrant innominate artery causes tracheal compression of various degrees. Why an innominate artery, which arises from the aortic arch to the left and crosses in front of the trachea to the right side, should compress the trachea in some cases and not others is not well understood. In innominate artery compression patients, the artery appears to originate somewhat more posteriorly and leftward on the aortic arch than usual. This condition is more frequently symptomatic when associated with tracheomalacia and/or oesophageal atresia (fig. 5). Severe compression of the trachea results in chronic or recurrent brassy cough, stridor, tachypnoea and recurrent respiratory infection (Gardella *et al.*, 2010). The most severe presentations in infancy include life-threatening events.

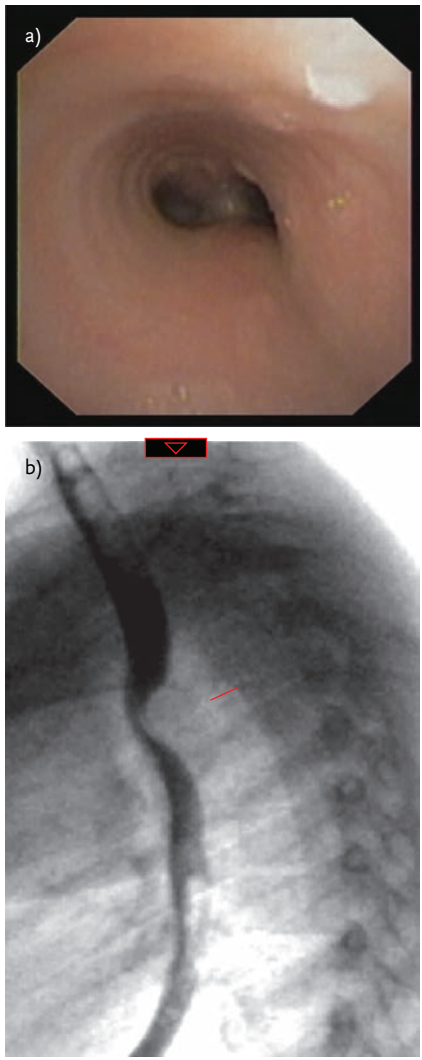

Figure 3. Vascular ring due to right aortic arch, aberrant left subclavian artery and left ligamentum arteriosum. a) Endoscopic image of tracheal lumen compressed on the right side. b) Same patient, persistent indentation on barium oesophagography from behind; lateral view. Clinically: mild dysphagia.

Diagnosis

Fetal ultrasound may detect malformation of several organs during the first trimester, including heart malformation and some aortic arch anomalies. As a consequence, the prenatal diagnosis of some aortic arch anomalies has become more common in the last decade due to the widespread use of fetal sonographic studies sufficient for delineation of the trachea, aortic arch, brachiocephalic arteries and ductus arteriosus (Avni *et al.*, 2007). After birth, the presence of respiratory distress, wheezing, stridor, dysphagia and recurrent respiratory infection may require consideration of a vascular ring or sling as the underlying cause.

The historical approach was to perform chest radiography and barium swallow as the first step to evaluate children with suspected extrinsic compression of the airways, while conventional angiography was reserved for confirmation of the diagnosis. These studies have now been widely replaced by MRI and multidetector CT (MDCT). However, the recent literature demonstrates variability in the preferred diagnostic strategies for these conditions.

Chest radiography In symptomatic patients, evaluation usually begins with frontal and lateral chest radiograph. On the frontal projection, the laterality of the aortic arch can be appreciated by its density and the side of the descending aorta by the presence or absence of the aortic stripe on the respective side. On the lateral projection, anterior bowing of the trachea and an increase in the retrotracheal density may also be appreciated. In pulmonary sling, chest radiographic findings include unilateral hyperinflation, tracheal narrowing and an unusual horizontal course of the left and right main bronchi, resulting in a "T-shaped" trachea. In any case, chest radiography can only arouse suspicion of the presence of a major vascular malformation.

Barium oesophagography Upper gastrointestinal study has historically been reliable and remains an excellent technique for the diagnosis of a vascular ring, as the location of the aortic arch in relation to the oesophagus can be determined (fig. 3b). Bilateral persistent indentations on the oesophagus on the anteroposterior view

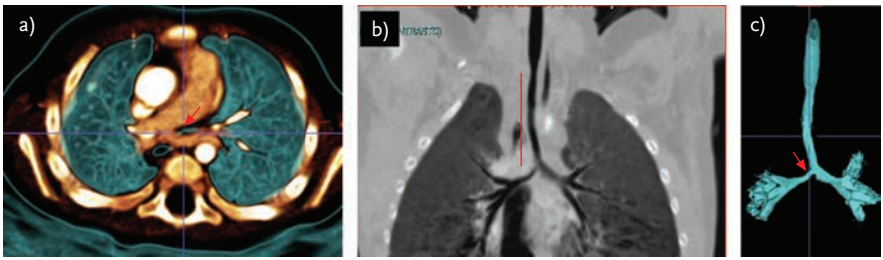

Figure 4. Pulmonary sling. a) MDCT axial view: the anomalous left pulmonary artery (arrow) arises from an elongated right pulmonary artery, turns dorsally encircling the right main bronchus, and passes to the left between the trachea and oesophagus before entering the hilum of the left lung. b) MDCT coronal view of the associated long-segment tracheal stenosis: two-thirds of the trachea are stenotic and show complete cartilage rings (line). c) MDCT three-dimensional imaging of the trachea and bronchi: the origin of the right main bronchus is stenotic due to compression by the anomalous left pulmonary artery.

suggest a double aortic arch, while posterior indentation with an oblique course angled toward the left shoulder suggests an aberrant subclavian artery. Anterior pulsatile indentation of the oesophagus is virtually pathognomonic for pulmonary artery sling.

Echocardiography and angiography
Echocardiography has the advantage of a comprehensive assessment of intracardiac anatomy and function. However, it is limited by acoustic windows, a lack of depiction of airway/oesophageal involvement and high interobserver variability. Conventional angiography is invasive and is limited by high radiation dose and the need for iodinated contrast material.

Although the diagnosis of a vascular ring can be established or suspected with chest radiography and oesophagography, the exact configuration of the vascular abnormality cannot be fully defined with conventional radiology alone. The exact anatomy of an aortic arch malformation and its relationship to adjacent structures can be accurately defined only by cross-sectional imaging techniques, as MRI and CT (Hellinger *et al.*, 2011).

MRI and MDCT Contrast-enhanced helical MRI or MDCT imaging allow excellent delineation of the aortic arch, its branches and their spatial arrangement. The multiplanar and three-dimensional imaging capabilities of magnetic resonance and CT noninvasive angiography have widely replaced other diagnostic techniques, such as the now obsolete catheter angiography. The direct multiplanar imaging capability of MRI allows accurate evaluation of vascular malformation and its relationships with adjacent organs and, possibly, associated intracardiac defects in a single sitting, without ionising radiation and iodinated contrast material. However, most MRI studies for vascular compression are quite prolonged (>30 min), the need for absolute immobility during image acquisition requires general anaesthesia with controlled ventilation, and sedation risks are increased in children with compromised airways. Contrast-enhanced MDCT overcomes this disadvantage by allowing accurate imaging in very short scanning times and mild sedation is sufficient in younger, uncooperative children. The disadvantages of MDCT include ionising radiation and the need for iodinated contrast material; however, recent adjustment of specific techniques minimises the radiation dose. If assessment of the airways is important, MDCT is currently more reliable than MRI for the definition of the airway by multiplanar and three-dimensional image reconstruction (figs 1b, 2c and 4c), including virtual bronchoscopy, without appreciable respiratory artefacts. For both MRI and MDCT, the major diagnostic limit is that an obliterated vascular segment (*e.g.* the ligamentum arteriosum or an atretic aortic

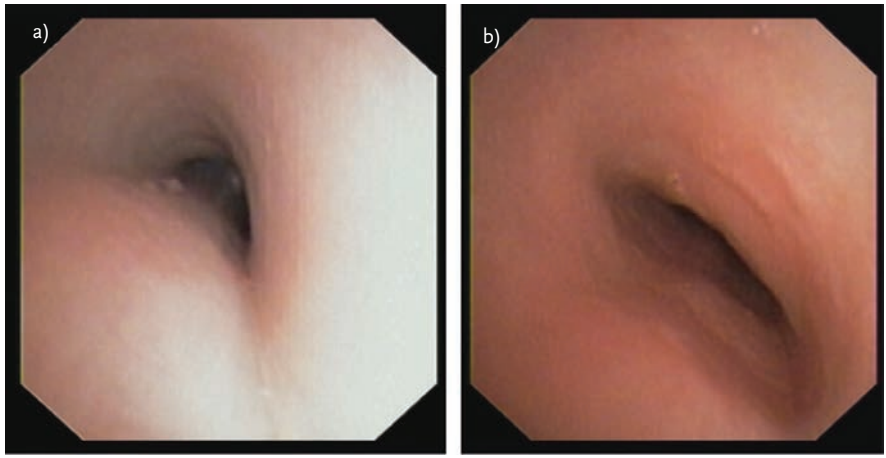

Figure 5. Tracheal compression by aberrant innominate artery in two patients, a) 15 and b) 20 months of age. a) Endoscopic image of tracheal lumen compressed on the front right side. Good vision of the tracheal rings is achieved and tracheal compression is visible without tracheomalacia. b) Patient with repaired oesophageal atresia and less well-delineated tracheal rings. The association of vascular compression and tracheomalacia caused a severe clinical picture with brassy cough, stridor and life-threatening events.

arch) can be visualised only rarely (fig. 2b). The final decision to image with MRI *versus* MDCT should take into consideration availability of equipment and ease of scheduling, as well as the patient's ability to cooperate. In practice, the increase in speed and quality of multiplanar reconstruction provided by MDCT technology means that CT is used more and more often than MRI in most centres.

Bronchoscopy and bronchography Despite the accuracy of both MRI and MDCT in evaluating the nature of the vascular compression of the airways, current MRI and MDCT techniques do not reliably distinguish between dynamic or static narrowing of the airways.

Such distinction can have important clinical consequences, as many children with

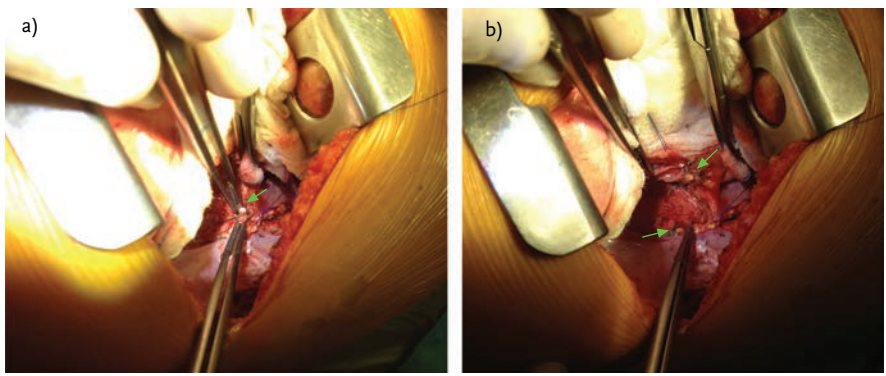

Figure 6. Vascular ring due to right aortic arch, aberrant left subclavian artery and left ligamentum arteriosum; same patient as in figure 3. Intraoperative view: a) ligamentum arteriosum (arrow) resection; b) the two ends of the ligamentum (arrows) spontaneously move >1 cm away soon after resection.

vascular malformation can have associated malacia of the compressed airway. Bronchoscopy and bronchography are still the best techniques to assess the presence of tracheo- or bronchomalacia (fig. 5b). Bronchoscopy and bronchography are performed at the same time, injecting isotonic, nonionic contrast down the working channel of the flexible bronchoscope. Intraoperative tracheoscopy can be indicated in the aortopexy procedure, to evaluate the resolution of the tracheal collapse during the manoeuvres of suspension of the aortic arch (Torre *et al.*, 2012). Bronchoscopy can be repeated 1–2 years after the surgical procedure to follow up the airway malacia evolution.

Treatment and outcome

Vascular rings and slings inducing severe symptoms usually require prompt surgical correction. Prolonged severe vascular compression of the airways is more likely to induce severe malacia of the compressed airway and interfere with the growth of the trachea or bronchi. In most children, the problem is self-limiting and eventually the cartilage regains sufficient stiffness for the symptoms to resolve. This clinical observation suggests that the surgical procedure should be performed without delay in symptomatic patients (Turner *et al.*, 2005). Children with a double aortic arch usually require usually surgical correction by resection of the nondominant arch. It is important to assess the arch anatomy and the dominant arch before surgery because such assessment determines the operative approach. If there is an atretic portion of an arch, this is the obvious site for arch division.

A right aortic arch with a left ligamentum arteriosum and/or an aberrant left subclavian artery is reported even in asymptomatic children. Relief of symptoms such as dysphagia can be achieved by resection of the tight ligamentum arteriosum and/or excision of the Kommerell diverticulum. The intervention will be adapted to the variant of the anomaly and is aimed at decompressing the upper portion of the gastrointestinal tract or the lower respiratory tract (fig. 6). In pulmonary sling, there is a strong association with long-segment congenital tracheal stenosis with complete tracheal cartilage rings. The surgical procedure is the re-implantation of the left pulmonary artery and, at the same time, a slide tracheoplasty to increase the tracheal calibre (Fiore *et al.*, 2005). Surgical treatment of patients with an aberrant right subclavian artery is almost never necessary; the artery has to be re-implanted only in the rare patients with severe dysphagia.

Patients with tracheal compression by an aberrant innominate artery may have concomitant tracheomalacia rather than pure extrinsic compression and this is particularly frequent in children with oesophageal atresia. Symptoms tend to regress, at least partially, with age if tracheomalacia is not associated, and tracheoscopy can be useful to assess the malacia (fig. 5b). Surgical correction, typically requiring aortopexy, is rarely needed and is reserved for patients with severe symptoms, such as apnoeic spells in newborns or recurrent barking cough in older children, when the compression decreases the tracheal lumen significantly (Gardella *et al.*, 2010).

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Aetiology, pathogenesis, prevention and evidence-based medical management

Robert I. Ross-Russell

Bronchopulmonary dysplasia (BPD) is a chronic lung disease that affects premature babies, usually following mechanical ventilation. Over the past 20 years, changes in antenatal steroid use, surfactant therapy and changes in ventilator strategy have led to major improvements in the outcomes of very premature infants. However, at the same time, the incidence of BPD has changed very little. This has meant that a greater number of affected infants are surviving into childhood and beyond. These infants have an increased need for healthcare, with frequent readmissions to hospital in the first 2 years and persistent abnormalities of lung function into adolescence and adulthood.

Key points

- BPD remains a significant cause of long-term respiratory illness despite major advances in the care of the preterm newborns.
- The primary pathological process is inflammation, driven through the NF-κB pathway, and triggered by a variety of genetic and environmental factors.
- Management is directed at minimising lung insults, by limiting oxygen toxicity and ventilator-induced lung trauma.
- Drugs that may influence development of BPD include caffeine and vitamin A, although new anti-inflammatory drugs are in development.

The disease was first described in 1967 but the pathophysiology has changed significantly since that time. Earlier descriptions of fibroproliferation, smooth muscle hyperplasia and decreased alveolarisation have changed in the post-surfactant era. BPD (commonly referred to as "new BPD") shows less regional variability, large alveoli and characteristic vascular changes. The features differentiating old from new BPD are shown in table 1.

The National Institutes of Health (NIH) diagnostic criteria for bronchopulmonary dysplasia are shown in table 2. All infants need to have been in room oxygen for at least 4 weeks. For infants born at less than 32 weeks gestation, assessment is made at 36 weeks post-menstrual age or discharge (whichever comes first), whereas for those infants born after 32 weeks, assessment is made at 56 days of age or discharge. Diagnostic criteria remain an important issue, as studies evaluating outcomes have historically used varying definitions of BPD, making comparison difficult. For example, different units may administer additional oxygen at varying levels of saturation.

The incidence of BPD varies with gestational age, and particularly birth weight. Infants with a birth weight between 500 and 750 g have a 42% chance of developing BPD whereas in infants weighing between 1250 and 1500 g the chance of incidence drops to 4%.

Aetiology and pathogenesis

The primary basis of respiratory disease in the preterm infant is a lack of surfactant leading to the development of respiratory

Table 1. Pathological differences between BPD before (old) and after (new) the introduction of surfactant

Old BPD	New BPD
Extensive fibroproliferation	Rare proliferative changes
Airway smooth muscle hyperplasia	Mild smooth muscle involvement
Areas of atelectasis and hyperinflation	More homogeneous lung changes
Reduced alveolarisation	Simplified, large alveoli
Pulmonary artery muscularisation	Abnormal pulmonary vascularisation

distress syndrome (RDS). Surfactant production only starts at around 24 weeks gestation and, coupled with the underdevelopment of alveoli, gas exchange in the extremely low birth weight infant is significantly compromised. This leads to a need for positive-pressure ventilation and increased oxygen administration, both of which cause lung injury. These and other factors (see later) influence the development of the pulmonary vasculature and alveoli, both of which are interdependent. Factors that impair vascular growth, such as post-natal infection, will also have a detrimental effect on lung development. Endothelial growth factors such as vascular endothelial growth factor (VEGF)-A are critical factors for both vascular branching and lung development. Factors affecting expression of VEGF-A will affect lung development. Similarly conditions such as pulmonary hypertension are known to worsen the outcome in BPD.

However, the development of BPD in such patients is quite variable and may require several "hits" or insults. Genetic, inflammatory, infective and traumatic factors may all influence development of lung injury. Other factors, such as nutrition or fluid overload, may also influence the degree of injury seen.

Genetics There is only limited understanding of the genetic factors influencing the development of BPD. It is well recognised that both sex and ethnicity can influence the incidence of BPD, and twin studies have also shown familial associations. Abnormalities in surfactant protein formation can lead to a greater risk of BPD, and there is a suggestion that human leukocyte antigen (HLA)-A2 may predispose to the condition.

Inflammation There is no doubt that inflammation is a major influence on the development of BPD. In particular, the role of nuclear factor (NF)-κB has been increasingly recognised as a major determinant of inflammation mediated injury. NF-κB normally exists in cells bound within the inhibitor of NF-κB (IκB) complex, but can be released from this by a variety of different mechanisms, including hyperoxia, trauma and infection. When released, NF-κB forms several subunits that may each allow transcription of different pro-inflammatory mediators. Hyperoxia (through oxidative stress) is known to increase expression of NF-κB and has been shown to cause injury to the newborn mouse lung. It also affects expression of VEGF-A which directly affects both vascular and alveolar development. Trauma will also increase NF-κB expression. Volutrauma has been shown to increase the incidence of BPD in sheep through NF-κB-mediated mechanisms.

Infection Infection has long been associated with the development of BPD. It has a direct effect on the expression of NF-κB, but can also stimulate inflammatory cytokines directly. *Ureaplasma* infection has long been thought to increase the risk of BPD, along with other genital mycobacteria. Isolation of *Ureaplasma* from the trachea of infants has been shown to be associated with increased BPD but, more recently, *Ureaplasma* infection in preterm lambs has not been shown to affect the incidence of BPD. Similarly to chorioamnionitis, early reports of an association with BPD have been followed by less clear data, and there is

Table 2. NIH criteria for the diagnosis of BPD based on gestation

	<32 weeks gestation	>32 weeks gestation
Mild	In room air at 36 weeks post-menstrual age	In room air by 56 days post-natal age
Moderate	Needing <30% oxygen at 36 weeks post-menstrual age	Needing <30% oxygen at 56 days post-natal age
Severe	Needing >30% oxygen with or without IPPV or CPAP at 36 weeks post-menstrual age	Needing >30% oxygen with or without IPPV or CPAP at 56 days post-natal age

IPPV: intermittent positive-pressure ventilation. Modified from Jobe *et al.* (2011).

some suggestion that the combination of antenatal steroids and chorioamnionitis may even be protective for BPD.

Other factors The role of nutrition in the pathogenesis of BPD remains unclear. Poor nutrition is associated with an increased incidence of BPD but equally there is no evidence that improving nutrition in these infants will reduce the risk of subsequent BPD. Tight control of fluid balance in high-risk infants may be beneficial. It is known that infants with a patent ductus arteriosus (PDA) have a greater risk of developing subsequent BPD. At the same time, aggressive treatment of a PDA with fluid restriction, indomethacin or surgery has been shown to reduce BPD, although the effect may be relatively minor.

Prevention and management

The ideal approach to the care of preterm infants would be to prevent BPD occurring. This either requires a reduction in premature delivery, or a method to prevent or attenuate BPD in those babies who are born early. However this is difficult in the context of a disease that is so multifactorial.

Prenatally, females who go into premature labour are routinely treated with oral steroids. It has been shown that this will increase lung maturity and surfactant production and reduce the likelihood of RDS. Disappointingly, this approach appears to have little impact on the prevalence of BPD. Similarly, an aggressive approach to both antenatal and post-natal infection would appear to be worthwhile in view of concerns about their effect on inflammation and the development of BPD. Again, however, there is little evidence that this approach will have a significant impact on the incidence of BPD.

Post-natally, there are several strategies that can help to minimise risk. In the resuscitation room there has been considerable interest in minimising lung trauma and hyperoxia. Recent studies have suggested that normal oxygen saturations in the neonate may well be lower than previously thought and that initial resuscitation with air, adding in oxygen only when needed, may reduce morbidity. A large study (SUPPORT) of 1300 babies evaluating CPAP against surfactant, and also high and low oxygen saturation, showed no difference in outcomes (including death, BPD and neurodevelopment); however, BOOST II (designed to specifically consider oxygenation targets) was terminated early due to an increase in mortality in the lower oxygenated group. The use of noninvasive ventilation (CPAP or noninvasive positive-pressure ventilation (NIPPV)) has been shown to be safe in neonates and studies suggest that this, used in conjunction with early surfactant and extubation, is as safe as conventional ventilation. However, this approach does not result in any significant reduction in BPD. Ventilation strategies have centred on low-volume ventilation with permissive hypercapnia to minimise traumatic injury to the lung, and a recent Cochrane review has shown reduced deaths and chronic lung disease in patients treated with volume-targeted ventilation. The use of high-frequency oscillation has not shown any significant impact on BPD.

As suggested earlier, the use of fluid restriction may affect the development of BPD although the evidence is somewhat ambiguous. Good nutrition is also important as avoidance of BPD is dependent on lung growth. Infants in the lowest quartile of growth develop more BPD and high calorie intake is needed for those infants who are fluid restricted.

In terms of drug therapy, a number of options have been tried. Given the central role of inflammation there has been disappointingly poor evidence of a protective role from anti-inflammatory treatment. Trials with azithromycin are ongoing and there may be a small effect. Similarly, vitamin A appeared to reduce the incidence of BPD in extremely low birth weight infants, but the drug needs to be administered by intramuscular injection three times a week and long-term follow-up studies for up to 2 years following treatment show no benefits in respiratory or neurological outcome. Consequently its use is not widespread. Nitric oxide has a measurable effect on oxidative stress and alveolar development in prematurely born animal models but the evidence in children remains controversial. Results from studies to date have been ambiguous and the 2011 NIH consensus statement concludes that current evidence does not support the use of nitric oxide in the neonatal period.

The use of post-natal corticosteroids is also controversial. It has been known for some time that dexamethasone can facilitate extubation and may reduce BPD, but there have been increasing concerns about adverse effects on development. It is likely that such adverse effects are more common in infants treated in the first week of life, where the risk/benefit ratio is high whereas the use of steroids for older children who are proving difficult to wean from ventilation may be of more value. There is renewed interest in the use of low-dose steroids (dexamethasone 0.05 $mg \cdot kg^{-1} \cdot day^{-1}$) in this group and early work suggests that this may be an option. Current advice, however, must remain that post-natal steroids, whether dexamethasone, hydrocortisone or inhaled steroids, may have significant adverse effects and their routine use, especially in the long-term, cannot be recommended.

The other medication that has been shown to have a beneficial effect on the development of BPD has been caffeine. This came as a coincidental finding in a study on apnoea of prematurity, when it was found that there was a significant reduction in BPD at 36 weeks gestation. The study also suggested that caffeine may provide some neuroprotection as well.

Conclusion

The complex nature of BPD makes it unlikely that any single approach will address all the problems. However, an understanding of the basic inflammatory drivers that cause lung injury will help deliver strategies that minimise iatrogenic injury and help protect against the long-term respiratory morbidity that is increasingly seen in ex-preterms.

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Nutritional care

Kajsa Bohlin

Neonatal care has undergone a dramatic development during the past decades. Survival rates, particularly for those born very preterm, have increased remarkably and there are growing numbers of preterm survivors. Despite great progress with improved ventilation strategies, antenatal steroids and surfactant treatment, bronchopulmonary dysplasia (BPD) remains the most frequent adverse outcome following very low birth weight. However, the picture of BPD has changed from that of ventilator-induced lung injury to the so called "new BPD", characterised by impaired lung development with reduced alveolarisation, dysplastic capillaries and interstitial fibroproliferation. Nutrition plays an important role in normal lung maturation and development. Nutritional status may directly modulate lung structure as general undernutrition in humans leads to lung emphysema and, in experimental settings, caloric restriction reduces alveolar number. Thus, sufficient nutrition is necessary for adequate lung growth and undernutrition can compromise repair of ongoing lung injury. Nutritional care is therefore to be considered a key factor, both in prevention and management of BPD.

Key points

- BPD is characterised by impaired lung growth and altered lung structure, which may be further aggravated by poor nutritional status.
- BPD is associated with increased work of breathing and a higher resting metabolic state; therefore, energy expenditure is high, making sufficient nutrition a challenge and growth restriction in preterm infants with BPD a common problem.
- The nutritional challenge continues after discharge, the growth pattern of infants with BPD must be closely monitored and, when needed, nutrition should be supplemented to ensure adequate catch-up growth.

Growth failure and BPD

Many preterm infants with BPD become growth restricted as sufficient nutrition is often difficult to achieve. Several factors contribute to the development of growth failure during the first year of life. Early challenges in the neonatal intensive care unit (NICU) are as follows:

- Delayed time to establish adequate intake following delivery in the small sick infant and frequent interruptions of enteral feeding because of feeding intolerance and clinical concerns.
- Decreased nutritional intake secondary to fluid restriction.
- Dysfunction in other organ systems, such as heart failure secondary to large patent ductus arteriosus, renal insufficiency or nerotising enterocolitis.
- Medications, such as methylxanthines and β-sympathomimetics, may increase energy consumption. Post-natal steroids can impair growth and alter the composition of weight gain by increasing fat and decreasing protein accretion.

Later challenges after discharge from the NICU are:

- increased energy expenditure secondary to increased work of breathing, tachypnoea, chronic hypoxia and anaemia of prematurity;
- poor feeding related to swallowing dysfunction, fatigue or gastrointestinal reflux as well as oral aversion secondary to repeated negative stimuli, such as intubation and prolonged tube feeding;
- undernutrition contributing to an increased risk of infections that further interfere with growth.

In addition, dietary needs are not well established in preterm infants. The fundamental principle is to provide a nutritional intake that meets the needs to ensure optimal growth and development. Compared with infants without BPD, infants with BPD have increased energy expenditure of up to 25% above total caloric needs. This is partly explained by increased work of breathing, but also by a higher resting metabolic state, and needs to be taken into account when determining target intake.

Nutritional management in BPD

The overall goal of the nutritional management of very preterm infants is to support a rate of growth that approximates the intrauterine rate of growth. This may be virtually impossible during the first weeks of life and later the recommended intakes are based on needs for maintenance and normal growth; no allowance is generally made for recovery or ''catch-up''.

In clinical practice, very preterm infants are often started on parenteral nutrition and enteral feeding is initiated through a nasogastric tube as soon as the infant's condition is stable. Enteral nutrition may start as trophic feeds of very small volumes: 5–10 $mL \cdot kg^{-1} \cdot day^{-1}$. The transition from parenteral to full enteral feedings may take many weeks. No specific feeding regimen has been proven superior in relation to BPD. Breast milk has benefits over formula feeding in reducing sepsis and necrotising enterocolitis, but does not affect the incidence of BPD. Caloric and protein supplementation is generally indicated in infants that are fed only breast milk to ensure adequate intake for sustained growth. Analysis of breast milk content will allow for individualised supplementation and a close collaboration with a paediatric dietician is essential to optimise nutritional management in the NICU.

Fluid restrictions High fluid intake during the first days of life is associated with an increased risk of developing BPD. Administration of excessive fluid can cause pulmonary oedema through patency of the ductus arteriousus. Data from the National Institute of Child Health and Human Development demonstrates a strong correlation of higher fluid intake and lower post-natal weight loss during the first 10 days of life to BPD. A recent meta-analysis also reports an association of restricted fluid volume administration in preterm infants with decreased incidence of patent ductus and death, and a trend toward reduced risk of BPD. For preterm infants with a birth weight <1000 g or intrauterine growth restriction, it is recommended to start fluid administration at 80 $mL \cdot kg^{-1} \cdot day^{-1}$ on the first day of life and then increase by 10–20 $mL \cdot kg^{-1} \cdot day^{-1}$ increments to a maintenance level of 120–150 $mL \cdot kg^{-1} \cdot day^{-1}$.

Energy, protein and lipid intake As mentioned above, the energy needs of infants with BPD are higher than those of age-matched healthy infants. To date, there are no randomised controlled trials that examine the effects of increased *versus* standard energy intake for preterm infants with developing or established BPD. The European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) have recently suggested that a reasonable range of energy intake for healthy growing preterm infants is 110–135 $kcal \cdot kg^{-1} \cdot day^{-1}$. A higher caloric intake may be beneficial for children with BPD, but may vary depending on respiratory status, clinical condition and activity level. Strict monitoring of growth and accordingly adjusted energy intake is therefore required.

Proteins are essential for fetal growth and the goal of post-natal protein administration is to match intrauterine growth and support protein accretion. Early intravenous

administration of amino acids is usually well tolerated and side-effects, such as metabolic acidosis and hyperammonaemia, are rarely seen. However, to avoid amino acid toxicity the right amount of protein should be given at the right time. ESPGHAN recommends aiming toward a higher intake for infants weighing $\leqslant$1000 g (4.0–4.5 g protein·kg^{-1}·day^{-1}) and less for infants weighing 1000–1800 g (3.5–4.0 g protein·kg^{-1}·day^{-1}). If the growth pattern of the infants is adequate, with signs of catch-up growth, protein intake can be reduced towards discharge.

Lipids are necessary to provide energy, essential fatty acids and improve bioavailability of fat-soluble vitamins. Moreover, lipid administration limits the metabolic conversion of carbohydrates to lipids, thereby decreasing carbon dioxide production, which might be important in BPD. However, the role of lipid administration in the development of BPD remains controversial. The current practice of most centres is to initiate lipids at 0.5–1 g·kg^{-1}·day^{-1} by the second day of life and advance by increments of 0.5 to 1 g·kg^{-1}·day^{-1} up to 3–4 g·kg^{-1}·day^{-1}. However, ESPGHAN states that a reasonable range for most preterm infants is 4.8–6.6 g fat·kg^{-1}·day^{-1}, corresponding to 40–55% of energy intake.

Electrolytes and vitamins Infants with BPD are often treated with diuretics to counteract a tendency to accumulate interstitial lung fluid. This, in combination with renal immaturity, makes them susceptible to sodium, potassium and chloride depletion and at increased risk for disturbed bone mineralisation. Calcium, phosphate and alkaline phosphatase must be closely monitored and supplementation of vitamin D, calcium and phosphate provided through premature formula or fortified breast milk.

Vitamin A is an important antioxidant as well as a key nutrient in maintaining lung epithelial cell integrity. In a recent meta-analysis, vitamin A has been shown to reduce the incidence of death or BPD. The number needed to treat was 12 to 13 infants to prevent one case of BPD and no long-term positive effect on respiratory or neurodevelopmental outcome was found. Taken together with the need to administer vitamin A as intramuscular injections three times a week, the use of vitamin A supplementation has not been widely adopted.

Catch-up growth and nutrition post-discharge

Despite good efforts, many preterm infants with BPD will grow poorly and accrue nutritional deficits during their long hospital stay. Malnutrition leads to reduced brain size and impaired neurodevelopmental outcome. A clear relationship exists between catch-up growth and development, but the time frame within which it needs to occur is not well delineated. There is a concern that rapid growth will lead to later development of insulin resistance and obesity. The challenge is to ensure not only weight gain, but lean mass accretion. Mature human breast milk is designed to meet the needs of the term infant and may not suffice for catch-up growth of the preterm infant. Therefore, all growth parameters, including length and head circumference, should be closely monitored during the first year of life, preferably in specialist clinics as part of a standardised follow-up programme after prematurity. In infants with pathological growth patterns, fortification of the breast milk or supplementation with nutrient-enriched formula should be considered to promote healthy development.

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Neurodevelopmental assessment and outcomes

Charles C. Roehr, Lex W. Doyle and Peter G. Davis

The aim of this chapter is to review the neurodevelopmental outcome of preterm infants with bronchopulmonary dysplasia (BPD). We discuss the influence of neonatal intensive care on the development of chronic lung disease and neurological development in preterm infants.

Mechanical ventilation (MV) and its adverse effects on the lungs

Advances in respiratory support of the preterm neonate The widespread use of antenatal corticosteroids and the introduction of exogenous surfactant replacement therapy, together with gentler MV, have led to better outcomes for preterm infants. Alongside these improvements came a change in characteristics of NICU patients. Whilst most NICU patients in the 1960s were more than 32 weeks of gestation and weighed >1500 g at birth, treatment is now offered to many infants <25 weeks of gestation and with a birth weight <500 g. Lungs of infants with BPD show characteristic radiographic changes (fig. 1).

Key points

- BPD is a distinct disease entity of survivors of preterm birth.
- The prevalence of BPD among survivors of very preterm birth is 20–40%.
- BPD is associated with a risk for significant neurodevelopmental delay.
- Compared with non-BPD peers, infants with BPD may exhibit poorer academic achievements and impaired emotional and physical development.

The clinico-pathological problem of BPD Despite the many advances, very preterm infants (defined as <32 weeks of gestation) still suffer from BPD, leading to long-term respiratory morbidity and oxygen dependency. Sadly, this morbidity is also found in survivors of preterm birth who have never been given MV. Our understanding of the underlying pathophysiology of BPD has changed. It is thought that affected infants with BPD now primarily suffer from a maturational arrest of alveolar differentiation (fig. 2).

Classification, incidence and disease burden of BPD According to the National Institutes of Health consensus definition, BPD is graded as mild, moderate or severe on the basis of oxygen requirements at 28 days and 36 weeks of corrected age. Despite many improvements in care, BPD still affects approximately 20–40% of very preterm infants. Infants with BPD are known to have a higher disease burden than their non-BPD preterm peers. Even after initial discharge, they require more adjunct therapy and have more hospital readmissions in the first 2 years of life.

Impact of premature birth and intensive care treatment on neurodevelopmental outcome

Effects of preterm birth and NICU admission on health The disruptive environment of NICUs *per se* results in poorer growth and impaired neurosensory development. According to a recent meta-analysis, the incidence of developmental delay or learning difficulties in very preterm infants is 60%, cerebral palsy is 27%, impaired vision or

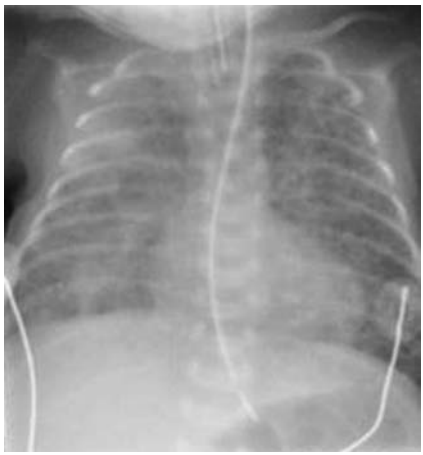

Figure 1. Chest radiograph of a ventilated infant with severe BPD.

blindness is 11%, gross motor and coordination deficits is 10%, and deafness is 7%. Preterm infants, compared with term-born infants, are more likely to:

- have poorer overall academic achievement;
- exhibit specific challenges in mathematical abilities and social relationships;
- have impaired emotional and physical development.

In general, the rate of developmental delay increases with falling gestational age. Bassler *et al.* (2009) used severity of illness as a predictor of neonatal outcome and established that a count of three neonatal morbidities (BPD, brain injury and severe retinopathy of prematurity) strongly predicts the risk of death or neurosensory impairment in extremely low birth weight infants. Male sex is increasingly recognised as a predictor for poor outcome following prenatal birth.

Additive effect of BPD on neurological outcome

Preterm birth and BPD Preterm infants with BPD are likely to have been sicker than non-BPD infants whilst in the NICU. They are likely to have been subjected to a higher intensity of treatment and will therefore be at increased risk for iatrogenic effects of treatment. The post-natal administration of corticosteroids has been linked to poorer neurological outcome, as well as repeated fluctuations in arterial oxygen concentration and apnoea and bradycardia, both of which are commonly found in BPD infants.

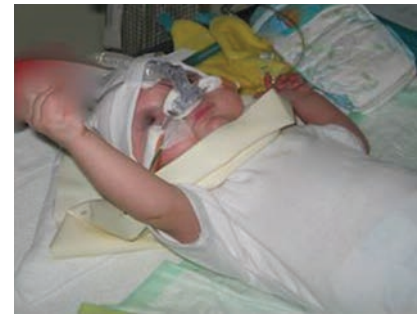

Figure 2. A 1-year-old child with severe BPD receiving respiratory support.

Testing the hypothesis that diagnosis of BPD predicts negative neurological outcome To test the hypothesis that BPD, defined as requirement of supplemental oxygen at 36 weeks of corrected age, predicted poor neurological outcome, Davis *et al.* (2002) analysed data from 945 preterm infants born with birth weights <1000 g. The authors found poor neurosensory outcome at follow-up in 34% of infants. Of these, 77% suffered cognitive delay, 37% cerebral palsy, 5% blindness and 7% severe hearing impairment. However, this definition of BPD had a sensitivity of only 45% for predicting poor neurodevelopmental outcomes, and an overall accuracy of 63%.

Long-term studies on neurodevelopmental outcome in infants with BPD Long-term neurodevelopmental impairment can affect:

- cognitive development (including visual–spatial perception);
- hearing;
- speech and language development;
- memory and learning capacity;
- gross and fine motor function.

The Victorian Infant Collaborative Study Group has studied large geographical cohorts

of preterm infants since 1979. Data from these studies and those of other groups indicate that preterm infants with BPD have poorer outcomes than their non-BPD peers

Prevalence of specific neurological impairments For general cognitive function, results from different studies suggest that BPD infants were rated 0.25–0.66 standard deviations lower for IQ than their non-BPD peers. For behaviour, the rate of attention deficit was 59% for BPD infants compared with 32% for non-BPD infants. Preterm survivors with BPD performed between 0.5–1 standard deviations below very low birth weight infants (birth weight <1500 g) without BPD or term controls on tests of reading and mathematics. Poor memory performance was significantly more common in BPD infants (65%) compared with 29% in a non-BPD group, and language skills at preschool and school age were found to be significantly delayed in BPD infants compared with non-BPD controls. 49% of the BPD infants tested at preschool age showed significantly delayed receptive language development, and 43% had significantly delayed expressive language development.

Conclusion

Preterm birth is strongly associated with abnormal neurodevelopmental outcome. Preterm infants with BPD suffer from poorer health and worse neurological outcome than their non-BPD peers. However, the diagnosis of BPD, given at the age of 36 weeks of corrected gestation, is not a highly sensitive predictive measure for negative neurological outcome. The increasing survival rates of very preterm infants and concurrent numbers of children with BPD will lead to more children with neurological problems. Therefore, reducing the rate of BPD will remain one of the biggest challenges in neonatal care.

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Long-term respiratory outcomes

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Chronic lung disease of infancy (CLDI) comprises a heterogeneous group of diseases that evolve as a consequence of a neonatal respiratory disorder. The most common form of CLDI is bronchopulmonary dysplasia (BPD). Due to the marked decline in mortality among very immature, extremely low birth weight infants in recent decades, there are increasing numbers of children and adults who have survived BPD. This means that not only paediatricians, but also adult physicians, will have to deal more and more often with the sequelae. Today, BPD is defined as the need for supplemental oxygen for at least 28 days after birth, and its severity is graded according to the respiratory support required near term.

An important effort has been made to characterise the extent of pulmonary disease and assess lung function in infants and children born prematurely, generating considerable information on the pulmonary outcome of BPD into adolescence.

Less is known about the respiratory health of adult survivors of BPD, since few studies are available on this topic. The available data are based mainly on cohorts born in the late 1970s and/or 1980s, and often include cases of "old" BPD, *i.e.* patients born before the introduction of exogenous surfactant and antenatal corticosteroids, who usually required prolonged mechanical ventilation. Acute lung injury (causing airway inflammation, bronchial smooth muscle hypertrophy, emphysema and parenchymal fibrosis) has a major role in the resulting chronic lung disease in such patients, so their functional outcome is not fully comparable with that of more recent cases of BPD, which include much more immature, smaller newborns, who are treated very differently (with less ventilatory support). This latter type of so-called "new" BPD is a developmental disease of the terminal airspaces, characterised mainly by

Key points

- Survivors of extreme prematurity, and those with BPD in particular, experience high rates of respiratory symptoms (mainly cough and wheeze) and hospital readmission in the early years of life.
- Into mid-childhood and adolescence, clinical symptoms become milder and less frequent, but spirometric studies show that many of those born very prematurely have scarcely reversible airflow obstruction (mean FEV_1 70–80% predicted).
- Although BPD survivors frequently suffer from asthma-like symptoms, BPD and asthma are distinct clinical entities resulting from different pathogenic mechanisms and caution is needed when recommending asthma treatments to BPD patients.
- Due to the natural age-related decline in respiratory function, it is reasonable to expect a phenotype resembling COPD to develop in some survivors of BPD, so these patients should be followed up into adulthood and efforts should be made to prevent them from smoking.

impaired alveolarisation. Although symptoms in the newborn are usually milder than those of the old form of BPD, whether or not patients with this new BPD will ultimately have better respiratory outcomes remains to be seen.

Morbidity associated with BPD

Infants with BPD may require oxygen supplementation on discharge from neonatal intensive care units. However, very few remain oxygen dependent beyond 1 year of age, reflecting some lung growth.

Upper airway problems (laryngo-tracheal stenosis, laryngomalacia, tracheomalacia and unilateral vocal cord paralysis) resulting from prolonged or reiterated intubation can worsen the respiratory course of infants with BPD, although the incidence of the more severe forms of stenosis requiring tracheostomy has fortunately declined in the last decade.

In the first 2 years after birth, infants born before 33 weeks of gestational age, and survivors of BPD in particular, are very susceptible to respiratory exacerbations, with higher rates of recurrent wheezing than in children born at term. Hospital readmissions for complications of respiratory tract infections are also frequent (up to 40% in the first 1–2 years), with a relevant burden of disease for patients, parents and the healthcare system. Strict measures to prevent viral infections (*e.g.* prophylaxis against respiratory syncytial virus with monoclonal antibodies) and to avoid adverse environmental factors (*e.g.* passive smoking) are of the utmost importance in this population.

Although respiratory symptoms (cough and wheeze) are very common at preschool age, the clinical condition of BPD survivors generally improves with time and their respiratory symptoms become less severe. By mid-childhood, respiratory exacerbations become less frequent. During their years of schooling, most of these children appear to live normally, although they experience more chronic coughing and wheezing (and other asthma-like symptoms), and they need to use inhaled asthma medication more frequently than term-born controls.

Into adolescence, symptoms progressively subside in survivors of BPD too, and most of them lead apparently normal lives. The relationship between clinical symptoms and lung function fades, and even patients with severe airway obstruction detected by spirometry may not have any clinically significant respiratory symptoms.

Data on adult respiratory health are limited and refer mainly to cases of old BPD in patients studied in their twenties. These patients seem to complain of more respiratory symptoms (especially shortness of breath and wheezing on exertion) than healthy controls. The same may not fully apply to new BPD cases, however, so a long-term follow-up of well-characterised cohorts of children born in the post-surfactant era is needed to ascertain the respiratory outcome after new BPD.

Pulmonary arterial hypertension associated with stabilised BPD

The clinical course of extremely preterm infants with BPD can be made worse by concomitant pulmonary arterial hypertension (PAH), defined as a mean pulmonary artery pressure (P_{pa}) >25 mmHg at rest (measured by cardiac catheterisation), or an estimated systolic P_{pa} >40 mmHg on echocardiography. PAH arises from the combination of an altered vascular development (normal lung angiogenesis is disrupted by premature birth), function (hypoxia-related increases in vascular tone and reactivity) and structure (vascular remodelling with smooth muscle cell proliferation). Although the true prevalence of PAH in infants with stabilised BPD is unknown, it has ranged between 17% and 25% in individual studies. Sustained and severe PAH, and the resulting cor pulmonale are linked to high mortality rates in infancy (up to 40%), so it is very important to detect PAH, not only for the purpose of prognostic considerations, but also to ensure an appropriate treatment. Echocardiography is recommended as the main screening tool and should be

performed in BPD infants whose clinical course is atypical (with high or increasing oxygen needs, recurrent cyanotic episodes and/or a poor growth rate), arousing the suspicion of underlying PAH. Cardiac catheterisation can assess the severity of PAH more precisely, but it is usually performed only in the more severe cases, when vasodilators other than oxygen (such as phosphodiesterase-5 inhibitors or endothelin receptor antagonists) are needed. Long-term supplemental oxygen therapy with a target oxygen saturation in the range of 91–95% is considered the standard treatment for PAH associated with BPD, because it may reduce pulmonary vascular resistance. Patients should be weaned off supplemental oxygen only gradually, and monitoring P_{pa} with serial echocardiography after it has been discontinued is mandatory, because the P_{pa} in these patients may remain persistently higher than normal in the early years of life despite their clinical improvement. By the time they reach school age, pulmonary vascular resistance and P_{pa} appear to return to normal in survivors, although pulmonary vascular reactivity to hypoxia may persist into adolescence and adulthood. A tailored cardiac and echocardiographic follow-up should then be assured for selected BPD survivors.

Long-term imaging anomalies in BPD patients

The radiographic pulmonary findings in survivors of BPD have changed. Traditional chest radiograph findings in survivors of old BPD during their childhood include fibrosis, patchy atelectasis and emphysema. Findings in new BPD are milder, with the chest radiograph picture improving over time. The sensitivity of radiography in diagnosing minor lung abnormalities is limited, however. Although HRCT of the chest is not performed routinely in BPD survivors, it can detect abnormalities in up to 80% of survivors of extreme prematurity and provides important information on the airways and parenchymal structural changes. Significant findings in children and adolescents surviving extremely preterm birth include:

- areas of reduced lung attenuation (due to small airway obstructions leading to obstructive emphysema);
- linear and triangular opacities (due to strands of atelectasis extending to the pleura);
- multifocal emphysema;
- bronchial wall thickening;
- bullae and air trapping on expiratory scanning.

These pathological features are more pronounced in cases previously diagnosed with BPD. Some validated scoring systems are available for assessing the extent of these structural abnormalities on HRCT; interestingly, a correlation has recently been reported between HRCT scores, duration of neonatal oxygen exposure and FEV_1 values in a cohort of children and adolescents surviving extremely preterm birth.

Radionuclide imaging is not usually part of the assessment of BPD patients, but it has the potential to add additional information about lung function. Single photon emission CT has recently been used to assess regional distribution of lung ventilation (V') and perfusion (Q') in a cohort of 30 BPD preterm infants at a median post-menstrual age of 37 weeks. Interestingly, in this study a significant proportion of BPD infants (40%) had an abnormal V'/Q' distribution, and a correlation between V'/Q' mismatch and time spent on mechanical ventilation was detectable.

Lung function studies in BPD patients

Analysing forced expiratory flows (obtained with forced expiratory manoeuvres) reveals substantial airflow limitation in BPD survivors during the first 3 years of life, with no significant improvements on serial measurements. The degree of airflow limitation in the early years of life seems to predict pulmonary function later on: in a small group of BPD survivors followed from birth, forced expiratory flow at 2 years of age correlated closely with FEV_1 at 8 years of age, indicating a tracking of lung function over time and a negligible ''catch-up'' in lung growth. This finding is suggestive of an

irreversible early airway remodelling process.

Spirometric studies have often been used for cross-sectional assessments of lung function in school-age and older BPD survivors. Their findings often refer to heterogeneous cohorts recruited mainly among patients born in the pre-surfactant era, and clearly indicate that BPD children of all ages have a significant airflow obstruction (generally achieving mean FEV_1 values between 70% and 80% of the expected levels) that proves scarcely reversible. Patients born prematurely but not developing BPD usually fare better, but they too have airflow limitation at school age and later. It is worth noting that recent cohort studies on children born extremely prematurely in the post-surfactant era report airflow limitations throughout their years of schooling. These studies found a clearly detectable trend toward an obstructive spirometric pattern even in very low birth weight children who did not develop BPD, raising concern that premature birth may *per se* impair lung maturation and growth, with life-long detrimental effects on pulmonary function. The benefits associated with better perinatal care may, therefore, be partially masked by the gradual improvement in the survival rates for the most immature infants. These preliminary findings also emphasise the need to develop novel therapies to reduce the long-term pulmonary effects of extremely premature delivery.

Only a few studies have been designed to provide longitudinal lung function data at multiple time-points in children with a history of BPD. Data from some of them indicate that lung function may deteriorate throughout childhood and adolescence in the more severe cases, suggesting that some forms of BPD may be progressive in nature.

Persistent airway obstruction with a significantly lower FEV_1/FVC ratio and a forced expiratory flow at 25–75% of FVC ($FEF_{25–75\%}$) than controls is also characteristic of BPD survivors in their twenties. In young adults, a history of BPD is often associated with a maximal FEV_1 <80% of the predicted value, and the well-known natural decline in respiratory reserves with ageing could mean that these individuals reach a critical threshold for significant respiratory symptoms in mid-adulthood. Given the lack of longitudinal studies into adulthood on survivors of prematurity and/or BPD, we still do not know whether their natural age-related rate of decline in respiratory function will be normal or accelerated, but it is reasonable to expect a new phenotype resembling COPD, but related to premature delivery, to emerge over the coming years. This risk emphasises the need to follow up BPD survivors into adulthood, and to minimise their exposure to risk factors associated with a faster decline of lung function, such as cigarette smoking.

Other major lung function anomalies reported in survivors of BPD during their childhood and adolescence include a higher residual volume and a higher residual volume to TLC ratio, probably due to air trapping. Exercise capacity (*e.g.* maximal oxygen consumption) is also slightly reduced, and gas exchange (*e.g.* T_{LCO}) is impaired in BPD children. Finally, a significant airway hyperresponsiveness (to histamine, methacholine or physical exercise) is detectable in BPD survivors, although the mechanism(s) behind it is not yet clear.

Airflow obstruction and asthma-like symptoms in BPD patients

The real nature of the airflow limitation detected in survivors of prematurity and BPD has yet to be fully elucidated and morphologically characterised, since no information is available on lung pathology in BPD patients beyond infancy. Airway obstruction has often been interpreted as the result of stable, not progressive, structural changes in the airways coupled with a poor or dysmorphic alveolar growth. In the new form of BPD, in particular, hypoalveolarisation would reduce the number of alveolar attachments per airway, prompting a more limited airway–parenchymal coupling and predisposing to airflow obstruction. A relevant question is

whether the long-term pulmonary consequences of prematurity and BPD depend only on a non-progressive reduction in airway calibre due to a stabilised airway disease, or whether they also reflect an ongoing active airway disease. A recent report of higher concentrations of 8-isoprostane (a reliable biomarker of oxidative stress *in vivo*) in the exhaled breath condensate of adolescents born preterm in comparison with healthy controls born at term suggests an ongoing oxidative stress in the airways of survivors of prematurity. This issue is important and warrants further investigation because the presence of ongoing airway disease would point to a greater risk of an accelerated age-related decline in lung function; however, it opens up the possibility of an active treatment with antioxidants.

Respiratory symptoms and the obstructive spirometric pattern encountered in BPD patients are often labelled as asthma, but caution is needed in dealing with this problem. Airflow obstruction in BPD patients is only partially reversed by β_2-agonists, suggesting a stable remodelled airway condition. Moreover, in BPD patients, unlike asthma sufferers, there is no evidence of eosinophil-driven airway inflammation; in fact, exhaled nitric oxide (a biomarker of eosinophilic inflammation and response to corticosteroid therapy) is reportedly low in BPD survivors. HRCT studies have also documented morphological differences in the lungs between children with asthma and cases of BPD. Although airway wall thickening and areas of low attenuation may be seen in both diseases, scattered parenchymal fibrosis (linear opacities facing triangular subpleural opacities) and architectural distortion are common findings in survivors of BPD but unusual in children with asthma. Finally, individuals with a history of BPD do not have a higher than normal prevalence of atopy (a major risk factor for childhood asthma). So, asthma and BPD are distinct clinical entities resulting from different pathogenic mechanisms, and care should be taken when treating BPD children with inhaled asthma medication because there have been no randomised controlled trials on these drugs for the treatment of BPD.

In conclusion, given the absence of morphological information and randomised therapeutic trials, the pathogenesis of long-term obstructive symptoms in survivors of prematurity remains elusive and their treatment empirical.

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Pleural effusion, chylothorax, haemothorax and mediastinitis

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Pleural effusion

The pleural space normally contains 0.3 mL per kg body weight of pleural fluid. Lymphatic vessels can cope with several hundred millilitres of extra fluid per 24 h. An imbalance between pleural fluid formation and drainage will result in a pleural effusion. In a previously well child, pleural effusions are usually secondary to acute bacterial pneumonia and less often due to chronic infection such as pulmonary TB. Other causes usually considered in adults, such as malignancies, cardiovascular diseases, or systemic inflammatory conditions, are uncommon in children.

Key points

- All children with parapneumonic pleural effusion or empyema should be admitted to hospital and managed following local or national guidelines.
- Intravenous antibiotics and careful consideration of pleural drainage procedures are the most important aspects of parapneumonic effusion/empyema management.
- Chylothorax is a rare condition in children usually caused by injury to the thoracic duct; simple chest drainage and dietary modifications are the mainstay of treatment.
- When haemothorax is diagnosed, blood should be promptly drained from the pleural cavity with a chest tube.

Clinical picture There are two usual patterns of presentation. In the first, the child has classic symptoms of pneumonia (fever, cough, breathlessness, abdominal pain and malaise) but they are usually more unwell than those with simple pneumonia alone, with pleuritic chest pain and even cyanosis. In the other clinical presentation, the child has been diagnosed with pneumonia but does not respond to 48 h of an appropriate treatment. On examination, a pleural effusion is suggested by unilateral signs of decreased chest expansion and dullness to percussion, reduced or absent breath sounds, and scoliosis.

Diagnosis Contrary to community-acquired pneumonia (CAP), which may be diagnosed on clinical grounds only, the diagnosis of parapneumonic pleural effusion requires an imaging technique to demonstrate the presence of fluid in the pleural space. The first imaging technique should be a posteroanterior chest radiograph. The earliest sign of a pleural effusion is obliteration of the costophrenic angle. A rim of fluid may be seen ascending the lateral chest wall (meniscus sign). If the film is taken in a supine position, the appearance can be of a homogeneous increase in opacity over the whole lung field without blunting the costophrenic angle, or a classic pleural-based shadow. A lateral chest radiograph rarely adds anything extra and should not be routinely obtained.

Once pleural effusion has been diagnosed or suspected by a chest radiograph, chest ultrasonography should be obtained to confirm the diagnosis, estimate the size of the effusion, differentiate between free and loculated pleural fluid and determine its

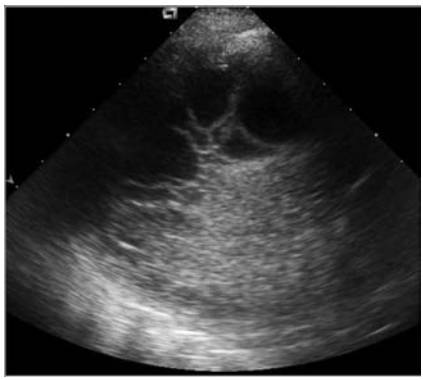

Figure 1. Chest ultrasound showing a loculated pleural effusion.

echogenicity (fig. 1). It may also be used to guide chest drain insertion or thoracentesis.

Chest CT scans involve radiation exposure that can be equivalent to 20–400 chest radiographs depending on technical factors and should not be performed routinely. It may have a role in complicated cases, including immunocompromised children where a CT scan can detect airway or parenchymal lung abnormalities, such as endobronchial obstruction or a lung abscess, or before surgery to delineate the anatomy.

Management Once the diagnosis of parapneumonic effusion has been established, the decisions on additional diagnostic tests and therapeutic interventions should be conducted by following local guidelines. Several national scientific societies have published their own guidelines and every paediatric centre treating children with pleural effusions should have their own protocol adapted to local circumstances.

All children with parapneumonic effusion should be admitted to hospital. Initial treatment should focus on general supportive measures and prompt intravenous antibiotic administration. General measures include assessing the need of supplemental oxygen (S_{PO_2} below local threshold, usually 92–94%), fluid therapy if the child is dehydrated or unable/unwilling to drink, pain control and antipyretics.

Intravenous empirical antibiotic treatment should begin as soon as possible. In the most common setting of a pleural effusion arising from CAP, empirical treatment must cover *Streptococcus pneumoniae*, *S. pyogenes* and *Staphylococcus aureus*. In most cases, cefotaxime (150 $mg \cdot kg^{-1} \cdot dose^{-1}$), co-amoxiclav or cefuroxime are appropriate. Penicillin allergic patients can be treated with clindamycin alone. If pneumatoceles are evident, anti-staphylococcal cover is mandatory (cloxaciline or flucoxaciline). However, in cases of hospital-acquired pneumonia or following surgery, trauma or aspiration, broader spectrum agents should be used to cover aerobic Gram-negative rods.

Further blood diagnostic tests should be obtained after diagnosis and before starting antibiotic therapy: full blood count (for anaemia, white cell count with differential and platelet count), electrolytes (to detect inappropriate anti-diuretic hormone syndrome), C-reactive protein or other acute-phase reactants and blood culture, including anaerobic bottle. If available, sputum culture can also be useful.

An important issue is whether to insert a pleural drain or not. It is generally accepted that isolated pleural taps for diagnostic purposes are not recommended in children with a small, uncomplicated parapneumonic pleural effusion, except if there are any atypical features suggesting the presence of malignancy, such as the absence of acute fever or pneumonia and evidence of an underlying mediastinal mass or lymphadenopathy. In these uncommon situations it is important to remember that large volume aspiration and general anaesthesia pose a significant risk of sudden death in children with superior mediastinal obstruction due to malignancy, therefore, the volume of aspirated pleural fluid should be small (5 mL) and general anaesthesia should be avoided.

Indications for pleural drain vary in different guidelines. As a general rule, there is a good deal of evidence suggesting that a pleural drain is not always necessary and that antibiotics alone can be enough to provide excellent clinical outcomes when there is not a clear indication for chest drainage. Tube thoracostomy must be performed if the child is in respiratory distress due to lung compression by the pleural effusion, or if toxic appearance and sepsis is suspected. It also may be considered if the effusion size is large (definitions vary from 10 mm thickness in ultrasonography or radiography to one-third of the hemithorax in radiography) or is enlarging, and the child is not responding after 48 h of antibiotic treatment.

Pleural drainage is rarely an emergency procedure and must be carefully planned and performed in the most appropriate setting by trained personnel, according to local guidelines. Two types of chest drains are usually used. Paediatric surgeons usually prefer large bore chest tubes (around 20 FG) surgically inserted in the operating theatre with general anaesthesia and paravertebral block with local anaesthetics to provide post-operative pain relief. Respiratory paediatricians, paediatric intensivists and interventional paediatric radiologists usually prefer smaller drains (around 10 FG), including pigtail catheters, inserted by the Seldinger technique in paediatric intensive care units (PICU) or interventional radiology rooms, with general anaesthesia or sedation. These two options are both appropriate and have the same outcomes, so the choice depends on local circumstances. The drain should be inserted by well-trained personnel, or trainees under expert supervision, to minimise the risk of complications. Ultrasonography guiding is mandatory and the appropriate site for chest tube insertion should be marked with an X when this test is being performed. Pleural fluid must be obtained during the procedure and sent for microbiological and cytochemical tests, including Gram staining, culture for standard pathogens and mycobacteria, PCR, glucose and pH.

All chest tubes should be connected to a unidirectional flow drainage system with an underwater seal, which must be kept below the level of the patient's chest at all times. The indications for suction are unclear in the management of pleural effusion but it is commonly believed that it improves drainage. A low suction pressure (5–10 cmH_2O) is usually applied in the underwater seal, and it is acceptable to stop suction for short periods (such as for radiographs or mobilisation). Regular flushing of small bore drains to prevent blockage has been recommended. Patients with chest drains do not need to remain in the PICU for only this reason and they can be managed on a ward by staff trained in chest drain management.

The role of intrapleural fibrinolytics in the management of parapneumonic pleural effusion is not completely clear. Only two fibrinolytics are currently available in most European countries (urokinase and alteplase) but only urokinase has been studied in a double-blind placebo-controlled randomised clinical trial in children, showing a significantly shorter hospital stay (7.4 *versus* 9.5 days) compared with placebo. Urokinase should be given twice daily for 3 days (six doses in total) using 40 000 units in 40 mL 0.9% saline for children aged $\geqslant$1 year, and 10 000 units in 10 mL 0.9% saline for children aged $<$1 year. The summary of product characteristics of alteplase does not include approval for empyema in adults or children, and only case-series have been published.

The drain should be removed when there is clinical resolution. An obstructed drain that cannot be unblocked should be removed too, but replaced if significant pleural fluid remains. Pain control is extremely important during the time in which the chest drain remains in place.

Another pleural drainage method to be considered is surgery. Three surgical methods are available.

- Video-assisted thoracoscopic surgery (VATS), which achieves debridement of fibrinous pyogenic material, breakdown

of loculations and drainage of pus from the pleural cavity under direct vision, leaving two or three small scars.
- Mini-thoracotomy, which procures debridement and evacuation in a similar way to VATS but as it is an open procedure leaves a small linear scar.
- Decortication, which involves an open posterolateral thoracotomy and excision of the thick fibrous pleural rind with evacuation of pyogenic material.

Early VATS should be considered an alternative to tube thoracostomy, with or without fibrinolytics, when a loculated effusion is present and its use will largely depend on local availability and expertise. It seems to offer the same clinical outcomes compared to simple chest tube drainage. Mini-thoracotomy should be reserved for more complex cases, and decortication should be performed only in symptomatic children with organised empyema not responding to previous treatment or in cases of lung entrapment.

Intravenous antibiotic treatment should continue until the child is afebrile or the chest drain is removed. Oral antibiotics, such as co-amoxiclav, are then administered for an additional 1–4 weeks after discharge or even for a longer period of time if there is residual disease.

Follow-up and long-term outcome At discharge, most children will have abnormal chest radiographs and clinical examination (diminished breath sounds and some dullness on the affected area due to pleural thickening), which must not cause concern. Most affected children will return to having normal radiographs and clinical examination in 3–6 months and after 12–18 months they will have a full clinical recovery. Opposite to what happens in adults, long-term prognosis of parapneumonic pleural effusion or empyema in children is excellent and significant complications or sequelae are uncommon.

Chylothorax

Chylothorax is the accumulation of chyle in the pleural space and is an uncommon cause of pleural effusion in children. It is usually caused by an injury to the thoracic duct during surgery. The thoracic duct collects lymph from the abdomen, lower limbs, left thorax, head, neck and upper limbs. Disruption of the duct between the diaphragm and T5 usually yields chylothorax on the right side, while a left-sided chylothorax can be seen when damage occurs above T5.

Aetiology Most cases of chylothorax in children are acquired and of iatrogenic origin. According to some studies, cardiothoracic surgery accounts for 65–80% of all paediatric chylous effusions. Congenital presentation represents only a small percentage in the paediatric age group, although it is the most common type of pleural effusion in the neonatal period (table 1).

Diagnosis Antenatal chylothorax can lead to restriction of normal lung development and cause lung hypoplasia. For this reason, severe respiratory distress can be present in some cases of congenital chylothorax. Respiratory symptoms depend on the size of the effusion and most patients will show varying degrees of dyspnoea, cough or chest discomfort. Large volumes of chyle can lead to significant cardiorespiratory compromise.

A chest radiograph will demonstrate a unilateral or bilateral pleural effusion (fig. 2). Chylothorax should be suspected when an extensive pleural effusion occurs in a neonate with a lymphatic malformation, some genetic syndromes, or after cardiothoracic surgery (table 1).

Although pleural fluid from chylothorax is typically milky it can appear completely clear when fasting. Definite diagnosis relies on the biochemical analysis of the fluid drained from the pleural space. This study will show an elevated level of triglycerides >110 mg·dL^{-1}, and the presence of chylomicrons. A high lymphocyte count may also be present.

Diferential diagnosis should be made with empyema and pseudochylothorax, which develops when an exudative effusion remains in the pleural space for a long

Table 1. Aetiology of chylothorax in children

Traumatic
Iatrogenic
Surgical
Cardiothoracic surgery
Scoliosis or neck surgery
Invasive procedures
Subclavian vein catheterisation
Non-iatrogenic
Forceful emesis or cough
Hyperextension of the neck or thoracic spine
Mechanism of birth
Blunt trauma
Penetrating chest trauma
Non-traumatic
Congenital
Abnormalities of the lymphatic system
Primary or secondary lymphangiectasis
Lymphangiomatosis
Lymphatic dysplasia syndrome
Genetic syndromes
Noonan syndrome
Turner syndrome
Down syndrome
Infectious
TORCH infections
Thoracic duct atresia/agenesia
Congenital diaphragmatic hernia
Congenital cystic malformation of the lung
Congenital heart disease
Congenital mediastinal/pleural tumours
Hydrops fetalis
Idiopathic
Antenatal primary fetal hydrothorax
Elevated venous pressure in the superior vena cava
Secondary to a Fontan-procedure
Venous thrombosis
Infectious
TB
Filariasis
Histoplasmosis
Malignancies
Lymphoma
Teratoma
Sarcoma
Neuroblastoma
Others
Transdiaphragmatic movement of chylous ascites
Systemic disorders
Cardiac failure
Benign tumours

TORCH: toxoplasmosis, rubella, cytomegalovirus and herpes simplex virus.

period of time and gradually becomes enriched with cholesterol.

Management Chest drainage with tube thoracostomy, together with nutritional modifications, has been the mainstay of treatment for many years. More recently, a dietary approach alone has been suggested as the initial treatment option.

Medical therapy *Nutritional*: the use of medium chain triglyceride milk formulas decreases overall lymphatic flow through the thoracic duct, while allowing spontaneous healing of the duct injury. Another option is total parenteral nutrition with bowel rest, although most reports indicate little difference in outcome compared to medium chain triglyceride enteral nutrition. Chest drainage cessation with this dietary approach ranges from 1 to 4 weeks.

Medications: somatostatin and synthetic analogues (octreotide) have been used in the treatment of chylothorax resistant to dietary modifications. Although their mechanism of action is not completely understood, it seems that they reduce the

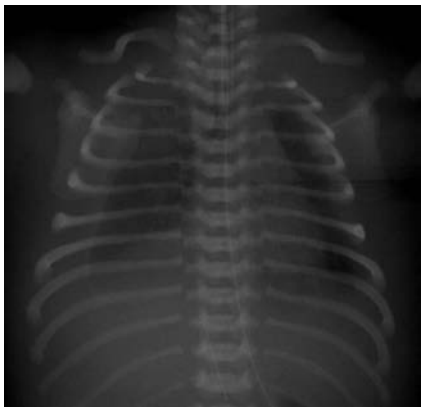

Figure 2. Chest radiograph of a small infant with bilateral chylothorax.

intestinal blood flow by vasoconstriction of the splachnic circulation with reduction of lymphatic fluid output. In addition, they decrease gastrointestinal motility, and gastric, pancreatic and biliary secretions, significantly diminishing the lymphatic flow. Dosage and method of delivery are not definitely established. Other medications such as nitric oxide, etilefrine and corticosteroids have been used in single case reports in adults.

Surgical therapy The main indication for surgery is persistent chest drainage despite nutritional modifications and bowel rest. The most frequently used surgical techniques are described below.

Pleurodesis: can be performed surgically or using chemical agents. Sclerosing substances (tetracycline, povidone-iodide and talc) can be administered directly through the thoracostomy tube or with the assistance of VATS. Chemical pleurodesis with povidone-iodide has shown good tolerance and relative success in congenital idiopathic chylothorax in neonates.

Thoracic duct ligation: although direct surgical ligation of the thoracic duct at the rupture site would seem the most definitive treatment, it has yielded variable results with success rates between 25% and 100% in different series including a small number of patients.

Pleuroperitoneal shunt: persistent chylothorax refractory to the standard medical or surgical therapies can be managed with pleuroperitoneal shunting. The pleural and peritoneal cavities are communicated by a valved catheter placed subcutaneously. Fluid is pumped from the chest into the abdomen where it is absorbed by peritoneal vessels. Possible complications include malfunction and infection.

If untreated, chylothorax can lead to nutritional compromise and immunological problems.

Haemothorax

Aetiology Haemothorax is a rare condition in children in which blood accumulates in the pleural space. It is usually caused by blunt or penetrating thoracic trauma and may be life threatening if a large-volume rapidly developing haemothorax occurs. Bleeding from lacerated intercostal vessels or bone surfaces in rib fractures are the most common sources for haemothorax in children. Other less frequent lesions such as pulmonary parenchymal lacerations or lung contusions may cause persistent and gradually increasing blood storage inside the chest. Massive haemothorax with hypovolaemic shock is indicative of injury to a great vessel or the heart, and has a mortality rate of >60%.

Diagnosis Clinical symptoms depend on the severity of haemothorax; tachypnoea, some degree of respiratory distress and decreased oxygen saturation are usually observed. In those cases with massive bleeding a diminished level of consciousness and clinical signs of haemodynamic instability are usually present. On auscultation, ventilation will be reduced or completely absent on the affected side. When two or more rib fractures are present there is a high probability of multisystem injury including pulmonary contusion and haemothorax. As in adults, children with lung contusions have the same incidence of serious complications associated to this condition, such as pneumonia or acute respiratory distress syndrome (ARDS).

If haemothorax is suspected a chest radiograph is the first image test to be performed. Due to the supine position, fluid present in the pleural space will be diffusely distributed across the lung field giving an image of generalised increased opacity. Ultrasound is a quick and useful test in demonstrating cardiac or lung injuries and haemothorax, but a chest CT scan is the most valuable diagnostic tool, especially if a great vessel injury is suspected (fig. 3).

Management Management of significant haemothorax must deal with two crucial conditions:

- increased intrapleural pressure with secondary lung collapse,
- reduced blood volume with possible haemodynamic instability.

Both situations can be severe enough to seriously compromise oxygenation and cardiac output. Initial management measures must be directed to correct both conditions by means of ensuring an adequate airway and restoring the intravascular volume. When diagnosed, blood should be promptly removed from the pleural cavity with tube thoracostomy. Large catheters are preferable although they should be matched to the patient's age and size. In some cases, haemodynamic collapse may occur with rapid evacuation of the blood inside the chest. This is explained because it may act as a tamponade reducing ongoing blood loss from the intravascular space. In this situation, intermittent clamping of the chest tube may be of some benefit in re-establishing the tamponade effect.

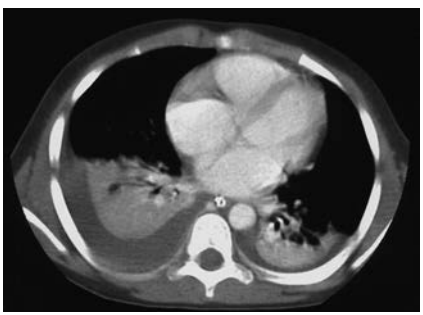

Figure 3. Chest CT showing bilateral haemothorax and lung contusion secondary to blunt trauma.

In most cases, bleeding will stop spontaneously within a short period of time without requiring any further surgical intervention. Drainage of the pleural cavity with effective lung expansion is all that is needed in this setting. Persistent bleeding in an unstable patient is an indication for urgent thoracotomy. Guidelines for operative intervention are: a bleeding rate of 2–3 $mL \cdot kg^{-1} \cdot h^{-1}$ in a child over 4 h (200–300 mL per hour in an adolescent), or a return of 20–30% of the blood volume in a child at chest tube placement (1000–1500 mL in an adolescent). As a general rule, the physiological response of the patient to volume resuscitation is the best guide in decision making and a prompt and sustained answer precludes surgical exploration. In selected cases of ongoing haemothorax, in an otherwise stable patient, thoracoscopy (VATS) may be considered instead of thoracotomy in order to identify and control the source of the bleeding.

Complications Hypovolaemic shock is the most frequent complication when massive or persistent haemorrhage is present. Renal failure, severe acidosis or cardiac ischaemia may occur in this setting. When blood inside the pleural space is not drained promptly it may become clotted and organised. Reabsorption may take place in the following weeks or months but in the meanwhile empyema or fibrothorax may develop. In order to prevent these complications, a VATS procedure to evacuate the retained haemothorax is recommended within 1 week of injury.

Mediastinitis

Aetiology Mediastinitis is an infection of the connective tissue of the mediastinum. Most cases of acute mediastinitis usually occur after sternotomy for cardiothoracic surgery but it can also be caused by some oesophagogastric diseases or injuries and from adjacent spread of retropharyngeal or odontogenic infections. In children, an

oesophageal perforation due to a foreign body should be ruled out.

Diagnosis Although mediastinitis is a rare post-operative complication of median sternotomy (0.1–5% of all paediatric patients undergo this procedure), it represents a significant source of morbidity and mortality. Risk factors include: young age, a high anaesthesiologist score, and a long duration of the surgical procedure.

Mediastinitis most often presents days to weeks after cardiac surgery. Clinical signs are variable, usually in the setting of an unfavourable post-operative course. Sepsis, pleural effusion, pneumothorax, pneumomediastinum, thoracic pain, subcutaneous emphysema and odynophagia may be present in a patient with acute mediastinitis. Less frequently, cardiac arrhythmias may occur.

The most common organism isolated in children is *Staphyloccus* spp. but Gram-negative organisms account for up to one third of cases in some series of post-operative mediastinitis. The microbiology of infection among heart and lung transplant patients may differ depending on the underlying condition as well as the use of post-transplant immunosuppression.

Management Treatment for acute mediastinitis involves aggressive intravenous antibiotherapy and surgical management. In post-operative mediastinitis the standard surgical approach includes debridement followed by open wound care with delayed closure. Other surgical alternatives include: closed suction with antimicrobial irrigation, vacuum-assisted closure and muscle flap closure. These strategies have been initially developed for adults and later applied to children. Recently, some authors have suggested treating acute mediastinitis with debridement and concomitant primary closure without prolonged suction or irrigation.

Chronic mediastinitis is characterised by diffuse fibrosis of the soft tissues of the mediastinum. It is a very rare entity that can be seen in granulomatous diseases, such as histoplasmosis, or infections like TB, and after radiation therapy. Treatment remains controversial.

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Pneumothorax and pneumomediastinum

Nicolaus Schwerk, Folke Brinkmann and Hartmut Grasemann

Pneumothorax

Pneumothorax is defined as an accumulation of air in the pleural cavity. It can be classified as primary spontaneous pneumothorax (PSP), secondary spontaneous pneumothorax (SSP) and traumatic or iatrogenic pneumothorax. Whereas PSP occurs in the absence of an underlying disease, SSP is the result of pre-existing lung affection (table 1).

Key points

- The most common cause of pneumothorax in paediatric patients is the rupture of bullae or blebs in the apex of the lung without an underlying predisposing lung disease or history of trauma.
- When pneumothorax is suspected, standard erect posterior to anterior chest radiograph in inspiration technique represents the diagnostic gold standard.
- Patients with pneumothorax who experience symptoms should be treated with oxygen supplementation and needle aspiration or chest catheter insertion independent of the size of the pneumothorax.
- In the setting of recurrent pneumothorax, surgical treatment is indicated. The preferred technique consists of the resection of the causative bleb or bulla and a pleurodesis procedure.

Epidemiology Epidemiological data in children and adolescents are scarce. PSP in adults shows male predominance with a reported incidence of 18–28 cases per 100 000 in males and 1.2–6 cases per 100 000 in females. In children, a male predominance is also consistently reported (65–80%), with a mean age at presentation of 14–16 years. While typically tall, thin boys with a below-average BMI are affected, it is important to note that a pneumothorax can occur in any age group. Smoking is a recognised risk factor for PSP.

Pathogenesis Apical subpleural blebs and bullae are often found in patients with PSP (55–88% at the ipsilateral side and 15–66% at the contralateral side). Rupture of these lung bullae or blebs that develop without an underlying lung disease or history of trauma is generally considered to be the cause of PSP. The gradient of negative pleural pressure increases from the lung base to the apex, so that alveoli at the lung apex, especially in tall individuals, are subject to significantly greater distending pressures than those at the lung base. Presumably, these pressure differences predispose to the development of apical subpleural blebs. However, the presence of blebs is not a reliable predictor to estimate the recurrence risk in patients suffering from PSP, and apical subpleural blebs and bullae can also be found in healthy subjects. In children with PSP and basilar subpleural bullae or blebs and a positive family history for PSP, Birt–Hogg–Dubé syndrome should be considered. Blebs or bullae in the lower lobes can be detected in almost all patients with this autosomal dominant disorder,

Table 1. Causes of secondary and traumatic/iatrogenic pneumothorax

Congenital pulmonary malformations (congenital cystic adenomatoid malformation), congenital emphysema and lung hypoplasia
Asthma
Bronchiolitis obliterans
CF
Diffuse parenchymal lung diseases
Systemic inflammatory diseases, *e.g.* rheumatoid arthritis, systemic lupus erythematodes, polymyositis and dermatomyositis
Sarcoidosis
Connective tissue diseases, *e.g.* Marfan syndrome and Ehlers–Danlos syndrome
Foreign body aspiration
Infections, *e.g.* *Pneumocystis jirovecii*, TB, parasitic necrotising pneumonia or abscess, and bronchiolitis
Langerhans cell histiocytosis
Malignancies, *e.g.* lymphoma, pleuropulmonary blastoma and metastasis
Post-surgical trauma
Sjögren syndrome
Ventilator-associated interstitial emphysema

which is caused by a mutation in the folliculin gene, and 40% will develop PSP.

A special form of pneumothorax is ventilator-associated interstitial emphysema. Rupture of alveoli during mechanical ventilation, especially in neonates, can lead to air entry into perivascular connective tissue. Gas then migrates into the interstitium and becomes trapped within the pulmonary perivascular sheaths, resulting in interstitial emphysema. Rarely, a pneumothorax results from infection with gas-producing microorganisms, penetrating tumours or chest wall defects. Chest wall defects can be traumatic or iatrogenic. SSP constitute a threat in patients with pre-existing underlying lung diseases and management in these individuals is potentially more challenging. SSP in patients with CF is associated with a significantly increased mortality risk. Treatment for SSP should be more aggressive than for PSP (*e.g.* broad indication for a chest drain insertion) and special consideration may need to be given to the treatment of the underlying disease. Therefore, following the initial treatment, patients with SSP should be transferred to a specialised centre whenever possible.

Symptoms PSP can develop following manoeuvres that result in increased intrathoracic pressures (*e.g.* lifting) but most commonly occurs at rest. Typical symptoms are chest pain and dyspnoea. Symptoms can be relatively minor and self-limiting within 24 h so that a high index of initial diagnostic suspicion is required. In patients with SSP, clinical symptoms are usually more severe than those associated with PSP and may include severe breathlessness, even with small pneumothoraces. Severity of clinical symptoms is therefore an unreliable indicator of pneumothorax size. Characteristic signs on physical examination include:

- diminished breath sounds,
- reduced lung expansion,
- decreased vocal fremitus,
- hyperresonance on percussion at the side of the pneumothorax.

These signs can be subtle or even absent, especially in neonates or infants. As pneumothorax in this younger age group is potentially life threatening, a chest radiograph in any situation of unexplained cardiorespiratory symptoms is required to rule out pneumothorax. At any age, in the case of cardiorespiratory distress with tachycardia, hypotension and/or cyanosis, a tension pneumothorax must be considered and rapid diagnosis and treatment is mandatory (fig. 1).

Imaging Standard erect posterior to anterior chest radiograph in inspiration technique remains the diagnostic gold standard, notwithstanding limitations including, for instance, the problem of quantifying the size of a pneumothorax. Typical radiological signs are displacement of the pleural line and an air–fluid level visible in the costophrenic angle (fig. 2). Supine and lateral decubitus chest radiographs are alternative options for patients who cannot be moved safely. In patients with cystic lung lesions, such as congenital pulmonary malformations or Langerhans cell histiocytosis (fig. 3), the lesions can lead to diagnostic errors, with potentially fatal consequences for the patient. Therefore, in uncertain cases alternative techniques such as ultrasound or CT can be helpful. It is important to note that CT scans are only justified when confirming the diagnosis is of clinical and therapeutic relevance.

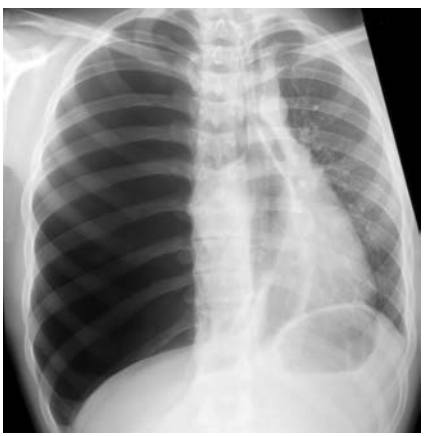

Figure 1. Tension pneumothorax.

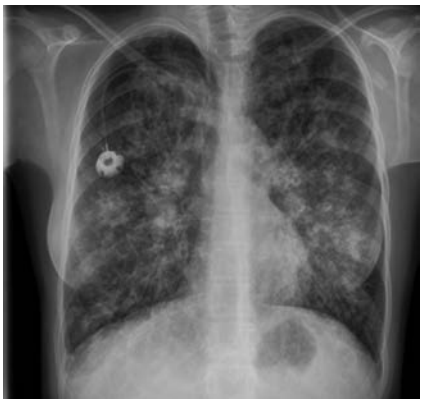

Figure 2. Pneumothorax in CF.

There are numerous different approaches to calculate the size of a pneumothorax. Commonly the erect radiograph has been used for these quantifications. According to the British Thoracic Society (BTS) guidelines a large pneumothorax is defined as a 2-cm gap between the entire lateral lung edge and the chest wall. In the guidelines of the American College of Chest Physicians (ACCP) a large pneumothorax is defined as an apical distance of 3 cm. However, since

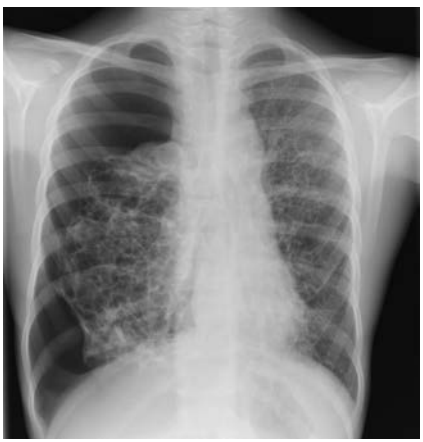

Figure 3. Pneumothorax in Langerhans cell histiocytosis.

pneumothorax size does not closely correlate with its clinical manifestations, a thorough clinical evaluation is probably more important for determining the proper management strategy than the estimation of its actual size.

Therapy There are no evidence-based guidelines for the treatment of pneumothorax in children, and recommendations of different national and international guidelines for adult patients are controversial. Therefore, treatment decisions are often made on the basis of institutional guidelines. It is generally agreed that a patient with pneumothorax who experiences symptoms should be treated independently of the size of the pneumothorax. Asymptomatic children should be observed in hospital for at least 24 h. A repeat chest radiograph should be obtained prior to discharge to exclude expansion of the pneumothorax.

Observation only (watch and wait) Conservative treatment with observation only in asymptomatic patients with small pneumothoraces has been shown to be safe. Up to 80% of patients are estimated to have no active air leak, and recurrence in those managed by observation only is equal or even less frequent than in those treated with chest drainage. Nevertheless, a long time to resolution of up to 30 days has to be considered.

Supplemental oxygen at high concentrations generates a partial pressure gradient between the pleural cavity and the capillary blood by decreasing the partial pressure contribution of nitrogen. This accelerates the absorption of gas from the pleural cavity. Small case series have shown a four-fold increase in the rate of pneumothorax resolution in patients treated with supplemental oxygen compared to patients managed by observation only. Therefore, supplemental high-flow oxygen should be given to all patients hospitalised for a pneumothorax.

Needle aspiration and intercostal chest catheter insertion There is an emerging body of evidence that, in adult patients with PSP, a single needle aspiration is not inferior to intercostal chest catheter (ICC) insertion with respect to success and recurrence rates. Moreover, needle aspiration is less invasive, more cost-effective and associated with lower complication rates compared to ICC. Unfortunately, no randomised controlled trial comparing needle aspiration to ICC has been conducted in paediatric patients to date. In the BTS guidelines for adult patients it is recommended that aspiration of a maximum of 2.5 L should not be exceeded in order to avoid re-expansion oedema. Control radiographs are suggested after single aspiration to assess the presence of ongoing air leak. ICC insertion should be considered in the case of:

- age <1 year,
- bilateral pneumothorax,
- tension pneumothorax,
- evidence for a big air leak (although this may result in bronchopleural fistula),
- pneumothorax recurrence within the first hours following aspiration,
- co-existence of a pleural effusion especially in the case of haemothorax.

Furthermore, chest drain insertion should be performed in all children with iatrogenic and traumatic pneumothorax, SSP or co-existing pneumomediastinum. The success rates for small-bore ICCs are comparable to large-bore ICCs while being less painful; however, large-bore ICCs are indicated when the rate of air leak exceeds the capacity of a smaller ICC. Needle aspiration or ICC insertion should only be performed by, or under the supervision of, medical staff experienced in the procedure. Initial chest radiograph imaging should guide the site of placement. An appropriate approach in the majority of cases is the ''triangle of safety'', which is bordered anteriorly by the lateral edge of pectoralis major, laterally by the lateral edge of latissimus dorsi, inferiorly by the line of the fifth intercostal space and superiorly by the base of the axilla (fig. 4). An alternative approach is the second intercostal space in the mid-clavicular line. Proper sedation should be given in addition to local anaesthetic. After insertion, ICCs should be connected to a Heimlich valve or

an underwater seal device. The benefit of continuous suction is unclear. Since initial suction might increase the risk of re-expansion pulmonary oedema it is only recommended if lung re-expansion has not occurred at 48 h or if there is a persisting air leak, which may indicate a bronchopulmonary fistula. Optimal suction should entail pressures of -10– -20 cmH_2O.

Surgical management The primary aim of a surgical intervention is to prevent recurrence of pneumothorax. Nevertheless, the detection of blebs or bullae in patients with their first PSP normally does not require surgical intervention. Current indications for surgical intervention include:

- second ipsilateral pneumothorax,
- first contralateral pneumothorax,
- bilateral pneumothorax,
- persistent air leak,
- associated haemothorax,
- following a first episode in professionals at risk, including pilots and divers.

Surgical treatment consists of the resection of the causative bulla or bleb associated with some type of pleurodesis procedure, either pleurectomy or pleural mechanical abrasion. Chemical pleurodesis is not used in children because of its potentially severe side-effects.

The current gold standard in the adult literature is blebectomy and apical parietal pleurectomy. Newer surgical techniques such as video-assisted thoracoscopic surgery (VATS) have also been shown to be safe and effective in children. Advantages of VATS are decreased post-operative pain, reduced length of hospital stay and improved lung function.

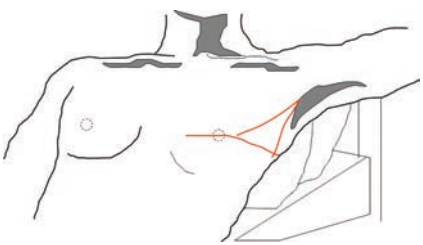

Figure 4. Schematic diagram of the triangle of safety.

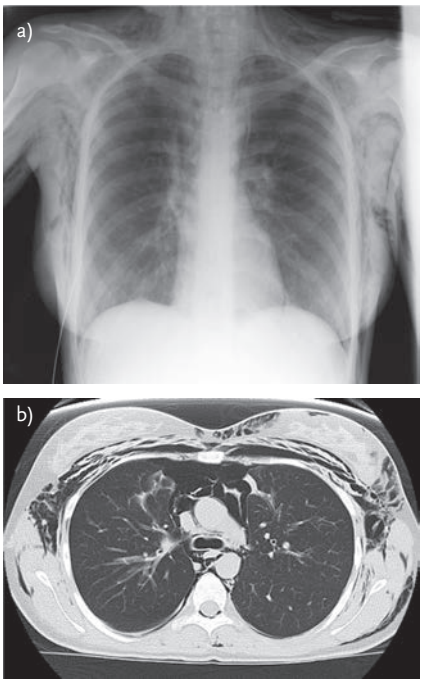

Figure 5. Pneumomediastinum. a) Radiograph and b) CT.

Recurrence Whether children with PSP have a higher rate of recurrence than adults remains unclear. Reported data from small case series range between 20% and 50% after first PSP and 1–15% after surgical treatment. Recurrence risk in paediatric patients with SSP depends on the course of the underlying disease.

Pneumomediastinum and subcutaneous emphysema

Pneumomediastinum is defined as the presence of free air in the mediastinum.

Epidemiology Currently there are no epidemiological data in the paediatric literature, but undoubtedly pneumomediastinum is an exceedingly rare condition in this age group.

Pathogenesis Rarely, pneumomediastinum can occur as spontaneous pneumomediastinum (*e.g.* Hamman's

Table 2. Predisposing conditions for pneumomediastinum

Allergic bronchopulmonary aspergillosis
Asthma exacerbation
Barotrauma
Blunt or penetrating trauma of the chest wall
Bronchiolitis obliterans
Bronchopulmonary dysplasia/chronic lung disease
Central venous or cardiac catheterisation
Connective tissue diseases-related interstitial lung disease
CF
Diffuse parenchymal lung diseases
Endoscopic/bronchoscopic interventions
Foreign body aspiration
Infections, *e.g.* influenza A/B virus, *Mycoplasma pneumoniae, Pneumocystis jirovecii* and *Aspergillus fumigatus*
Mechanical ventilation
Oesophageal perforation
Penetrating tumours
Pneumothorax (PSP and SSP)
Surgical interventions

syndrome) in the absence of a specific underlying disease. In these cases it is thought to be the result of a sudden increase in intrathoracic pressure (*e.g.* emesis, cough, physical activity or defecation) and subsequent alveolar rupture. Further leakage of air throughout the interstitium and bronchovascular tissue follows a centripetal pattern towards the mediastinum. In most cases, however, pneumomediastinum is thought to be a complication of a specific underlying disease or the result of a specific pathological event leading to rupture of lung parenchyma or the bronchial tree (fig. 5). Given the grave clinical consequences of pneumomediastinum and the necessity to institute specific treatment of an underlying cause, responsible predisposing conditions have to be excluded (table 2).

Symptoms The severity of symptoms depends on pneumomediastinum size and the underlying cause. While symptoms in children with spontaneous pneumomediastinum can be mild, pneumomediastinum as a complication of an underlying disease can be life threatening with reported mortality rates of up to 40%. Typical clinical signs are chest pain, dyspnoea and cough. In 30–40% pneumomediastinum is associated with subcutaneous emphysema with soft tissue swelling of the neck, the face and sometimes the whole chest wall in conjunction with characteristic subcutaneous crepitations.

Imaging As for pneumothorax the diagnosis of pneumomediastinum is made by radiography. However, up to 30% of cases of pneumomediastinum are missed on chest radiographs, therefore CT has become the gold standard for diagnosis, especially when the underlying predisposing condition is unknown.

Therapy In the adult literature, several surgical techniques have been reported to treat pneumomediastinum and subcutaneous emphysema including mediastinal drain insertion, subcutaneous pigtail or large-bore drains with or without suction. All of these methods are invasive and have an increased risk of infection. The most important therapeutic approach is the treatment of the underlying cause. In addition to this, conservative treatment including analgesics, bed rest and avoidance of Valsalva manoeuvres may be beneficial. Symptoms generally improve within 3–15 days without sequelae. It is not clear whether preventive antibiotic therapy can reduce the risk of secondary infections of the mediastinum. Nevertheless, antibiotic treatment should be initiated generously in patients with extended trauma of the bronchial tree, the oesophagus, or a known infection as the underlying cause of pneumomediastinum.

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Neuromuscular disorders

Anita K. Simonds

Prevalence

While some neuromuscular diseases are very rare, as a group the neuromuscular disorders in childhood are quite common, with an overall prevalence of about 1:3000. Most are inherited in origin, the commonest being Duchenne muscular dystrophy, spinal muscular atrophy, congenital muscular dystrophies and myopathies. The probability of respiratory complications varies according to diagnosis, genotype and age (table 1) and in the past 20 years an increasing amount has been learned about genotype–phenotype correlations and respiratory management strategies. In some conditions, the natural history has changed significantly with the introduction of ventilatory support.

Assessment of pathophysiology

Children with neuromuscular weakness have a restrictive pattern of spirometry on pulmonary function testing. This is caused by variable combinations of reduced inspiratory muscle strength, the presence of a thoracic scoliosis and reduced chest wall and pulmonary compliance – the latter caused by micro- or macro-atelectasis. Inspiratory and expiratory muscle strength mostly decrease in parallel, but when diaphragm strength is preserved expiratory muscle weakness may predominate *e.g.* in spinal muscular atrophy. Expiratory muscle weakness combined with inspiratory muscle weakness leads to poor cough efficacy and secretion clearance and can be measured by cough peak flow – values less than 270 $L \cdot min^{-1}$ in children aged approximately 10 years and above suggest reduced cough power, and values less than 160 $L \cdot min^{-1}$ are associated with increased frequency of chest infections. A vital capacity of $\leqslant 60\%$ predicted is predictive of the presence of sleep disordered breathing, which initially occurs in REM sleep and then spreads to all sleep stages. Usually this appears as nocturnal hypoventilation, but obstructive hypoventilation may be seen in some conditions *e.g.* Duchenne muscular dystrophy. Sleep studies should be carried out routinely in these children or in any with sleep-related symptoms or recurrent chest infections, in those requiring hospitalisation, or in failure to thrive. Scoliosis is common and will occur in virtually all children with spinal muscular atrophy types 1 and 2, and in 70–90% of those with Duchenne muscular dystrophy. Scoliosis progresses with the adolescent growth spurt and transition to permanent wheelchair use. Use of steroid therapy and preservation of standing using frames may reduce scoliosis severity. Scoliosis surgery is carried out to prevent progression of the

Key points

- Neuromuscular disorders are relatively common, with a prevalence of 1:3000.
- Sleep disordered breathing is likely when vital capacity falls to <60% predicted.
- NIV is indicated to control symptomatic sleep disordered breathing.
- Use of NIV in Duchenne muscular dystrophy may double life expectancy.

curvature and achieve comfort rather than to increase lung volumes.

Bulbar involvement is inevitable in type 1 spinal muscular atrophy and some conditions such as myotubular myopathy and myotonic dystrophy, but in others, *e.g.* Duchenne muscular dystrophy, it is a late-stage phenomenon. Assessment of swallowing function is a key part of respiratory management in any child with neuromuscular disease – weakness is suggested by slow feeding, choking, aspiration and recurrent chest infections. Nutritional assessment is also crucial and if adequate nutrition cannot be achieved safely orally, then percutaneous gastrostomy placement may significantly improve quality of life and reduce respiratory complications.

Sleep studies

Overnight oximetry is often used to screen for sleep disordered breathing in children with neuromuscular disease. While a normal trace in a child who has slept well usually excludes a significant problem, values of arterial oxygen saturation within the normal range can occasionally be seen in children with mild obstructive sleep apnoea/hypopnea and can be accompanied by hypercapnia in children using CPAP or NIV. If there is a high suspicion of sleep disordered breathing, multichannel monitoring including a measure of overnight carbon dioxide tension (*e.g.* transcutaneous CO_2) is preferred.

Long-term assisted ventilation

Measurement of CO_2 control is also required to assess ventilator efficiency in children started on NIV. NIV is recommended in children with daytime hypercapnia or symptomatic nocturnal hypoventilation. Noninvasive approaches are preferable providing bulbar function is adequate. Pressure-preset ventilators are usually used. Care should be taken to ensure ventilator performance meets the child's ventilatory needs: for example, if the inspiratory trigger is insensitive, work of breathing increases; but if it is too sensitive, auto-triggering resulting in asynchrony may occur. In addition, mask rotation and avoidance of tight-fitting interfaces should be employed to reduce the risk of pressure over facial structures resulting in mid facial hypoplasia and pressure sores. Customised masks reduce the occurrence of mask-related problems in children.

Research has shown that NIV in Duchenne muscular dystrophy extends survival – pre-ventilatory support, median survival was about 18 years; about a third of patients with the disease now live into their 30s and 40s. Similarly in type 2 spinal muscular atrophy and the congenital muscular dystrophies, NIV is associated with a reduction in respiratory tract infections, with improved school attendance and quality of life. Type 1 spinal muscular atrophy comprises a spectrum of infants ranging from those with profound floppiness and inability to feed or smile within weeks of birth and those at the opposite end who are almost able to sit and have later-onset respiratory problems similar to those with type 2 disease. A nuanced response to ventilatory support is required – in some instances, this may be life saving and extend life by many years, while in others with more severe disease NIV may palliate symptoms or respiratory distress and allow hospital discharge but is not intended to extend life expectancy. Goalsetting and an anticipatory care plan (see below) are an important part of the care of any child with neuromuscular weakness.

Chest physiotherapy and cough augmentation

Standard chest physiotherapy is vital to successful management and may be complemented by manual cough augmentation and breath stacking to improve lung recruitment, using an ambu-bag. Use of NIV alone may help with secretion clearance, and physiotherapy should be performed while the child uses the ventilator. However in those with cough peak flow <270 $L \cdot min^{-1}$, and/or poor cough in whom the above simpler techniques are not sufficient, a cough in–exsufflator device may improve cough peak flow and reduce pulmonary morbidity. A randomised controlled trial in children and adults has

Table 1. Respiratory complications of neuromuscular disorders

Condition	Respiratory failure	Secretion clearance difficulty	Recurrent pneumonia	Progression	Disease-specific features
SMA					
Type 1	All by 2 years	Marked	All	Rapid	All require full-time respiratory support
Type 2	~40% in childhood	Early	~25% in first 5 years	Slow	
Type 3	Rare in childhood	Rare in childhood	Rare in childhood	Slow	
SMA with respiratory distress type 1	All by 6 months	Marked	All	Rapid in first year, then slows	All require full-time respiratory support
DMD/severe childhood onset limb-girdle muscular dystrophy	After loss of ambulation	After loss of ambulation	Late		Cardiomyopathy usually occurs after respiratory problems but may precede them
Facioscapulohumeral muscular dystrophy	When onset <20 years	With infantile onset	With infantile onset	Slow	Severe infantile onset type is frequently associated with sensorineural deafness
Congenital muscular dystrophy					
All types	Any age depending on severity	Any age depending on severity	Any age depending on severity	Slow	
Ullrich	70% in adolescence	Mild	Infrequent		Proximal contractures with marked distal laxity
Rigid spine muscular dystrophy	Early while ambulation preserved	Mild	Infrequent		Hypoventilation may occur in ambulant children with relatively preserved vital capacity
Congenital myopathy					
Central core	Uncommon except in severe recessive type	Uncommon	Uncommon	Slow	Susceptible to malignant hyperthermia
Minicore	Early while ambulation preserved				
Nemaline	Early in severe neonatal form, mild later onset form may develop early while ambulation preserved	In severe form	In severe form	Slow	
Myotubular	85% in severe X-linked form	In severe form	In severe form	Slow	Ophthalmoplegia, rare coagulopathy and liver haemorrhage

Table 1. Continued

Condition	Respiratory failure	Secretion clearance difficulty	Recurrent pneumonia	Progression	Disease-specific features
Fibre type disproportion	Depends on genotype	Uncommon	Uncommon		
Myotonic dystrophy					
Myotonic dystrophy 1	Common in severe congenital onset, usually improves	Common in severe congenital onset	Common in severe congenital onset	Initial improvement, later slow deterioration	Prominent learning difficulty, somnolence, central hypoventilation
Myotonic dystrophy 2	Uncommon	Uncommon	Uncommon		
Congenital myasthenic syndromes	Often in neonatal period, may occur during inter-current illnesses	Especially during inter-current illnesses	Possible if weakness severe and persistent		Weakness may fluctuate, episodic apnoea in some. Congenital stridor in those with *DOK7* mutations
Mitochondrial myopathy	Common	Possible	Possible	Acute deterioration possible	
Charcot–Marie–Tooth	With severe early onset, especially with GDAP1 mutation	With severe early onset	With severe early onset		Stridor, especially with *GDAP1* mutation
Pompe	Infantile onset, may be early in later onset while ambulation preserved	Infantile onset	Infantile onset	Infantile rapid, late onset slow	Variable relationship between motor and respiratory progression

SMA: spinal muscular atrophy; DMD: Duchenne muscular dystrophy. Reproduced from Hull *et al.* (2012) with permission from the publisher.

shown that in–exsufflation can increase cough peak flow and is well tolerated. Although there are no randomised controlled trials of long term use, the combination of NIV and cough in–exsufflation with or without enteral feeding may reduce the need for a tracheostomy in children with mild-to-moderate bulbar/swallowing dysfunction.

Tracheostomy ventilation

NIV is usually preferable to tracheostomy, as it is simpler for child and family, but invasive ventilation is indicated in the situations listed in table 2. The risk management of a tracheostomy ventilator-dependent child clearly differs from that of a child using NIV.

Acute respiratory complications and intercurrent surgical interventions

Chest infections are the commonest cause of hospital admissions in those with

Table 2. Indications for tracheostomy ventilation

Severe bulbar weakness leading to aspiration
Upper airway problems limiting delivery of NIV
Failure to control ventilation with noninvasive mode
Intractable interface problems
Near 24-h ventilator dependency, especially in early infancy
Patient/family preference

respiratory muscle weakness. Active steps should be taken to reduce pulmonary morbidity with influenza and pneumococcal vaccination, physiotherapy, then active secretion clearance techniques and intensive NIV if a chest infection develops resulting in ventilatory compromise. Some children require NIV only during respiratory tract infections. Physiotherapy while using NIV is less tiring than breathing unsupported, and oxygen can be entrained into the ventilator circuit to normalise arterial oxygen saturation. A small increase in expiratory positive airway pressure (EPAP) setting – *e.g.* from 5 to 7 cmH_2O – may be useful if there is atelectasis; the inspiratory positive airway pressure (IPAP) setting should be titrated to control CO_2 levels. In addition to broad-spectrum antibiotics, nebulised bronchodilators may be useful in children with asthma or bronchial hyperreactivity, but there is no evidence to support routine bronchodilator use in neuromuscular disease.

The manoeuvres listed above can be useful in children in the post-operative period *e.g.* following scoliosis correction or other major surgical procedures. It should be noted that individuals with central core myopathy are at risk of malignant hyperthermia during anaesthesia.

Other systems/complications

A cardiomyopathy is seen in all Duchenne muscular dystrophy patients by the mid-to-late teenage years and should be treated with angiotensin-converting enzyme inhibitor and beta blocker. Cardiac involvement is also highly prevalent in Becker muscular dystrophy, myotonic dystrophy and the lamininopathies such as Emery Dreyfuss muscular dystrophy. The limb girdle muscular dystrophies are a very heterogenous group and cardiac surveillance should be adapted to the underlying disorder – for example cardiac disease is common in the sarcoglycanopathies (LGMD2C-F), but less frequent in the dysferlinopathies (*e.g.* LGMD2B) and calpainopathies (*e.g.* LGMD2A).

Oesophageal reflux and feeding problems are common and may require supplemental feeding. In young adults with Duchenne muscular dystrophy, and in patients managed on ventilator support for many years, a new set of problems are emerging – renal and bladder calculi, and intermittent episodes of bowel pseudo-obstruction probably caused by a combination of autonomic dysfunction and reduced abdominal muscle tone.

Palliative care

Many children with neuromuscular disorders experience muscle, back and joint pain; in fact 40% of older Duchenne muscular dystrophy patients report daily pain and fatigue. Good supportive care and symptom palliation are vital and do not equate with end-of-life care, as symptom relief may be required for many months or years before death. Analgesia should not be stinted for fear of respiratory failure. Careful up-titration of opioids usually avoids this problem and ventilatory support can always be added if respiratory insufficiency ensues.

In all children receiving NIV, an anticipatory care plan should be drawn up by joint consultation between the care team, the patient and family. This covers escalation of therapy during acute exacerbations, and the agreed limits to intervention in the face of long-term irreversible decline.

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Chest wall disorders

Daniel Trachsel, Carol-Claudius Hasler and Jürg Hammer

Paediatric chest wall disorders include the congenital structural anomalies of the rib cage, spine, and thoracic musculature, and a number of acquired chest wall diseases such as costal Ewing sarcoma. Congenital chest wall diseases may be apparent at birth or become apparent with time, usually as a result of disturbed growth and development. In this chapter, the most important features of congenital disorders will be highlighted; a discussion of acquired chest wall diseases is beyond its scope.

Key points

- Despite obvious deformations, lung function remains surprisingly preserved in most individuals with adolescent idiopathic scoliosis, pectus excavatum and pectus carinatum.
- In contrast, severe thoracic restriction conveys a high risk of pulmonary morbidity and respiratory failure in early-onset scoliosis and complex syndromal thoracovertebral malformations.
- Surgical correction rarely improves lung function but may significantly deteriorate the natural history if young individuals undergo early fusion of the thoracic spine.
- Recent developments in orthopaedic techniques allow timely intervention in early-onset scoliosis promoting spinal and chest wall growth, but the potential for improving lung function remains to be clarified.

Pathophysiology of respiratory compromise in chest wall disorders and scoliosis

Long-term respiratory stability requires a sufficient ventilatory reserve and the expectoration of accumulating airway secretions. While infants are limited in their respiratory stability by increased chest wall compliance and collapsibility of the airways, older children with thoracovertebral deformatities are more hindered by abnormal stiffness of the chest. The recruitment of inspiratory reserve to full expansion of the thoracic cage depends on the free mobility of the costo-vertebral and costo-sternal articulations, and on a diagonal resting position of the rips on the vertebrocranial to sternocaudal axis, which allows widening of the chest by lifting the ribs into a horizontal position. For this to be accomplishable with minimal effort, the alignment of the respiratory muscles must provide optimal leverage angles.

The severity of a thoracovertebral malformation often correlates with the degree at which these structural requisites for respiratory stability are lost in affected children who then become more and more exclusively dependent of diaphragmatic breathing, which in turn can be hindered by distortion and flattening of the diaphragm.

Congenital chest wall and sternal defects

Poland syndrome, or Poland sequence, describes a unilateral hypoplasia or aplasia of the pectoral muscle which is associated with a more or less pronounced malformation of the ipsilateral upper extremity, typically a synbrachydactyly, and

occasionally absence of one or more ribs. Concomitant Moebius syndrome may be present. Poland syndrome does not usually affect respiratory function but may have a significant psychosocial impact.

Pectus carinatum The pectus carinatum deformity is three times rarer than pectus excavatum, occurring sporadically, with a familial preponderance in 25% of cases, or as part of genetically determined syndromes such as Marfan syndrome, Noonan syndrome, prune belly syndrome or homocysteinuria. In most affected individuals, cardiopulmonary function is not impaired, but many suffer from the psychosocial impact that may justify surgical correction.

Pectus excavatum The pectus excavatum deformity has a prevalence of 1 in 400 with a male preponderance of 3–5:1. As with the carinatum deformity, its occurrence is sporadic, familial, or syndromic (Marfan or Noonan); in addition, it may be seen in survivors of congenital diaphragmatic hernia, or secondary to longstanding significant upper airway obstruction. Pectus excavatum can become apparent at any age during growth and is not spontaneously reversible except for the secondary form.

Significant pectus excavatum is associated with mild restrictive lung function with a decrease in mean vital capacity (VC) to about 80–85% predicted. The probability of significant restriction is four times higher if the Haller index, defined as the ratio between the transverse thoracic diameter and the narrowest distance between sternum and vertebra, is >7. Significant airway obstruction is rare. Although measurable lung function abnormalities are usually mild, many affected individuals complain about shortness of breath and reduced exercise tolerance.

Available data report no benefit of corrective surgery to lung function but a possible favourable effect on exercise capacity, independently of the therapeutic approach, *i.e.* treatment with a vacuum bell, an open surgical procedure, or minimally invasive repair of pectus excavatum (MIRPE).

The majority of patients, anyhow, seek correction for aesthetic reasons.

Sternal clefts Congenital sternal clefts can be complete or partial. Partial superior clefts prevail; partial lower clefts are often associated with ectopia cordis or Cantrell pentalogy. Other concurrent malformations, *e.g.* midline defects, are found in up to three-quarters of cases, but many individuals with sternal clefts are asymptomatic. Reported complaints include exercise intolerance, cough and vulnerability to lower respiratory tract infections. Early surgical repair is often recommended, the more theoretical rationale being concerns about chest instability and risk of trauma.

Cantrell pentalogy Cantrell pentalogy is a rare, combined midline defect including the pentade supra-umbilical abdominal wall defect with or without evisceration, inferior sternal cleft, pericardial defect or ectopia cordis, median diaphragmatic defect, and congenital heart defect, *e.g.* ventricular septal defect or tetralogy of Fallot. The outcome depends on the extent of the malformation and the complexity of the congenital heart defect. Mortality in children with the complete pentalogy is high.

Thoracoverebral deformities

Isolated congenital scoliosis and adolescent idiopathic scoliosis The period of fastest spine growth is from birth to age 5 years (T1–L5 grows 2.2 cm per year), when spinal length gain is almost 50%. Growth then transiently slows to 1.1 cm per year, and re-accelerates again for the pubertal growth spurt to 1.8 cm per year, starting at age 10–11 years in girls, and 2 years later in boys. The thoracic volume makes up about 6% of its adult size at birth, 30% at age 5 years and 50% at age 10 years.

Early onset scoliosis (EOS) is defined as any scoliosis manifesting before the age of 5 years irrespective of its origin, *i.e.* a congenital (thoraco-)vertebral malformation, neuromuscular disease, specific syndrome or the infantile idiopathic type. 70% of EOS worsen over time and require treatment, approximately half by surgical intervention. The hallmark of EOS is

its propensity to progressive respiratory failure and associated mortality. The overall prognosis is worse in the presence of concomitant thoracic cage malformations or in neurogenic EOS. The best outcome may be expected in cases of idiopathic scoliosis with little rotational deviation (Mehta rib angle difference of <20°).

Survival improves dramatically if idiopathic scoliosis is diagnosed between 5 and 10 years of age, and is normal in *adolescent idiopathic scoliosis* (AIS) patients.

Most individuals with AIS have normal lung function. When scoliosis progresses, however, lung function decreases by the reduction of both the volume and the compliance of the chest, and by the change of the lever arm vectors of the respiratory muscles. TLC is preserved longer than VC, resulting in an extrinsic (asymmetrical) overinflation with an increased residual volume/TLC ratio. Ventilation becomes increasingly inhomogeneous, but bronchial obstruction is found in fewer than 20% of cases. The degree of pulmonary restriction is underestimated if height-based reference values of normal lung function are used.

The Cobb angle cannot reliably depict the three-dimensionality of scoliosis, and it correlates only moderately with the degree of pulmonary limitation. A decrease of the FVC below 80% pred may be expected in AIS from Cobb angles of 70–100° onwards, but the variability of pulmonary restriction remains significant. Rotation in the transverse plane is an important feature of scoliosis, clinically manifesting as rib hump or lumbar hump depending of the height of the scoliosis, and additionally impairs lung function in patients with advanced scoliosis or concomitant thoracic hypokyphosis. It is estimated that height and length of the scoliotic curvature and the presence of hypokyphosis (<10° sagittal angulation) account for up to 20% of FVC reduction.

AIS patients often complain about reduced exercise tolerance. Maximum inspiratory and expiratory pressures (MIPS and MEPS) are about 70% pred on average, which is in part attributable to the disadvantaged leverage vectors of the respiratory muscles, but likely also reflects a generalised muscle weakness that has repeatedly been found in AIS patients and might contribute to the pathogenesis of scoliosis.

Complex syndromal thoracovertebral malformations The complex syndromal thoracovertebral malformations comprise a heterogeneous group of combined malformations of the spine and thoracic cage that lead to severe kyphoscoliosis and/or narrowing and stiffening of the thoracic cage. Respiratory function of affected children is impaired by the thoracic restriction, reduced respiratory muscle function, weak cough and impaired airway clearance. Additional symptoms may arise from associated malformations, gastro-oesophageal reflux and heart failure. These malformations not only cause physical suffering but also enormous psychosocial stress from social marginalisation, school absenteeism and concerns about the future. Medical care, therefore, requires a multidisciplinary approach. Numerous syndromes may manifest with complex thoracovertebral malformations, including diastrophic dysplasia, infantile Marfan, Klippel–Feil, Jeune, and Jarcho–Levin syndromes.

Concept of thoracic insufficiency syndrome (TIS): The severe thoracic restriction is associated with respiratory failure and lung hypoplasia. This common feature led Campbell *et al.* (2003) to propose the concept of TIS in 2003, defined as the inability of the thorax to allow normal respiration and lung growth. TIS has been divided into 4 different types of volume depletion deformities (table 1).

Patients with unilateral absent ribs and associated flail chest have a high mortality in the first years of life. Death is usually caused by respiratory failure and/or right heart failure. The unilateral fused ribs type is the most common form and typically leads to worsening of scoliosis and pulmonary function with growth. The differentiation into the four types of TIS guides the surgical management. For the paediatric pulmonologist, it is important to recognise

Table 1. Types of volume-deficiency deformities causing TIS

Type	Characteristics
I	Unilateral absent ribs with scoliosis and hemihypoplasia of the thorax
II	Unilateral fused ribs with scoliosis and hemihypoplasia of the thorax
IIIa	Vertebral malformation with loss of thoracic height and kyphosis Bilateral longitudinal restriction of the lungs (*e.g.* Jarcho–Levin syndrome)
IIIb	Global thoracic hypoplasia with windswept deformity and lateral lung constriction on both sides (*e.g.* Jeune syndrome)

that both chest radiography and lung function testing do not reliably reflect the degree of respiratory morbidity. Studies suggest that sleep studies may be more sensitive to detect respiratory limitation.

Asphyxiating thoracic dystrophy is a rare osteochondrodysplasia with autosomal recessive inheritance and variable expression that occurs in all ethnicities with an estimated incidence of 1 in 130 000. A narrow, bell-shaped and very stiff thorax with an almost normal-sized vertebral column is the hallmark of the syndrome. Chest width is reduced in both the sagittal and the coronal plane with shortened ribs typically bowed inwards at the tips, resulting in a cloverleaf appearance of the thoracic cage in the transverse plane. Other skeletal features of the pelvis and extremities are common and associated with short stature, and vertebral malformations of the neck need special attention for their potential to damage the cervical medulla. One-third of affected individuals have renal disease including cysts, tubular atrophy and renal failure. Other frequently encountered organ manifestations involve the liver, the pancreas, and the eyes. There is apparently no correlation between the severity of thoracic dystrophy and the extent of parenchymal involvement.

More than 120 cases have been described in the literature. Mortality is as high as 50%, with up to 80% dying within the first 2 years due to respiratory failure and cor pulmonale. Most survivors need some sort of ventilatory support. Thorax-expansion surgery increases the transverse cross-sectional area, but its effect on lung growth remains uncertain. Jeune patients surviving into adolescence are at risk of developing end-stage renal disease.

Spondylocostal and spondylothoracic dysostosis (Jarcho–Levin syndrome/Lavy–Moseley syndrome): The Jarcho–Levin syndrome encompasses individuals with a very short spine and malformed vertebral bodies, and a dysplastic rip cage with fused, dysplastic or absent ribs. Various gene mutations have been found and underlie the phenotypic variations. Spondylo*costal* dysostosis (Jarcho–Levin syndrome *sensu stricto*) may be distinguished from spondylo*thoracic* dysostosis (Lavy–Moseley syndrome). Severe pulmonary restriction leads to chronic respiratory failure, recurrent pneumonias, and right heart failure.

Spondylocostal dysostosis occurs both as autosomal recessive and autosomal dominant trait, and is mainly characterised by:

- an abnormal segmentation of at least 10 consecutive vertebral bodies,
- a costal malalignment, fused ribs and costal bifurcations, or occasionally absent ribs,
- a mild scoliosis with variable potential for progression, depending on the asymmetry of the costal malformations (TIS type II or type IIIa).

Multiple associated malformations are known. Without early thoracic expansion, progression of scoliosis occurs in 75% of cases. Mean survival has improved significantly, but long term prognosis is as yet unknown.

Spondylothoracic dysostosis is an autosomal recessive syndrome seen mostly

in individuals of Puerto Rican descent, characterised by an extremely short spine with posteriorly fused rips giving a crab-like appearance to the chest radiograph (TIS type IIIa). Among other malformations, it may be associated with congenital diaphragmatic hernia which further worsens the prognosis of these children who are almost exclusively dependent on diaphragmatic breathing. Mortality is very high and generally attributable to respiratory failure, pulmonary arterial hypertension and heart failure.

Orthopaedic treatment of scoliosis and thoracovertebral malformations, and impact on lung function Early multiple-level vertebral fusions have been completely abandoned because they result in a short straight or bent spine and a reduced growth of the ribcage that is associated with respiratory compromise and back and chest pain. Up to 50% or 10 cm of the spine length can be lost by spinal fusion before 5 years of age, with a corresponding significant loss of the thoracic volume. At least 22 cm length of the thoracic spine is deemed necessary as a prerequisite for satisfactory lung function.

In contrast, bilaterally implanted spine-based growing rods improve the scoliosis and stimulate the growth of the vertebral column. They have no direct beneficial impact, however, on chest growth and are therefore standard for treatment for EOS without vertebral or costal malformations. EOS that is associated with ribcage malformations tends to progress rapidly and to end in respiratory failure. The primary goal of therapy is thus to partially correct the deformation and stabilise the correction, beginning usually at the age of 1.5–2 years. Rib-based implants such as the vertical expandable prosthetic titanium rib (VEPTR) primarily focus on improving the space available for the lungs, thereby allowing lung expansion and, hopefully, stimulating lung growth. In the near future, new magnetically extensible rods may obviate the need for the repeated surgical interventions required to expand current VEPTR devices with growth, allowing lengthening of the rods in frequent small steps and reducing anaesthetic and infection risks.

Whether these interventions stimulate pulmonary catch-up growth is not yet clear. CT scans have revealed a 25 –90% increase of the thoracic cage after VEPTR, likely consequent to the enlargement of the coronal chest diameter and the stimulation of spinal growth. Reported clinical benefits of expansion thoracoplasty include improved exercise tolerance, reduced ventilatory support, increased body weight, and reduction of polyglobuly. Whether the improvement of these surrogate markers results from improved breathing mechanics, a larger chest volume or even alveolar catch-up growth is a matter of debate. Preliminary longitudinal lung function studies failed to document any significant catch-up growth in children with TIS after repeated thoracic expansion. It is not known whether an age limit exists for possible pulmonary catch-up growth, or whether VEPTR halts the progression of scoliosis and thoracic deformation in children with complex thoracovertebral malformations.

Spinal fusion of AIS rarely leads to improved lung function. Rib hump resection is even accompanied by a 15–20% decrease of FVC in the first postoperative months that slowly recovers to the preoperative level within 2 years. In contrast, in patients with neuromuscular disease, specifically in those with Duchenne muscular dystrophy, timely spinal fusion seems to halve the rate of pulmonary function decline.

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Physiology and pathophysiology of sleep

Sedat Oktem and Refika Ersu

The two-process model of sleep and wakefulness predicts the day-to-day synchronisation of an organism with its environment by the interaction of a circadian (process C) and a homeostatic process (process S). This section provides an overview of basic sleep physiology and pathophysiology, and describes the characteristics of rapid eye movement (REM) and non-REM (NREM) sleep. Sleep and circadian-generating systems are also discussed.

Key points

- The two-process model of sleep and wakefulness predicts the day-to-day synchronisation of an organism to its environment by the interaction of a circadian (C) and a homeostatic process (S).
- Circadian rhythms are driven by an endogenous circadian pacemaker, located in the suprachiasmatic nucleus (SCN) of the hypothalamus. Circadian sleep rhythm controls the sleep–wake cycle, modulates physical activity and food consumption, and over the course of the day, regulates body temperature, heart rate, muscle tone and hormone secretion.
- The SCN sets the body clock to ~24 h. The main influence of the SCN on sleep is due to a series of relays through the dorsomedial nucleus of the hypothalamus, which signals to the sleep–wake systems to coordinate their activity with day–night cycles.
- There are two types of sleep state, NREM and REM sleep.
- NREM sleep is conventionally divided into three or four stages, each with its own distinguishing characteristics.

Sleep may be defined as a state of natural unconsciousness from which a person can be aroused. Despite the advances that have been made in related areas, sleep remains a complicated physiological entity that is not yet fully understood.

For many years, sleep was thought to be a purely passive state. However, sleep is an active process and the brain is actually quite busy during sleep. It is now known to affect both physical and mental health, and is essential for the normal functioning of all the systems of the body. Since the body is known to require sleep as part of its homeostatic regulatory and repair mechanisms, it seems logical that the body can exert considerable influence on the sleep process.

The physiology of sleep and sleep–wake regulation

Sleep is a part of the daily routine for everyone, even when the "normal" sleep–wake pattern is disrupted by outside factors. In humans, the circadian cycle operates in an ~24-h cycle, measured from awakening after one sleep period to awakening from the next sleep period.

The physiological mechanisms of circadian rhythm begin when light strikes special cells within the retina of the eye, which, in turn, causes these cells to secrete melatonin, which causes an area of the brain known as

the suprachiasmatic nucleus (SCN) to signal the pineal body to stop secreting the hormone melatonin, which has been shown to reach its highest levels during sleep. As the day progresses, adenosine accumulates within the brain as the level of melatonin falls.

As night falls, the inhibitory effects of the retinal secretions on the pineal body are removed and this allows the pineal to begin secreting melatonin once again. It is the presence of higher melatonin levels within certain areas of the brain (*e.g.* the thalamus and hypothalamus) that controls the urge to sleep.

Body system changes during sleep are listed in table 1 (NHLBI, 2003; Douglas, 2005).

There have been several theories advanced concerning the biological function of sleep. While no one theory can explain all the observations that have been made regarding sleep, some are more widely accepted than others.

- The *Restorative Theory* of sleep holds that sleep is a time of growth and repair. Some have cited the rise in certain growth hormones during periods of deeper sleep as supporting this hypothesis. However, no one has been able to demonstrate any significant degradation of organ function during periods of sleep deprivation. This theory currently has very little support in the scientific community.
- The *Preservation Theory* states that our sleep cycles are the result of an evolutionary process that grew from our remote ancestors' habits of resting/sleeping at night, a time when predator species enjoyed an advantage in vision and stealth. Over time, the ''sleep when it's dark'' and ''work in the daylight'' behaviors were amplified by natural selection and are present in the brain's neurochemistry.
- The *Memory Encoding* explanation draws upon the large body of evidence demonstrating that learning is facilitated when the body is well rested and that memory retention is enhanced by resting after some new lesson is learned.

None of these theories adequately explain all the facets of sleep as a phenomenon. It is also just as likely that a single theory will never be proposed that will incorporate the ever-expanding knowledge base related to the physiology and function of sleep.

The two-process model of sleep and wakefulness predicts the day-to-day synchronisation of an organism to its environment by the interaction of processes C and S.

Process C Most physiological and behavioural variables in humans, such as heart rate, blood pressure, core body temperature (CBT), hormone levels, food consumption, muscle tone, cognitive performance, subjective alertness and the sleep–wake rhythm, undergo circadian rhythms with an ~24-h periodicity. Circadian rhythms are driven by an endogenous circadian pacemaker, located in the SCN of the hypothalamus. The SCN is the master pacemaker in the mammalian brain that synchronises the circadian oscillators of most neuronal cells and peripheral tissues. The SCN sets the body clock to ~24 h. Light is the strongest zeitgeber for all species, synchronising the endogenous circadian clock to the 24-h day of the environment. Photobiotic activation is transmitted to the SCN *via* the retinohypothalamic tract. When external zeitgebers are absent, the endogenous circadian clock ''free-runs'' with a period that is slightly different from 24 h in humans.

The circadian profile of melatonin secretion and CBT are reliable physiological ''hands of the clock'' and good markers of the circadian process in humans. Under entrained conditions, the onset of melatonin secretion occurs ~13 h after habitual wake-up time and CBT crests in the afternoon with a nadir ~2 h before habitual wake time. Sleep timing and structure are highly dependent on circadian phase. It has been shown that the circadian drive for sleep is highest in the early morning, whereas the circadian drive for wakefulness is highest in the late evening, shortly before bedtime. The paradoxical character of these two extremes

Table 1. Physiological changes during sleep

	Sleep periods	Physiological changes
Cardiovascular system	NREM	Overall reduction in heart rate, cardiac output and blood pressure
	REM	Variations in blood pressure and heart rate but, overall, the rates are increased
Respiratory system	NREM	Slight hypoventilation
	REM	Slight hypercapnia Reduction in total ventilation Reduction in sensitivity to inspired carbon dioxide Reduction in tidal volume Increase in respiratory rate Reduction in rib cage movement Increase in upper airway resistance
Nervous system	NREM	Overall, decreased discharge rate, brain metabolism and blood flow Active inhibition of the reticular activating system Increase in parasympathetic activity similar to relaxed wakefulness Sympathetic drives remain at about the same level as during relaxed wakefulness
	REM	Total blood flow and metabolism in REM sleep are comparable to wakefulness Metabolism and blood flow increase in certain brain regions during REM sleep compared to wakefulness, *e.g.* limbic system, visual association areas During tonic REM sleep, sympathetic activity decreases, resulting in an overall predominance of parasympathetic activity During phasic REM sleep, both sympathetic and parasympathetic activity increase Sympathetic activation is generally favored
Endocrine system		Stage 3 sleep is associated with increased secretion of growth hormone, thyroid hormone, melatonin and prolactin Sleep onset inhibits the release of cortisol
Gastrointestinal tract		Motility and gastric acid secretion decrease during sleep Swallowing reflex slows down during sleep.
Kidney		Decrease in excretion of Na^+, K^+, Cl^- and Ca^{2+} during sleep that allows for more concentrated and reduced urine flow Secretion of aldosterone increases, as does ADH, both of which contribute to the decreased production of urine Decrease in glomerular filtration rate and renal plasma flow
Thermoregulation		At sleep onset, body temperature set point is lowered and body temperature falls

ADH: antidiuretic hormone.

of the circadian system can be explained by the interaction of process S with process C. In the course of a normal 16-h day, when homeostatic sleep pressure increases, a stronger wake-promoting signal is needed in the evening than in the morning, when sleep

pressure is low, to counteract upcoming physiological and behavioural decrements. In contrast, throughout the night-time sleep episode, when homeostatic sleep pressure dissipates, a circadian sleep-promoting signal is necessary to prevent premature waking and to maintain sleep. This concept is drawn from studies with nonhuman primates and indicates that one function of the circadian system is to provide an alerting stimulus, which opposes the accumulating homeostatic sleep drive during waking hours. Besides the circadian, there are also >24-h and <24-h processes, which oscillate in or out of phase with the endogenous circadian pacemaker and have additional modulatory influences on sleep–wake rhythms in humans (Dijk *et al.*, 1995).

Process S Process S was originally assumed to be global, and its parameters were mainly gleaned from central or fronto-central derivations. The general view is that the amount of sleep pressure accumulated during wake time is reflected in the amount of slow-wave sleep (SWS) that occurs during the following period of sleep. Process S depends on prior sleep and wakefulness, and reflects the need for or pressure of sleep. Sleep pressure rises during waking, declines during sleep and increases with sleep deprivation. The build-up or dissipation of sleep pressure is usually represented by an exponential function. Slow-wave activity serves as a marker for sleep homeostasis and, thus, for modelling of process S. Slow-wave activity shows a decline in the course of sleep that can be approximated by an exponential decrease across NREM sleep episodes (Achermann *et al.*, 2011). The level of slow-wave activity in the first NREM sleep episode is dependent on the duration of prior waking and is best described with a saturating exponential function.

The central nervous system regulation of sleep

Wakefulness and arousal from sleep Waking and consciousness depend on the activity of neurons in the ascending reticular activating system of the brainstem. Specifically, there are two ascending pathways. The first pathway, which originates from cholinergic neurons in the upper pons, activates parts of the thalamus that are responsible for maintaining the transmission of sensory information to the cerebral cortex (Saper *et al.*, 2005). The second pathway, which originates in cell groups in the upper brainstem that contain the monoamine neurotransmitters (norepinephrine, serotonin, *etc.*), enters the hypothalamus, rather than the thalamus, where it picks up inputs from nerve cells that contain peptides (orexin or hypocretin and melanin-concentrating hormone). These inputs then traverse the basal forebrain, where they pick up additional inputs from cells containing acetylcholine and γ-aminobutyric acid (GABA). Ultimately, all of these inputs enter the cerebral cortex, where they diffusely activate the nerve cells, and prepare them for the interpretation and analysis of incoming sensory information.

Arousal from sleep could be an important defence mechanism against potentially dangerous situations during sleep. Such situations include severe obstructive apnoea, oesophageal reflux, cardiac rhythm abnormalities and external suffocation. Arousal from sleep that is triggered by abnormal levels of carbon dioxide and oxygen is essential for the initiation of protective airway responses; indeed, head turning and escape to fresh air are critical for survival from an asphyxial microenvironment. Arousal involves a progressive activation of specific subcortical-to-cortical brain structures, and consists of ascending and descending components that mediate cortical and subcortical arousal, respectively, with feedback loops between them. Cortical arousal involves noradrenergic, serotonergic, dopaminergic, cholinergic and histaminergic neurons in the brain stem, basal forebrain and hypothalamus, which excite the cerebral cortex and cause cortical activation. Subcortical arousal, however, is mediated mainly by brain-stem pathways that increase heart rate, blood pressure, respiration and postural tone without changes in cortical activity.

NREM and REM sleep The transition between wakefulness and sleep occurs through a process of reciprocal inhibition between arousal- and sleep-promoting neurons by way of a ''flip-flop'' switch.

The ''switch'' for sleep is considered to be the ventrolateral pre-optic nucleus (VLPO) of the anterior hypothalamus. This area becomes active during sleep and uses the inhibitory neurotransmitters GABA and galanin to initiate sleep by inhibiting the arousal regions of the brain. The VLPO innervates and can inhibit the wake-promoting regions of the brain including the tuberomammillary nucleus, lateral hypothalamus, locus coeruleus, dorsal raphe, laterodorsal tegmental nucleus and pedunculopontine tegmental nucleus. The hypocretin (orexin) neurons in the lateral hypothalamus help stabilise this switch. REM sleep occurs with activation of cholinergic neurons in the laterodorsal and pedunculopontine tegmental nuclei. This cholinergic activation occurs when withdrawal of the aminergic arousal systems (noradrenergic neurons in the locus coeruleus and serotonergic neurons in the dorsal raphe nuclei) produces disinhibition. This causes the release of acetylcholine, which triggers the increased neural activity that is a feature of REM sleep. Suppression of motor activity, the other marker of REM sleep, is generated by glutamate-mediated activation of descending medullary reticular formation relay neurons. The activity of these neurons is inhibitory to spinal motor neurons *via* the release of glycine, and to a lesser extent, GABA.

Neurochemistry of sleep Sleep results from the complex interaction of multiple neurotransmitter systems, as well as the influence of other physiological or psychological states.

Wakefulness Waking and consciousness depend on the activity of neurons in the ascending reticular activating system of the brainstem. These neurons project into the thalamus, hypothalamus and basal forebrain, and eventually send projections to the cortex. There are particular neurotransmitters, such as the catecholamines, acetylcholine, histamine, glutamate and aspartate, that are localised within the reticular formation and have important roles in cortical activation and arousal.

NREM sleep The thalamus, dorsal raphe, nucleus tractus solitarius, anterior hypothalamus and adjacent forebrain areas are important in producing NREM sleep. Neurotransmitters such as serotonin and GABA, which may be important in sleep mechanisms, are located in these brain regions and play an important role in sleep. Serotonin (5-hydroxytryptamine), found in raphe neurons of the brainstem, may be involved in sleep onset. Insomnia occurs when serotonergic cells of the dorsal raphe are lesioned. In addition, there is evidence that substances in the biosynthetic pathway of serotonin (such as tryptophan and vitamin B_6) may facilitate sleep (Jones, 1989). However, in spite of all the evidence supporting the role of serotonin in sleep onset, there are studies that suggest that the role of serotonin in sleep is not clear.

The inhibitory neurotransmitter GABA is released in its highest concentrations during NREM sleep. GABAergic neurons are located throughout the brain, including the basal forebrain, hypothalamus, thalamus, brainstem and cortex. Hypnotics, such as benzodiazepines and barbiturates, tend to work by potentiating GABA-mediated inhibitory processes. They may shut off neurons in the reticular activating system and inhibit transmission and activity of neurons that project to the cortex and thalamus.

Overall, hypnotics increase total sleep time, decrease sleep latency, decrease the number of awakenings, decrease the amount of time spent in NREM sleep stage 3 and, in some cases, REM sleep.

REM sleep Acetylcholine is located within neurons in the pontine tegmentum and is involved in REM sleep generation. ''REM-on'' cells are cholinergic cells in the lateral pontine and medial medullary reticular areas that innervate the thalamus, hippocampus and hypothalamus. These cells discharge at

high rates during REM and show little or no activity during NREM. Physostigmine, which inhibits catabolic enzymes, precipitates the appearance of REM sleep during NREM. The injection of carbachol, a muscarinic agonist, into the pontine tegmentum induces REM sleep. Blocking muscarinic receptors will retard the appearance of REM sleep.

''REM-off'' cells are noradrenergic and serotonergic cells found in the locus coeruleus and raphe. These cells are slow or silent during REM sleep. Affecting levels of noradrenaline or serotonin can have an effect on REM sleep. In general, antidepressants have the effect of decreasing REM sleep, which is elevated in human endogenous depression.

Sleep architecture

Stages of sleep Sleep is staged in 30-s epochs. Sleep begins in NREM and progresses through deeper NREM stages (stages 1–3), before the first episode of REM sleep occurs approximately 80–100 min later. Thereafter, NREM sleep and REM sleep cycle with a period of ~90 min. NREM and REM sleep alternate cyclically. The function of alternations between these two types of sleep states is not yet understood, but irregular cycling and/or absent sleep stages are associated with sleep disorders.

NREM and REM sleep cycles NREM sleep constitutes about 75–80% of the total time spent asleep and REM sleep constitutes the remaining 20–25%. REM sleep follows NREM sleep and occurs four or five times during a normal 8-h sleep period. The first REM period of the night may be <10 min in duration, while the last may exceed 60 min. The NREM–REM cycles vary in length from 70–100 min initially to 90–120 min later in the night.

The first cycle of sleep in the normal young adult begins with stage 1 sleep, which usually persists for only 1–7 min at the onset of sleep. Stage 2 NREM sleep follows this brief episode of stage 1 sleep and continues for approximately 10–25 min. Slow-wave sleep (SWS), often referred to as deep sleep, consists of stages 3 and 4 of NREM sleep, according to the Rechtschaffen and Kales standard of 1968. The American Academy of Sleep Medicine (AASM) has discontinued the use of stage 4, such that the previous stages 3 and 4 now are combined as stage 3. Slow wave sleep usually lasts between 70 and 90 min in normal individuals. REM sleep in the first cycle of the night is usually short-lived (1–5 min). Stage 3 sleep occupies less time in the second cycle, and might disappear altogether from later cycles, as stage 2 sleep expands to occupy the NREM portion of the cycle. The NREM–REM cycles vary in length from 70–100 min initially to 90–120 min later in the night. Across the night, the average period of the NREM–REM cycle is approximately 90–110 min (Carskadon *et al.*, 2011).

The three *stages of NREM sleep* are each associated with distinct brain activity and physiology. As one progresses through stages 1–3, sleep gets deeper and waves become more synchronised.

Stage 1 sleep is a very light stage of sleep with a low arousal threshold. Aside from newborns and those with narcolepsy and other specific neurological disorders, the average individual's sleep episode begins in NREM stage 1. It generally lasts for <10 min, constituting 2–5% of total sleep, and is easily interrupted by a disruptive noise. Electroencephalography (EEG) is characterised by low-voltage, mixed-frequency activity (4–7 Hz). Stage 1 is scored when <50% of an epoch contains α-waves and the criteria for deeper stages of sleep are not met. α-waves are associated with a wakeful relaxation state and are characterised by a frequency of 8–13 Hz. Well-developed α-wave activity is present in most normal children by 8 years of age (fig. 1). Slow rolling eye movements are often present in the tracings, and the level of muscle tone is equal or diminished compared to that in the awake state. Vertex waves are common in stage 1 sleep and are defined by a sharp configuration with a maximum over the central derivations (fig. 2).

Stage 2 sleep lasts approximately 10–25 min in the initial cycle and lengthens with each successive cycle, eventually constituting

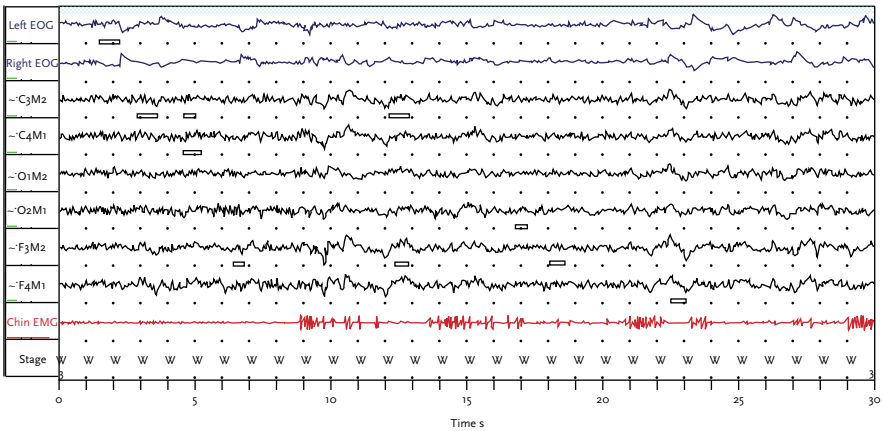

Figure 1. 30-s epoch of wakefulness. During eyes-open wake, the EEG is characterised by high-frequency, low-voltage activity. Electro-oculography (EOG) shows REM and the chin EMG activity is relatively high. During eyes-closed wake, the EEG is characterised by prominent α-wave activity. The amplitude of the channels is 70 μV. W: wake.

between 45% and 55% of the total sleep episode. An individual in stage 2 sleep requires more intense stimuli than in stage 1 to awaken. The EEG during stage 2 sleep shows relatively low-voltage, mixed-frequency activity characterised by the presence of sleep spindles and K-complexes. Sleep spindles are oscillations of 12–14 Hz with durations of 0.5–1.5 s. The K-complex is a high-amplitude, biphasic wave of $\geqslant$0.5 s duration. A K-complex consists of an initial sharp, negative voltage (by convention, an upward deflection) followed by a positive deflection (down) slow wave. Spindles are frequently superimposed on K-complexes (fig. 3).

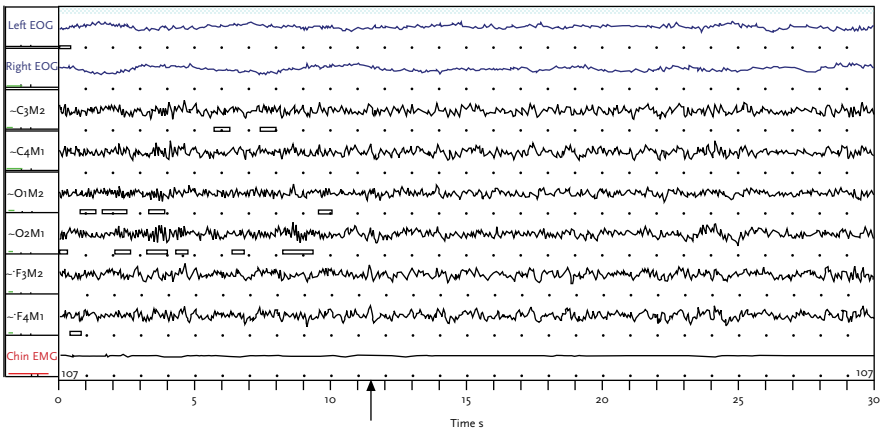

Figure 2. 30-s epoch of stage 1 sleep. EEG is characterised by low-voltage, mixed-frequency activity. Slow rolling eye movements often are present. Vertex waves are common in stage 1 sleep (arrow). The amplitude of the channels is 70 μM. EOG: electro-oculogram.

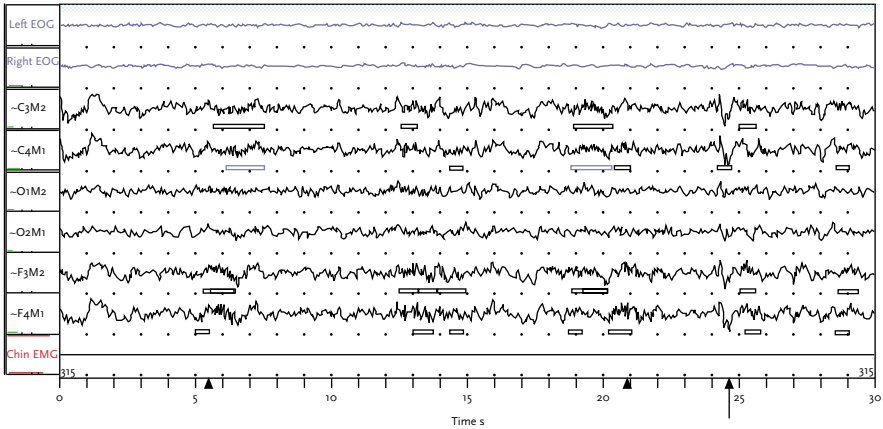

Figure 3. 30-s epoch of stage 2 sleep. Stage 2 sleep is characterised by the presence of one or more K-complexes (arrow) or sleep spindles (arrowheads). The amplitude of the channels is 70 μM. EOG: electro-oculogram.

During *stage 3 sleep* (SWS), the EEG is synchronised. Stage 3 lasts approximately 20–40 min in the first cycle and makes up about 14–32% of sleep. This stage is characterised by increased amounts of high-voltage, slow-wave activity on the EEG. δ-wave (slow wave) activity is defined as waves slower than 2 Hz (>0.5 s duration) with a peak-to-peak amplitude >75 μV. During SWS, we see the highest auditory arousal threshold, especially in children (fig. 4).

REM sleep is defined by the presence of desynchronised (low-voltage, mixed-frequency) brain wave activity, muscle atonia and bursts of REMs. "Sawtooth" wave forms, θ-wave activity (3–7 Hz) and slow α-wave activity also characterise REM sleep. During the initial cycle, the REM

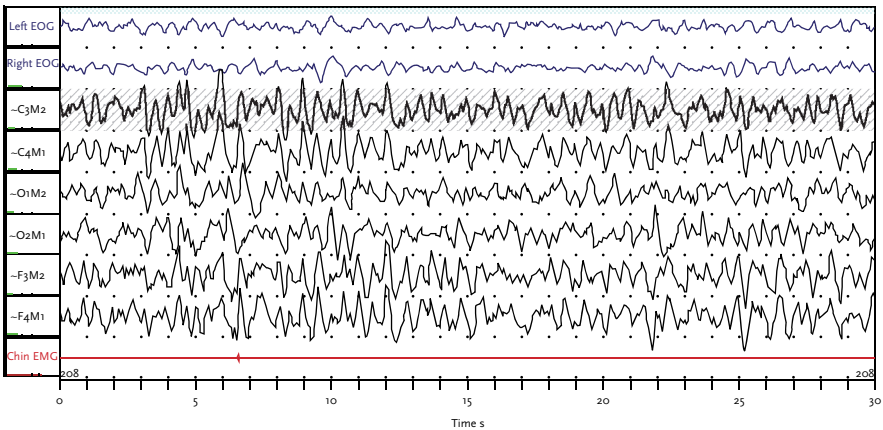

Figure 4. 30-s epoch of stage 3 sleep. Stage 3 NREM sleep is called slow-wave, δ-wave or deep sleep. Stage 3 is scored when slow-wave activity (frequency <2 Hz and amplitude >75 μV peak to peak) is present for >20% of the epoch. The amplitude of the channels is 70 μM. EOG: electro-oculogram.

period may last only 1–5 min; however, it becomes progressively prolonged as the sleep episode progresses. REM sleep generally makes up 20–25% of total sleep time in adults. In infants, REM sleep may account for up to 50% of sleep. REM sleep consists of tonic and phasic characteristics. Tonic characteristics are persistent throughout the entire REM sleep period, while phasic characteristics appear intermittently during the REM sleep period. Tonic characteristics include a desynchronised EEG, muscle atonia and a lack of thermoregulation. Phasic characteristics include REMs, clitoral and penile tumescence, and dreams (fig. 5).

Typically, stage 3 sleep is present more in the first third of the night, whereas REM sleep predominates in the last third of the night. This can be clinically helpful, as NREM parasomnias such as sleep walking typically occur in the first third of the night with the presence of stage 3 sleep. This contrasts with REM sleep behaviour disorder, which typically occurs in the last half of the night. There are numerous physiological differences between NREM and REM sleep (table 1).

Important developmental changes occur in sleep over an individual's lifetime. In newborns, the total sleep duration in a day can be 14–16 h. Over the first several months of life, sleep time decreases; by age 5–6 months, sleep consolidates into an overnight period with at least one nap during the day. Total sleep time continues to decrease during childhood as nap duration and frequency decrease.

In newborns, sleep can be categorised into two main patterns, active sleep (REM precursor), and quiet sleep (NREM precursor), but a proportion of sleep time is not attributable to either of these patterns and is accordingly classed as indeterminate. Non-EEG correlates are very helpful in recognising NREM and REM sleep in infants 6 months post-term or younger. These correlates in REM sleep include the presence of irregular respiration, chin electromyogram (EMG) atonia and REMs. In NREM sleep, correlates include regular respiration, no or rare vertical eye movements and preserved chin EMG tone. REM sleep in infants represents a larger percentage of the total sleep (newborn to 3 months, 50%; by 3–5 months, 40%; by the end of the first year, 30% of total sleep time). After 3 months, NREM sleep begins to dominate. The percentage of REM sleep is reduced to adult levels by 10 years of age. Until the age of 3 months, newborns

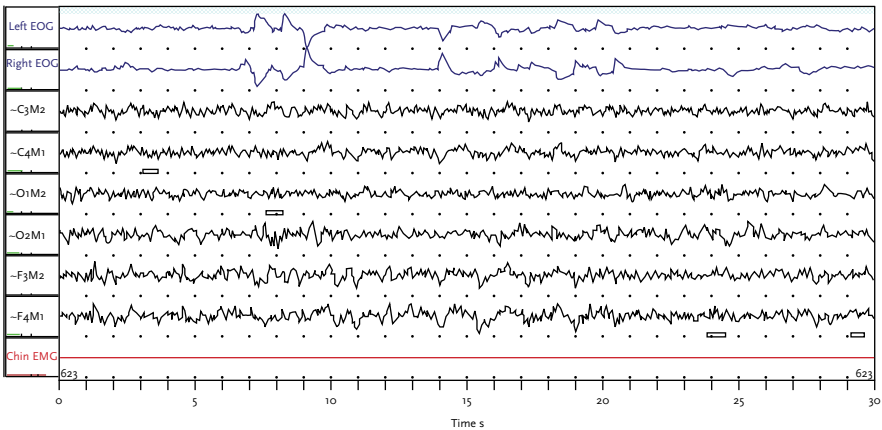

Figure 5. 30-s epoch of REM sleep. REM sleep is characterised by a low-voltage, mixed-frequency EEG, the presence of episodic REMs, and a relatively low-amplitude chin EMG. ''Sawtooth'' waves also may occur in the EEG. The amplitude of the channels is 70 μM. EOG: electro-oculogram.

transition from wake into REM sleep. However, sleep-onset REM may continue up to ~6 months of age. Thereafter, sleep starts with NREM sleep. At 3 months of age, clear differentiation of NREM sleep states by EEG criteria is quite difficult. By 6 months, NREM sleep can typically be differentiated into three distinct states (stages 1 and 2, and SWS) (Anders *et al.*, 1995).

Effects of sleep deprivation

As the function of sleep has not been fully determined, the absolute number of hours necessary to fulfil its function is still unknown. Some individuals claim full effectiveness with only 3–5 h of sleep per night, while others claim to need ⩾8 h of sleep per night to perform effectively. Sleep deprivation is a relative concept. Small amounts of sleep loss (*e.g.* 1 h per night over many nights) have subtle cognitive costs, which appear to go unrecognised by the individual experiencing the sleep loss. More severe restriction of sleep for a week leads to profound cognitive deficits similar to those seen in some stroke patients. Glucose positron emission tomography (PET) studies in individuals deprived of sleep have shown that after 24 h of sustained wakefulness, the metabolic activity of the brain decreases significantly. In humans, sleep deprivation also results in a decrease in core body temperature, a decrease in immune system function as measured by white blood cell count and activity, and a decrease in the release of growth hormone. Sleep deprivation has also been implicated as a cause of increased heart rate variability (Banks *et al.*, 2007).

Short-term sleep deprivation has been implicated in contributing to obesity as well as glucose dysregulation contributing to poor control of type II diabetes.

Children differ from adults in their response to acute restriction in sleep. When sleep has been restricted by ⩾4 h, there is a decrease in all stages of sleep (except SWS), a reduction in sleep onset latency, stage 3 latency and REM latency. Multiple sleep latency tests show a significant increase in daytime sleepiness, which persists into the morning after sleep restriction. In addition, children do not show recovery rebound of SWS and REM sleep similar to that reported for adults. Children seem to require more time to recuperate fully from nocturnal sleep restriction than adults. The effect of sleep restriction on daytime sleepiness, performance of children in school and behaviour is prominent.

Sleep disorders

A sleep disorder is loosely defined as any condition or process that alters the patient's previously established sleep–wake cycle. Sleep disorders are divided into two general classes: dyssomnias and parasomnias.

Dyssomnias are conditions that manifest themselves as either hypersomnia (abnormal sleep cycles causing the urge to sleep at times when the circadian cycle would suggest that wakefulness was appropriate) or insomnia (the inability to sleep). The dyssomnias can be further subdivided into three classes that are dependent on the source of the sleep interference.

- Intrinsic (arising within the body): primary insomnia, OSA, restless leg disorder and unspecified limb movements.
- Extrinsic (arising outside the body): environmental conditions not conducive to uninterrupted sleep, such as noise or ambient temperature.
- Alteration or interference with the circadian rhythm: jet lag or variations in occupational schedules (shift work).

Parasomnias include sleep terror (sudden awakening and unreasonable fear), bedwetting, somnambulism (sleep walking) and somniloquy (talking in one's sleep) (American Academy of Sleep Medicine, 2005).

This AASM classifies sleep disorders into eight major categories:

1. insomnia,
2. sleep-related breathing disorders,
3. hypersomnias of central origin,
4. circadian rhythm sleep disorders,

5. parasomnias,
6. sleep-related movement disorders,
7. isolated symptoms and normal variants,
8. other sleep disorders.

Conclusion

Humans spend about one-third of their lives asleep, yet most individuals know little about sleep. Although its function remains to be fully elucidated, sleep is a universal need of all higher life forms including humans, absence of which has serious physiological consequences. Sleep is divided into two periods: NREM sleep and REM sleep. NREM sleep is conventionally divided into three or four stages, each with its own distinguishing characteristics. Sleep begins in NREM and progresses through deeper NREM stages (stages 1–3) before the first episode of REM sleep occurs approximately 80–100 min later. Thereafter, NREM sleep and REM sleep cycle with a period of ~90 min. NREM and REM sleep alternate cyclically. The function of alternations between these two types of sleep states is not yet understood but irregular cycling and/or absent sleep stages are associated with sleep disorders.

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OSAS and upper airway resistance syndrome

Maria Pia Villa and Silvia Miano

OSAS in children is defined as a disorder of breathing during sleep characterised by prolonged partial upper airway obstruction and/or intermittent complete obstruction (obstructive apnoea), which disrupts normal ventilation during sleep and normal sleep patterns. Prevalence ranges from 1.2% to 5.7%. Although no specific genes have been identified for OSAS to date, it has become apparent that OSAS is probably a polygenic disease. Specific genes impacting on factors such as oral mucosa thickness and facial structure may play a deterministic role in OSAS.

Key points

- OSAS in children is a complex, multi-organ syndrome consisting of habitual snoring, witnessed apnoea, sleep fragmentations and diurnal consequences.
- The most frequent cause is adeno-tonsillar hypertrophy and treatment involves adeno-tonsillectomy; however, many children do not resolve and need further therapy, such as orthodontic therapy.

Diagnosis

Signs and symptoms Paediatric OSAS is accompanied by habitual snoring ($\geqslant$3 nights·week^{-1}) and major nocturnal and diurnal symptoms and signs (table 1). Other conditions that may be associated with OSA are:

- allergic rhinitis,
- asthma,
- Down syndrome,
- nasoseptal obstruction,
- cleft palate repair and velopharyngeal flap,
- craniofacial syndromes (Treacher–Collins, midfacial hypoplasia, Crouzon syndrome, Apert syndrome, Pierre Robin sequence, *etc.*),
- achondroplasia,
- mucopolysaccharidoses,
- macroglossia,
- sickle-cell disease,
- myelomeningocele,
- cerebral palsy,
- prematurity,
- neuromuscular disorders.

Other rare conditions include foreign body aspiration, vascular haemangioma or other tumours.

One of the mechanisms implicated in the pathogenesis of OSAS is increased collapsibility of the upper airway during sleep, because the activity of the upper airway dilator muscles is not enough to compensate for an anatomically small upper airway. Children with OSAS often have significantly large adenoids and tonsils, causing the upper airway to collapse. However, enlarged adeno-tonsillar tissues may not always lead to OSAS. A complex interaction between the anatomical component and other elements, such as upper airway tone, respiratory drive, *etc.*, has been postulated. Several anatomical and functional mechanisms may lead to OSAS in children and in adults, one being a smaller upper airway, which predisposes subjects to airway collapse during sleep in all age groups. Orthodontic and craniofacial abnormalities associated with OSAS are,

Table 1. Major signs, symptoms and other conditions accompanying paediatric OSAS

Symptoms	Signs	Other conditions
Laboured breathing during sleep	Underweight or overweight	African–American
Gasps/observed episodes of apnoea	Tonsillar hypertrophy	Allergic rhinitis
Sleep enuresis	Adenoidal facies	Asthma
Sleeping in a seated position or with the neck hyperextended	Micrognathia	Prematurity
Cyanosis	Retrognathia	Neurological conditions (cerebral palsy or neuromuscular diseases)
Headaches on awakening	High-arched palate	Craniofacial syndromes
Daytime sleepiness	Failure to thrive	Down syndrome
Attention deficit/hyperactivity disorder and or learning problems	Hypertension	Rare diseases such as achondroplasia or mucopolysaccharidoses

Data from Marcus *et al.* (2012) and Bhattacharjee *et al.* (2009).

despite their impact on public health, widely ignored. A narrow upper airway with maxillary constriction and/or some degree of mandibular retrusion is a common paediatric phenotype of OSAS. In such cases, children are typically described as having a narrow, long face, they may have retrognathic mandibles and increased posterior facial height associated (or not) with severe tonsillar hypertrophy. Whether this skeletal conformation is genetically determined or influenced by the early onset of habitual snoring has yet to be assessed. Another common abnormality in patients with OSAS is a high arched (ogival) palate, which results in posterior tongue displacement forcing the lateral palatine processes to expand over the abnormally placed tongue.

Comorbidities Paediatric OSAS is associated with a multitude of end-organ morbidities, such as daytime sleepiness, neurocognitive impairment, behavioural problems, failure to thrive, hypertension, cardiac dysfunction and systemic inflammation.

In recent years, research from many paediatric sleep centres has accumulated substantial evidence suggesting that paediatric OSAS constitutes a systemic low-grade inflammatory condition. The induction of systemic inflammatory responses is most likely related to the generation of systemic oxidative stress secondary to the recurrent hypoxic and arousal episodes that characterise OSAS.

Failure to thrive was extremely frequent and attributed to increased metabolic expenditure caused by the elevated work of breathing during sleep, reduced nutrient intake due to tonsillar hypertrophy and, most likely, to disrupted growth hormone–insulin growth factor pathways in the presence of recurrent hypoxaemia and disturbed sleep patterns. In more recent years, however, obesity has emerged as a frequent finding and it is likely to amplify the morbidities of OSAS and obesity alone. The concomitant presence of OSAS in obese children further amplifies the risk for lipid disturbances and reveals the presence of an interaction between adiposity and insulin resistance. Adipokines, including leptin, are cytokines released from adipose tissue that are important in the regulation of appetite, metabolic homeostasis, sleep and respiratory control. A recent study reported on the elevation of circulating leptin levels in

children with OSAS, independent of the degree of obesity.

The exact prevalence of excessive daytime sleepiness (EDS) in paediatric OSAS is unclear and, when objective measurements on sleep propensity are used (*i.e.* multiple sleep latency test), the prevalence of EDS in paediatric OSAS ranged from 13% to 20%. Furthermore, the presence of obesity appeared to increase the likelihood of EDS.

It is estimated that 30% of all children with frequent and loud snoring will manifest significant hyperactivity and inattention (attention deficit-hyperactivity disorder (ADHD)), and learning problems. Moreover, children with OSAS have a lower global intelligence compared to controls, with positive correlations between sleep fragmentations and global intelligence and ADHD scores, while a positive correlation was found between ADHD scores and oxygen saturation during the night. This study indicated that arousal is a protective mechanism to preserve cognitive function by counteracting the respiratory events, at the expense of sleep maintenance. A study previously reported a high prevalence of paroxysmal activity in a population of children with OSAS (14.3% of the sample investigated). Interictal epileptiform discharges (IEDs) mostly occurred over the centro-temporal regions, suggesting some similarities with IEDs of benign epilepsy with central temporal spikes. Since the occurrence of IEDs during sleep may disrupt cognitive abilities and impair learning and memory in children, the findings may represent a new possibility to explain the neurocognitive dysfunction in children with OSAS.

Of particular interest are the cardiovascular complications that may develop in children with OSAS, since they may have not only an immediately significant impact on cardiovascular health during childhood, but may also affect cardiovascular outcomes during adult life. Studies in children with OSAS have reported increased blood pressure, changes in cardiac structure and function, increased fasting insulin and lipid levels, and endothelial dysfunction as signs of cardiovascular damage. The few studies that have evaluated autonomic dysfunction reported an increase in diastolic blood pressure, both during wakefulness and sleep, as well as an increase in sympathetic activity demonstrated by peripheral arterial tonometry and catecholamine concentration measurements in plasma and urine. An increase in basal sympathetic activity during wakefulness has been demonstrated in patients with OSAS. In children with OSAS, an increase in the baseline systolic and diastolic blood pressure and heart rate has been observed, whereas the autonomic cardiovascular tests revealed a greater variability of blood pressures during the supine-to-orthostatic posture change, as well as less heart rate variability during deep breathing. Cardiovascular diseases reported in patients with moderate-to-severe OSAS also include pulmonary hypertension with cor pulmonale, left ventricular (LV) hypertrophy or dysfunction, cardiac arrhythmias, atherosclerosis and coronary artery disease. A common pathophysiological aspect of these alterations is the presence of a condition of oxidative stress and increased reactive oxygen species generation, which directly or indirectly promotes the development and progression of LV dysfunction or hypertrophy and vascular remodelling. Oxidative stress and asymptomatic (subclinical) proinflammatory state, as demonstrated by the higher serum levels of high-sensitivity C-reactive protein (hsCRP), have been observed in adults and children with OSAS and have been interpreted as pathogenetic factors that promote cardiac remodelling and LV structural and functional adaptations in these patients. The presence of both left and right ventricular hypertrophies, as well as diastolic abnormalities, detected by means of conventional Doppler examination of LV filling patterns, in children with severe OSAS, hypertension or obesity have been demonstrated. A two-dimensional colour Doppler cardiac examination with LV mass assessment and systolic and diastolic function evaluation revealed that LV diastolic dysfunction was significantly more frequent in patients with severe OSAS, associated with higher hsCRP levels.

Sleep polysomnography analysis The American Academy of Pediatrics recommends that if a child or adolescent snores on a regular basis and has any of the major symptoms then clinicians should obtain a polysomnograph (PSG). Although history and physical examination are useful to screen patients and determine which patients need further investigation for OSAS, the sensitivity and specificity of the history and physical examination are poor. Recently, a simple Sleep Clinical Record based on physical examination, subjective symptoms and clinical history has been validated. In children with a score less than 6.5 PSG is not performed.

However, the gold standard test remains overnight, attended, in-laboratory PSG (sleep study). This is a noninvasive test involving the measurement of a number of physiological functions overnight, typically including electroencephalography (EEG), pulse oximetry, oronasal airflow, abdominal and chest wall movements, partial pressure of carbon dioxide, oxygen saturation and video recording. Specific paediatric measuring and scoring criteria should be used. Central, obstructive and mixed apnoea events were counted according to the criteria established by the American Academy of Sleep Medicine (AASM). Obstructive apnoea was scored when there was a >90% drop in the signal amplitude of airflow for >90% of the entire event, compared with the pre-event baseline amplitude with continued chest wall and abdominal movement for a duration of at least two breaths. Central apnoea was defined as the absence of airflow, with the cessation of respiratory effort, lasting >20 s or at least two missed breaths (or the duration of two baseline breaths), associated with an arousal, an awakening or a >3% desaturation. Central apnoea occurring after gross body movements or after sighs was not considered a pathological finding. Mixed apnoea was defined as apnoea that usually began as central and ends in obstruction, according to changes in the chest, abdominal and flow traces. An event could be scored as hypopnoea if there was a >50% drop in airflow signal amplitude compared with the pre-event baseline amplitude for at least 90% of the duration of the event; the event had to last at least two missed breaths and be associated with an arousal, awakening or a >3% desaturation (fig. 1). The AHI is defined as the average number of apnoeas, hypopneas and respiratory event-related arousals per hour of sleep. The diagnosis is defined by an obstructive AHI >1 event·h^{-1}.

As part of the OSAS spectrum of severity, upper airway resistance syndrome and another PSG feature of obstructive alveolar hypoventilation constitute mild forms of OSAS, characterised by an increased number of arousals that can be attributed to increased respiratory effort (upper airway resistance syndrome) and increased end-tidal carbon dioxide levels during sleep.

If PSG is not available, then clinicians may perform alternative diagnostic tests, such as nocturnal video recording, nocturnal oximetry, daytime nap PSG or ambulatory PSG, although they have weaker positive- and negative-predictive values than PSG. If an alternative test fails to demonstrate OSAS in a patient with signs and symptoms, a full PSG should be performed with extended EEG montage in order to exclude the presence of IEDs.

Treatment

Adeno-tonsillectomy is recommended when a child with OSAS has a clinical examination consistent with adeno-tonsillar hypertrophy and does not have a contraindication to surgery. Clinical judgment is required to determine the benefits of adeno-tonsillectomy compared with other treatments in obese children with varying degrees of adeno-tonsillar hypertrophy. Other treatment options, such as anti-inflammatory medications, weight loss or tracheostomy, are less effective. Risk factors for post-operative complications of adeno-tonsillectomy are:

- children <3 years of age,
- severe OSAS on PSG,
- cardiac complications,
- failure to thrive,
- obesity,

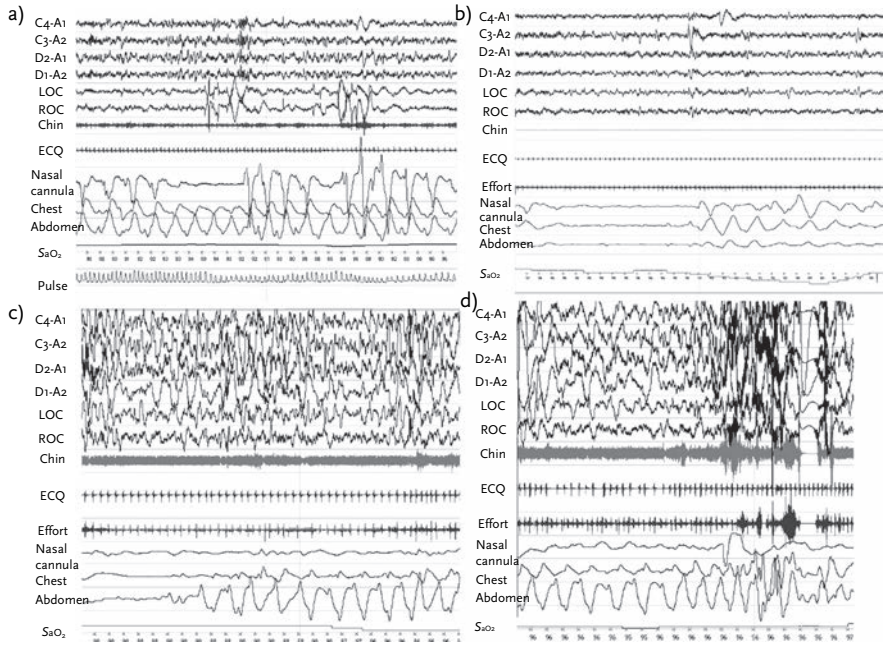

Figure 1. Examples of a) obstructive apnoea, b) central apnoea, c) mixed apnoea and d) hypopnea sleep epochs of 120 s. ROC: right electro-oculogram; LOC: left electro-oculogram.

- craniofacial anomalies,
- neuromuscular disorders,
- current respiratory infection.

It is also recommended that all patients with an oxygen saturation <80% and an AHI $\geqslant$24 events·h^{-1} should be observed as inpatients.

Clinicians should refer patients for CPAP management if symptoms and signs or objective evidence of OSAS persists after adeno-tonsillectomy or if adeno-tonsillectomy is not performed. There is no clear advantage of using bilevel pressure over CPAP. Clinicians should recommend weight loss in addition to other therapy if a child/adolescent with OSAS is overweight or obese. Clinicians may prescribe topical intranasal corticosteroids for children with mild OSAS in whom adeno-tonsillectomy is contraindicated or for children with mild post-operative OSAS (AHI <5 events·h^{-1}).

Orthodontic treatment by means of oral devices is considered to represent a potential or supplementary treatment in children presenting with OSAS. Although the use of oral appliances has received relatively little attention in the literature, interest in this approach is growing rapidly. Oral appliances may improve upper airway patency during sleep by enlarging the upper airway and/or by decreasing upper airway collapsibility, thereby improving upper airway muscle tone. The treatment options available for growing children are rapid maxillary expansion, mandibular retropositioning and a modified monobloc. Rapid maxillary expansion, which is a dentofacial orthopaedic treatment procedure routinely used in young patients >4 years with constricted maxillary arches, is considered to be an effective treatment for OSAS.

Conclusion

There is a great need for further research into the prevalence of OSAS, consequences of OSAS and the best treatments. In particular, randomised controlled trials of treatment are needed. Figure 2 shows an

Figure 2. Algorithmic approach to the diagnosis and treatment of paediatric OSAS. ORL: otoringolarhingologic examination; PSG: polysomnography. #: refer to the orthodontist for ORL, assess for obesity, and perform cardiologic (ECG, blood pressure holter) and neuropsychological assessment.

algorithm for the diagnosis and treatment of paediatric OSAS using a multi-step approach. As multi-therapies might act synergistically, a greater degree of collaboration between sleep medicine, ENT specialists and orthodontists is warranted to establish the contribution of each therapy to the outcome of paediatric OSAS.

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Central sleep apnoea and hypoventilation syndromes

Malin Rohdin and Hugo Lagercrantz

Sleep alters the function and control of the respiratory system. These changes may result in clinically significant abnormalities in upper airway function and pulmonary gas exchange among healthy children as well as those with an underlying disease. Sleep disordered breathing (SDB) is a common cause of morbidity in childhood that can result in severe complications if left untreated. Central sleep apnoea, hypoventilation syndromes and OSA are sleep-related breathing disorders, and this section will focus on the first two conditions. Central sleep apnoea is characterised by a decreased or absent respiratory drive that results in reduction or cessation of breathing for at least two breaths. Central sleep apnoea can be idiopathic but it can also occur secondary to another medical condition. Central apnoeas are common in the neonatal period, particularly among pre-term newborns, and this is viewed as a physiological immaturity of breathing control and ceases spontaneously around term post-conceptional age. Central hypoventilation is caused by an inability of the central nervous system to maintain ventilation sufficient to overcome the respiratory load. Alveolar hypoventilation syndromes are often caused by an abnormal central integration of chemoreceptor signals and can be primary, as in congenital central hypoventilation syndrome (CCHS), or secondary to diseases of the central nervous system or neuromuscular disorders. Early diagnosis and comprehensive treatment will minimise the number of sequelae and improve individual outcomes.

Key points

- Central sleep apnoea and hypoventilation syndromes are causes of morbidity in childhood that may result in severe complications if left untreated.
- Complications of sleep apnoea include pulmonary hypertension, cor pulmonale, systemic hypertension, cardiac arrhythmias, hypoxic cerebral injury and seizures.
- PSG is the gold standard test for SDB and is required to diagnose sleep-related disorders.
- Treatments include supplementary oxygen, caffeine (apnoea of prematurity), diaphragm pacing, CPAP, BiPAP and mechanical ventilation *via* tracheostomy.

Clinical features

Sleep apnoea should be considered in children of all ages who present with nonspecific symptoms of daytime dysfunction. More specific signs and symptoms of SDB include nocturnal or early-morning headache, poor sleep quality with nocturnal awakenings, failure to thrive, and daytime breathing disturbances. Children with daytime sleepiness due to SDB often "act out" behaviourally (*e.g.* hyperactivity, impulsivity and increased aggression) rather than complaining verbally. Younger children are less likely than older children to show signs of tiredness (*e.g.* yawning and rubbing eyes).

Sequelae of SDB The reason why some children become hypoxic and others arouse from sleep in response to respiratory compromise is unclear. Intermittent hypoxia is an important mediator of neurocognitive deficit in children. Animal models simulating isolated intermittent hypoxia have shown neuronal cell loss in brain areas critical for executive function and memory, namely the pre-frontal cortex and hippocampus.

Sleep-related hypoxaemia in children is associated with neurobehavioral, cognitive and cardiovascular morbidities. Other sequelae in infants and young children include pulmonary hypertension, failure to thrive, cor pulmonale, systemic hypertension, cardiac arrhythmias, hypoxic cerebral injury and seizures. Perturbation in neonatal respiratory control and chronic intermittent hypoxia in premature infants may contribute to later SDB.

Severe apnoea that lasts >20 s is usually associated with bradycardia or desaturation, which may lead to disturbances of cerebral haemodynamics and possibly affect neurodevelopmental outcome. However, it is difficult to demonstrate a link between apnoea and poor neurodevelopmental outcome due to a number of comorbidities and confounding factors affecting neurological development. In addition, reports of severity may be unreliable, and impedance monitoring techniques may fail to identify mixed and obstructive events. Therefore, evaluating the consequences of apnoea and hypoventilation on long-term neurological development remains a challenge.

Central sleep apnoea The word "apnoea" comes from the Greek word meaning "without wind". The brainstem respiratory network contains neurons critical for respiratory rhythmogenesis (pre-Botzinger complex). This network receives inputs from peripheral and central chemoreceptors, and from forebrain structures. Manifestations associated with disorders of this network include sleep apnoea and dysrhythmic breathing. Common disorders associated with impaired cardiorespiratory control include brainstem stroke or compression, syringobulbia, Chiari malformation, high cervical spinal cord injuries, encephalitis, multiple system atrophy, and autonomic disorders such as Rett syndrome and familial dysautonomia. Respiratory dysfunction constitutes an early and relatively major manifestation of several neurological disorders, and may be due to an abnormal breathing pattern generation due to involvement of the cardiorespiratory network or more frequently to respiratory muscle weakness.

Apnoea of prematurity is a common problem affecting pre-term infants and probably secondary to a physiological immaturity of respiratory control. The incidence of apnoea is inversely correlated with gestational age and birth weight. During rapid eye movement (REM) sleep, these infants have more paradoxical breathing with a less stable baseline oxygen saturation. Therefore, apnoeas occur more frequently in REM sleep than in quiet sleep. Apnoea of prematurity may be exacerbated by diseases such as infections, intracranial haemorrhage, hypoxic–ischaemic encephalopathy, seizures, patent ductus arteriosus, and glucose or electrolyte imbalance. Resolution of apnoea and establishment of a normal respiratory pattern is a major developmental milestone for many pre-term infants.

Rett syndrome is a severe neurodevelopmental disorder that almost exclusively affects females. After Down syndrome, Rett syndrome is the most common specific cause of severe cognitive impairment in females, affecting one in 10 000. Rett syndrome causes severe autonomic dysregulation, probably due to brainstem dysfunction. The patients have severely disturbed breathing and heart rate both when awake and when asleep (Rohdin *et al.*, 2007). The cardiorespiratory morbidity is characterised by hypoventilation, central apnoea, episodic hyperventilation, tachycardia, bradycardia and poor peripheral circulation. A mouse model of Rett syndrome revealed breathing disturbances that probably originate from a deficiency in noradrenergic and serotonergic modulation of the medullary respiratory network.

Familial dysautonomia is a neurodevelopmental disorder that affects autonomic and sensory functions. Familial dysautonomia is caused by mutations in the *IKBKAP* gene on chromosome 9 and transmitted as an autosomal recessive disorder. Patients with familial dysautonomia have SDB with both central and obstructive apnoea. Many individuals with familial dysautonomia initially increase ventilation during shorter periods of hypoxia but have a decreased ventilatory drive during prolonged hypoxia. It follows that familial dysautonomia patients must be cautious in settings where the partial pressure of oxygen is decreased, such as at high altitudes or during aeroplane travel.

Alveolar hypoventilation syndromes are often caused by an abnormal central integration of chemoreceptor signals and could be primary, as in CCHS and Prader–Willi syndrome (PWS), or secondary to diseases of the spinal cord or brainstem. The respiratory deficit is typically more severe during sleep than wakefulness and is characterised by alveolar hypoventilation, resulting in hypoxaemia and hypercarbia.

The goddess Ondine and her curse According to a Medieval folk tale, the water nymph Ondine would became mortal only when she fell in love with a human. She sacrifices her immortality by marrying a knight, Sir Lawrence, and bearing his child. Sir Lawrence promises Ondine that his every waking breath will be a testimony of his love, but he is soon unfaithful to her. Witnessing Sir Lawrence's adultery, the king of the nymphs curses the knight. The king's curse makes the mortal responsible for remembering to perform all bodily functions. When Sir Lawrence falls asleep, he ''forgets'' to breathe and dies.

''Ondine's curse'' is a term used to denote CCHS, a rare neurological condition causing lifelong failure of respiratory regulation. CCHS is characterised by sleep-related, life-threatening hypoventilation requiring lifetime mechanically assisted ventilation during sleep. The severity of ventilatory dysregulation ranges from hypoventilation during sleep and adequate ventilation during wakefulness, to complete apnoea during sleep and severe hypoventilation during wakefulness. CCHS is, however, far more complex than a simple orphan disorder of respiratory control. Patients with CCHS also have disturbances of autonomic nervous system regulation. Characteristically, patients have diminutive tidal volumes and monotonous respiratory rates both while awake and asleep, although more profound alveolar hypoventilation primarily occurs during sleep. Furthermore, CCHS patients display a reduced influence of breathing on cardiac rate variation as well as a range of disturbances in both sympathetic and parasympathetic nervous system control. Despite reduced ventilatory responses to hypercapnia and hypoxaemia, peripheral chemoreceptor responses are partially preserved, particularly among children who are able to sustain near-adequate ventilatory output during wakefulness. There is stage-related cardiorespiratory and autonomic regulation that can be learned from the care of infants with CCHS (fig. 1). Polysomnography (PSG) often shows different ventilatory responses depending on sleep stage, with more severe hypoventilation during non-REM sleep than during REM sleep in CCHS patients. Huang *et al.* (2008) speculated that this phenomenon may be due to increased excitatory inputs to the respiratory system during REM sleep. CCHS appears to be the only respiratory disorder in which breathing is better during REM than during non-REM sleep (Huang *et al.*, 2008).

In most cases, CCHS is diagnosed in the newborn infant, although an increasing number of patients are diagnosed after the neonatal period and even up to adulthood (late-onset CCHS). An increased clinical awareness of CCHS may prevent potential life-threatening decompensation or neurocognitive impairment. Clinical suspiciousness towards unexplained alveolar hypoventilation is likely to identify a higher incidence of milder cases of CCHS.

A mutation in the disease-defining gene *PHOX2B* (paired-like homeobox) is a

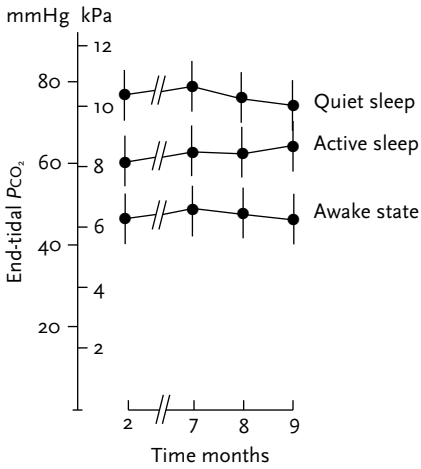

Figure 1. End-tidal carbon dioxide tension (P_{CO_2}) in a toddler (3-year-old girl) with CCHS. End-tidal P_{CO_2} was highest during quiet sleep and lowest during wakefulness, while it was moderately elevated during active (REM) sleep. It illustrates how the suprapontine respiratory drive can sustain ventilation during wakefulness and, to some extent, during REM sleep, but not during quiet sleep.

requisite to the diagnosis of CCHS. The *PHOX2B* gene promotes neuronal differentiation and development of the autonomic nervous system. Knowledge of the specific *PHOX2B* mutation aids in anticipating CCHS phenotype severity (Weese-Mayer *et al.*, 2010). CCHS is associated with an increased risk of Hirschsprung's disease and tumours of neural crest origin. A fairly recent study from the French CCHS registry estimates an incidence of one per 200 000 live births (Trang *et al.*, 2005). *PHOX2B* mutation-confirmed CCHS confers a risk of adverse neurocognitive outcome, though the range of observed functioning raises questions about factors that may contribute to neurocognitive variability. The recommended management options in optimising CCHS patient care and neurocognitive outcome are summarised in an official American Thoracic Society clinical policy statement (Weese-Mayer *et al.*, 2010).

Prader–Willi syndrome is a complex disorder with hypothalamic dysfunction where the clinical features vary with age. Early symptoms include hypotonia, feeding difficulties and failure to thrive, and later symptoms are hypogonadism, hyperphagia–obesity, and behavioural and cognitive problems. PWS is a genetic disorder where a majority (70–75%) of the affected individuals have a deletion in the paternally derived chromosome 15q11–q13. Individuals with PWS are at risk for a variety of abnormalities of breathing during sleep, including alveolar hypoventilation, central apnoeas and OSA. The incidence and severity of alveolar hypoventilation are related to the degree of obesity. Individuals with PWS may have a restrictive lung disease due to muscle weakness or scoliosis. They also have impaired ventilatory control during sleep with abnormal ventilatory responses to hypercapnia and hyperoxia, and reduced arousal responses to hypoxia. Excessive daytime sleepiness is a common feature and is suggested to be a primary feature of PWS rather than a consequence of insufficient sleep quantity or quality.

Patients with PWS, particularly if they are obese or have symptoms suggestive of SDB, require a PSG to exclude or characterise abnormal breathing. An early diagnosis of SDB and appropriate treatment may delay or prevent the development of cor pulmonale.

Secondary hypoventilation syndromes

Alveolar hypoventilation syndromes can be secondary to an underlying disease and therefore cause an abnormal central integration of chemoreceptor signals. Examples include diseases affecting the central nervous system (trauma, tumours and cerebrovascular incidents), neuromuscular disorders, chest wall deformities and obesity. This is a heterogeneous group of diseases and incurs variable degrees of damage to the respiratory control centres.

Neuromuscular disorders SDB is now well recognised in children with neuromuscular disorders and may lead to significant morbidity and increased mortality.

Predisposing factors include reduced ventilatory responses, reduced activity of respiratory muscles during sleep and poor lung mechanics due to the underlying neuromuscular disorder. Children with different neuromuscular disorders are at risk of developing both central and obstructive apnoea and hypoventilation during sleep. These neuromuscular disorders include Duchenne muscular dystrophy, myotonic dystrophy, spinal muscular atrophy, cerebral palsy, poliomyelitis, myasthenia gravis, peripheral neuropathies, metabolic myopathies and congenital muscle diseases (Arens *et al.*, 2010). Symptoms of SDB in children with neuromuscular diseases may be subtle. The physician should be especially vigilant for any of the following complaints: snoring, increasing numbers of nocturnal awakenings, daytime sleepiness, or morning headache that may be caused by cerebral vasodilation due to hypoventilation and carbon dioxide retention. Additional symptoms, such as fatigue, exertional dyspnoea, orthopnoea, swallowing difficulties, weakened cough, weight loss and frequent respiratory infections, could suggest progression of the underlying respiratory muscle disorder and worsening of nocturnal ventilation and SDB. Abnormal respiration during sleep in these disorders is often not predicted by awake pulmonary function testing, arterial blood gases or the degree of muscle involvement.

Polysomnography

PSG is the gold-standard test for SDB in infants and children. It is a noninvasive method to diagnose sleep-related hypoventilation due to central mechanisms or upper airway obstruction, or mixed apnoeas. This in-laboratory, multichannel method obtains information about sleep architecture, respiratory effort, movements during sleep, respiratory events and gas exchange, facilitating the evaluation of children with suspected SDB. Children should preferably be studied in a sleep laboratory equipped for, and staffed with personnel comfortable with and experienced in, PSG in children. Overnight PSG studies are preferred because negative nap studies have been shown not to exclude the possibility of SDB. Studies should be performed without sedation in order to most accurately mimic the child's normal sleep. PSG requires an overnight stay at a sleep laboratory and the attachment of multiple sensors to the patient. Qualitative respiratory effort is detected using thoracic and abdominal belts, which is essential in distinguishing between central and obstructive respiratory events. Sleep stages can be assessed by behavioural criteria using video recording or determined using electroencephalography (EEG), chin electromyography (EMG) and electro-oculography (EOG). Gas exchange is assessed by monitoring S_{pO_2} and end-tidal or transcutaneous carbon dioxide. Airflow can be assessed with a thermistor, nasal pressure or capnography. ECG is essential to evaluate cardiorespiratory regulation, as respiratory events may be associated with different heart rate regulation. Audio and digital video recordings are useful in documenting snoring, body position and movements.

Respiratory events during PSG Apnoea is often defined as a cessation or decrease in airflow by $\geqslant$90% compared to the baseline flow observed before the event when the event meets duration and respiratory effort criteria for an obstructive, mixed or central apnoea (Berry *et al.*, 2012). Partial airway obstruction is characterised by shallower or slower breathing, and has been described by the term ''hypopnoea''. Hypopneas are defined as a $\geqslant$30% reduction in airflow, for the duration of two or more breaths in association with either $\geqslant$3% oxygen desaturation or an arousal. The apnoea–hypopnoea index (AHI), expressed as the number of apnoeas and hypopneas per hour of sleep, is an important measure for quantifying disease severity. Apnoeas and hypopnoeas can be further classified as being central, obstructive or mixed in nature.

A *central apnoea* is when the event meets criteria for an apnoea, there is an absence of

inspiratory effort throughout the event and at least one of the following conditions is met:

- the event is $\geqslant$20 s in duration,
- the event is associated with an arousal or $\geqslant$3% oxygen desaturation,
- in infants ($<$1 year of age) only, the event is associated with a decrease in heart rate to $<$50 beats per minute for $\geqslant$5 s or $<$60 beats per minute for 15 seconds (Berry *et al*., 2012).

The respiratory pause in central apnoea is not associated with a physical attempt to breathe: the PSG shows no breathing movements from the thoracic cage or abdomen. *Obstructive apnoea* is a cessation of airflow at both the nose and mouth associated with out-of-phase movements of the rib cage and abdomen. A *mixed apnoea* has no inspiratory effort in the initial portion of the event, followed by resumption of inspiratory effort before the end of the event. *Periodic breathing* is defined as more than three episodes of central apnoea lasting $>$3 s separated by $\leqslant$20 s of normal breathing. *Alveolar hypoventilation* is when P_{aCO_2} (or a surrogate measure) is $>$50 mmHg for $>$25% of total sleep time. Surrogates of P_{aCO_2} are end-tidal or transcutaneous carbon dioxide tension.

Treatments for SDB

Clinical management of apnoea of prematurity includes continuous positive or nasal intermittent positive pressure ventilation to prevent pharyngeal collapse and alveolar atelectasis. Methylxanthine compounds such as caffeine, theophylline and aminophylline stimulate the central nervous system and respiratory muscle function, and probably reduce apnoea by multiple physiological and pharmacological mechanisms.

Other treatments for SDB include supplementary oxygen, CPAP, bi-level positive pressure ventilation (BiPAP) and mechanical ventilation *via* tracheostomy. In hypoventilation syndromes, the primary goals are often to secure the airway, and ensure optimal ventilation and oxygenation with artificial ventilation. For CCHS, unfortunately, only symptomatic treatments exist, including positive pressure ventilation *via* tracheostomy, BiPAP, negative pressure ventilation or diaphragm pacing. It is of utmost importance to select the best mode of artificial ventilatory support for each individual patient. CCHS does not seem to improve with age, except in rare anecdotal cases.

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Impact of obesity on respiratory function

Andrea Bon, Martina Tubaro and Mario Canciani

Obese children present different lung anatomy and function and have more respiratory symptoms than their normal-weight peers. Paediatric obesity is now considered a major public health problem and data from many observational studies show an increase of this disease in recent decades, in all age-groups: about 7% of the world population is obese. In Europe the prevalence of childhood obesity ranges from 10–20% in the north to 20–40% in the cities of the Mediterranean basin. In the USA, the prevalence of overweight children has tripled in the past 20 years. Globally, an estimated 43 million preschool children (under age 5 years) were overweight or obese in 2010, a 60% increase since 1990.

The commonest and simplest method of measuring and determining obesity is BMI, defined as: mass (kg)/[height (m)]^2. In adults, a BMI >30 kg·m^{-2} defines obesity, but as the normal BMI changes throughout childhood and is age- and sex-specific, a centile chart has to be used in children. In UK centile charts, overweight is taken as a BMI >91st centile and obesity a BMI >98th centile. Other methods of assessment include Ideal Body Weight (IBW), waist circumference, waist/hip ratios, skinfold thickness, abdominal fat from CT/MRI scans, bioelectrical impedance and dual energy X-ray absorptiometry (DEXA).

Key points

- Obesity is defined as BMI >98th centile according to age- and sex-specific centile charts.
- Obesity is associated with a change in static and dynamic lung volumes.
- Obese children experience more respiratory symptoms compared to their normal-weight peers.
- There is a parallel increase in asthma and obesity prevalence, but a true relationship is controversial.
- Obese children should be screened at routine visits for the presence of snoring, apnoea, sleep disordered breathing and daytime drowsiness.

Lung function in obesity

There are limited data on obese children, but studies on adults show that obesity has a profound effect on the anatomy and physiology of breathing (table 1).

The upper airways may be directly narrowed by fatty infiltration of muscles and subcutaneous fat deposits.

An important respiratory abnormality in obesity is a decrease in total respiratory system compliance. The primary reason is a decrease in chest wall compliance associated with the accumulation of fat. Lung compliance is decreased as well and may relate to the increased pulmonary blood volume seen in obese individuals. Total respiratory compliance is reduced markedly, mainly in supine position. This reduction increases the work of breathing, along with an increase in nonelastic work and inefficiency of respiratory muscles. The nonelastic work comes from the raised upper and lower airway resistance, the latter resulting from a reduction in lung volumes due to obesity. Moreover, studies suggest that the pressures generated by the

Table 1. Main changes in lung physiology in obesity

↓ **Total respiratory compliance**
↓ chest wall compliance
↓ lung compliance
↑ **Work of breathing**
↑ nonelastic work
↓ muscle efficiency
Change in static lung volumes
↓ ERV
↓ FRC
Change in dynamic lung volumes
↓ FEV_1
↓ FVC
↑ **Gas exchange**

↓: decrease; ↑: increase.

respiratory muscles in obese patients are lower than those of nonobese patients at all lung volumes. This may result from diaphragm dysfunction due to increased abdominal and visceral adipose tissue deposition, or from overstretching of diaphragm fibres leading to length-tension disadvantage.

In obese individuals, there are changes in static and dynamic lung volumes. Among the static lung volumes, expiratory reserve volume (ERV) and functional residual capacity (FRC) are decreased, and this is more evident in the supine position due to the increased gravitational effects of the abdomen. TLC and vital capacity (VC) may be reduced, while residual volume (RV) is usually maintained. These changes influence ventilation:perfusion ratio mainly at the bases, where airway closure and alveolar collapse are responsible for underventilation. Dynamic lung volumes are affected only in morbidly obese subjects. An increase in body mass correlates with reduced FEV_1 and FVC. Generally, in mild obesity, spirometry is normal. Patients with mild-to-moderate obesity present a restrictive pattern whereas with severe and morbid obesity spirometry is more likely to show true airflow obstruction. One mechanism may be related to small airway collapse due to decreased lung volumes with increasing obesity.

Finally, gas exchange, assessed by the carbon monoxide diffusion capacity (D_{LCO}), is increased in obesity. This may be explained by increased pulmonary blood volume and flow. This rise has been observed without evidence of pulmonary congestion or heart disease.

Asthma and obesity

The relationship between asthma and obesity in children is controversial. The increasing prevalence of asthma in children in recent decades, demonstrated by several epidemiological studies, goes hand in hand with the rise in obesity, making these diseases among the top priorities in childhood health both in Western countries and in the developing world. The definition of asthma is crucial if we are to find any definite correlation with obesity. Asthma is characterised by increased airway responsiveness with chronic inflammation, resulting in reversible airway obstruction. The criteria for asthma diagnosis and asthma definition vary between studies and frequently rely on self-reported symptoms (or on physician diagnosis based solely on self-reported symptoms). Review of the evidence suggests that a higher BMI in children is associated with a higher prevalence of symptoms commonly attributed to asthma, such as wheeze, but not a higher prevalence of objective asthma. Obese children are less fit and may have more symptoms of breathlessness on exertion than their peers. An increased perception of symptoms in the obese may further complicate this issue.

However the parallel increases in prevalence suggest a link between the two conditions, even if the pathophysiological basis of this relationship remains unclear. Correlation mechanisms seem to be possible: sedentary lifestyle, dietary factors, systemic inflammation, reduced chest wall compliance, insulin resistance, the presence of comorbidities and common genetic predispositions.

Cross-sectional studies show a weak link between asthma and obesity. However, a number of longitudinal studies in children and adolescents show a positive association, in particular supporting the correlation between overweight and future risk of developing asthma. In addition, obesity may be associated with asthma severity and/or poor asthma control. Studies in adult asthma patients show that obese patients are more symptomatic, require more medications and make more emergency department visits than their nonobese counterparts. However, such reports in the paediatric population are controversial.

Asthma and obesity are both characterised by chronic inflammation. Asthma is, by definition, a chronic inflammatory disease. Obese patients show a low degree of systemic inflammation involving a number of mediators, known as adipokines. The adipokines include tumor necrosis factor-α, interleukin-6, eotaxin, vascular endothelial growth factor and chemotactic proteins for monocytes. These factors have been associated with asthma and may play a role in the common state of inflammation. Leptin, one of the main hormones involved in the regulation of inflammation in obesity, is potentially relevant in asthma as well. High levels of leptin are associated with an increased prevalence of asthma during life, especially nonatopic asthma. Leptin serum levels in asthmatic patients are high independently of BMI, possibly because leptin contributes to the typical inflammatory cascade of asthma.

Obesity is often associated with sedentary lifestyle leading to dyspnoea and breathlessness during exercise, which could be interpreted easily as asthma or wheezing. These symptoms lead to a further reduction in physical activity and increase in body weight in a vicious circle. Poorly controlled exercise-induced asthma as well may contribute to reduction in physical activity and to weight gain, showing an overlap among obese and asthmatic phenotypes. The Childhood Asthma Management Program (CAMP) Study has shown that children with mild or moderate asthma have a significant risk of becoming overweight.

Paediatricians should be cautious about diagnosing asthma in an obese child on the basis of self-reported symptoms alone, and should seek objective evidence from peak-flow recordings, exercise tests or laboratory measurement of airway reactivity.

Obstructive sleep apnoea syndrome

OSAS is a disorder of breathing during sleep characterised by prolonged partial upper airway obstruction and/or intermittent complete obstruction (obstructive apnoea) that disrupts normal ventilation during sleep and normal sleep patterns. Obese children have a 4.5-fold increased risk for OSAS compared with the general population. In the pathophysiology of OSAS in obese children, anatomical and functional factors play a role. In the first group, adenoid and tonsillar hypertrophy is found in 45% of obese children with OSAS. However, after adenotonsillectomy OSAS persists in nearly half of obese paediatric patients, compared to 10–20% residual OSAS in nonobese children. Other anatomical factors, such as fat pads, soft palate, lateral pharyngeal wall, and tongue may restrict upper airway size. A recent study suggests that the development of OSAS in obese children is linked to marked visceral adiposity, increased parapharyngeal fat pads and upper airway lymphoid hypertrophy, even if the size of these tissues do not correlate with the BMI. Obese children have an increased incidence of both the presence and marked enlargement of the lingual tonsils. This enlargement can be responsible for persistent OSAS after adenotonsillectomy and require specific treatment. In obese children, as previously stated, there is a change in chest wall mechanics, reducing compliance and FRC, leading to hypoventilation, atelectasis, and ventilation:perfusion mismatch. Functional factors leading to airway collapsibility may be neuromotor tone, tissue properties and increased resistance. Studies on obese adults with OSAS have demonstrated higher critical closing pressure of the pharynx, a direct sign of increased airway collapsibility. It is possible that obese children have altered ventilatory

responses, although the role of the ventilatory drive in OSAS in children is unclear.

Although true cardiovascular diseases are not detected in young children with OSAS, predisposing conditions such as the dysregulation of blood pressure, cardiac function, autonomic function and endothelial function are independently associated with it. Studies suggest OSAS as a possible independent cause of metabolic syndrome, augmenting insulin resistance, dyslipidaemia, hypertension and inflammation through increased sympathetic tone, intermittent hypoxaemia, sleep fragmentation and insufficient sleep.

Obese children should be screened at routine visits for the presence of snoring, apnoea, disordered breathing during sleep and daytime drowsiness. Polysomnography is considered the gold standard for the diagnosis of OSAS. Other methods, such nocturnal pulse oximetry or daytime nap polysomnography are specific but need confirmation if negative. Weight loss is associated with a significant reduction in sleep apnoea and is the most effective long-term treatment, but the least likely to take place. However, the majority of patients continue to experience sleep disordered breathing. In obese children with OSAS and adenotonsillar hypertrophy, adenotonsillectomy is an important option, with effective resolution of symptoms in about 50%. CPAP is considered in patients without adenotonsillar hypertrophy or ineffective adenotonsillectomy. Other treatments include oral appliances, uvulopalatopharyngoplasty and positional therapy, with variable results.

Obesity hypoventilation syndrome

Obesity hypoventilation syndrome (OHS), also known as Pickwickian syndrome, is defined as a combination of obesity and awake arterial hypercapnia (arterial carbon dioxide tension >45 mmHg) in the absence of other causes of hypoventilation. This disorder is associated with gross obesity, with only few case reports in children. The pathophysiology is thought to be the exasperation of the mechanical loading of the respiratory system with muscular exhaustion leading to chronic hypoxia and hypercapnia, with blunting of chemoreceptor responsiveness in susceptible individuals. The chronic fatigue, daytime sleepiness and headaches of these patients are associated with hypercapnia and hypoxaemia; with time these patients develop polycythaemia, pulmonary hypertension and later right ventricular failure. The most appropriate treatment includes weight loss and nocturnal NIV.

Breathing disorders in obesity-associated syndromes

Prader–Willi syndrome Commonly associated characteristics of this syndrome include neonatal hypotonia, obesity due to excessive intake and inactivity, mental retardation, short stature, scoliosis, hypogonadotropic hypogonadism, strabismus, and small hands and feet. Typically these children may present a variety of abnormalities of breathing, including OSAS and sleep-related alveolar hypoventilation. Although the abnormal response to hypercapnia is probably related to obesity, there is an altered ventilatory response to hypoxaemia and chemoreceptor responsiveness both in obese and nonobese patients with Prader–Willi syndrome. They may not arouse normally following prolonged airway obstruction, leading to increased risk of morbidity, including sudden death. Severely obese patients with respiratory impairment receiving human growth hormone are potentially at risk of sudden death especially in the first 12–18 months of therapy.

The treatment of OSA in Prader–Willi patients includes weight loss, which is particularly difficult for these patients, adenotonsillectomy, and NIV, which could be challenging with the behavioural problems associated with this syndrome.

Down syndrome Many features that characterise this syndrome, such as micrognathia, hypotonia, macroglossia, midfacial hypoplasia, along with obesity, increase the risk of airway obstruction. The first-line treatment is adenotonsillectomy.

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Lung injury

Andreas Schibler

A multitude of endogenous and exogenous factors can cause acute lung injury in infants and children. The clinical picture is characterised by an increased work of breathing and impaired gas exchange. Depending on the severity of the lung injury mechanical respiratory support is needed. An adult-based definition for acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) has been developed for the purpose of clinical trials. The definition of ALI or ARDS has changed little over the past 20 years and is mainly defined by a bilateral pulmonary infiltrate on chest radiography (fig. 1), a pulmonary capillary wedge pressure of <18 mmHg (for paediatric purpose excluding heart failure due to congenital heart disease or cardiomyopathy) and a $P_{a}O_{2}$/inspiratory oxygen fraction ($F_{I}O_{2}$) ratio <200 or <300 for ARDS and ALI, respectively. A recent review of the ARDS and ALI criteria defines severe ARDS as a $P_{a}O_{2}/F_{I}O_{2}$ ratio <100 and moderate ARDS as a $P_{a}O_{2}/F_{I}O_{2}$ ratio 100–200. ALI is defined as a $P_{a}O_{2}/F_{I}O_{2}$ ratio 200–300. This definition doesn't consider the considerable large range of possible causes for lung injury and fails to accurately characterise the severity if significant ventilation/perfusion mismatch exists (a false low $P_{a}O_{2}/F_{I}O_{2}$ ratio). Lung injury can be seen as part of a systemic inflammatory process (sepsis, pancreatitis and post-blood transfusion), or directly related to local injury caused by infection, aspiration or toxic gas inhalation. The histopathological characteristics are a widespread destruction of the capillary endothelium, extravasation of protein-rich fluid and interstitial oedema followed by damage to the alveolar membrane, and fluid leaks into the alveolar space.

Key points

- ALI can be caused by endogenous or exogenous factors.
- VILI causes additional harm in the presence of lung injury.
- Protective ventilation strategies have reduced the mortality of ARDS.

ARDS is characterised by two distinct stages. The acute phase is defined by disruption of the alveolar–capillary membrane with leakage of protein-rich fluid in interstitial and alveolar space combined by release of cytokines and inflammatory cells. This leads to a secondary leakage of inflammatory proteins into the circulation (systemic inflammatory response syndrome (SIRS)). The second reparative stage shows fibroproliferative changes with organisation of lung tissue. Although any lung injury is a diffuse process, it is also a heterogeneous disease and not all lung units are affected equally. This causes two different pathophysiological outcomes. First, ventilation-induced lung injury (VILI) is more likely to affect the open and less injured lung unit than the closed and hardly aerated diseased lung. Secondly, the ventilation/perfusion mismatch increases intrapulmonary shunting, which decreases oxygen delivery. Hence the corner stone of optimal mechanical support is to open the previously closed lung units and have them participating in the gas exchange. In achieving this, airway pressures are more

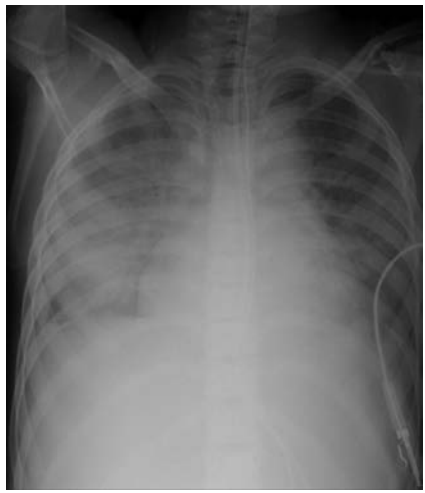

Figure 1. Chest radiograph from a 5-year-old girl with sepsis-induced ARDS. Note, the bilateral chest infiltrate affecting the majority of the lung fields.

evenly distributed throughout the lung and less damage is seen to the healthier parts of the lung. Intrapulmonary shunts are decreased and oxygen uptake improved.

The two-hit model

For a comprehensive understanding of the characteristics of lung injury the concept of the "two-hit" model needs to be discussed. The initial primary hit consists of the underlying pathological process such as hyaline membrane disease, bacterial or viral infection, or aspiration of meconium or water in drowning. In case mechanical ventilatory support is required for adequate gas exchange a secondary hit may occur, previously described as VILI. This secondary hit causes an augmentation of the already pre-existing inflammatory response of the lung, which is commonly defined as biotrauma caused by positive pressure ventilation. Most of the recent research efforts aimed to reduce and minimise this secondary insult have improved ventilation strategies with significantly better outcomes and reduced morbidity and mortality. Many experts in the field even argue that ARDS is a partially man-made disease. Avoiding high airway pressures and potentially even avoiding invasive mechanical ventilation may improve outcome of patients with ARDS. Human and experimental studies in healthy lungs have shown that the mechanical stress inflicted on the tissue and skeleton of the lung during positive pressure ventilation can be seen within 20 min of ventilation. For a better understanding of the differences between healthy and sick lungs knowledge of ventilation distribution is important. In healthy lungs the alveolar structure hardly changes its geometry during tidal breathing and volume changes occur mainly in the peripheral airways and alveolar ducts. The alveolar structure is maintained by the elastic stretch and recoil forces of the lung parenchyma and the presence of surfactant within the alveoli. Hence the lung parenchyma does not experience significant mechanical stress during regular tidal breathing. This delicate balance and geometry is destroyed in lung disease and alveoli may additionally be filled with secretion containing loose alveolar or epithelial cells, neutrophils, macrophages, lymphocytes and airway secretion. This then leads to collapse or atelectasis, especially of the dependent lung regions. Gas exchange is consequently impaired and these so-called closed lung regions experience significant shunting of pulmonary blood flow, which adds to low systemic oxygen saturation. Mechanical ventilation directs positive pressure into these affected lung regions and causes cyclic opening and closing of the alveoli. Alveoli do not tolerate these extreme stress forces and the previously mentioned rupture of the alveolar–capillary membrane occurs. In the past, rather large tidal volumes were delivered during mechanical ventilation (10–15 $mL \cdot kg^{-1}$), which were detrimental to the lung and led to significant secondary lung injury. The newer approach of mechanical ventilation these days is to reopen and stabilise the collapsed lung regions and expose the lung to small tidal volumes (protective ventilation). This is mainly achieved by using recruitment manoeuvres of the lung and the use of high positive end-expiratory

pressures (PEEP). Studies using CT-guided lung recruitment have shown significantly improved respiratory mechanics and gas exchange, but this has not yet translated into reduced mortality. The concept of protective ventilation with high PEEP and low tidal volumes as a general strategy has improved outcome overall (mainly studied in adult patients with ARDS). In clinical practice, however, we lack good monitoring tools indicating optimal lung recruitment and mechanical support. In general, tidal volumes of 6 $mL \cdot kg^{-1}$ and generous PEEP have been accepted also in paediatric ventilation. The personal experience of many ventilation experts is that the severity, morbidity and mortality of children with ARDS have been reduced. Mortality of ARDS has been reported for infants and children to as high as 40% and, for ALI, 20%. The availability of extracorporeal membrane oxygenation (ECMO) in combination with the use of protective ventilation has further improved outcome. Newer adult figures show an ARDS mortality of 25% and it is suspected that the current paediatric figure is well below 25%. Most of the patients die because of the associated multiorgan failure and not lung failure. Pulmonary oedema can present clinically and on radiography is very similarly to ARDS. Hence, in all patients echocardiography of the heart needs to be performed.

Cause and pathophysiology of ALI needs to be discussed based on the following three factors: stage of lung development at which the insult occurred, and endogenous or exogenous cause for the injury.

Insult during lung development

There are fundamental differences in the remodelling process during and after lung injury between adults and children despite similarities in the structural changes of the disease process. In adults, the lung injury occurs in a fully developed lung whereas, in contrast, in infants and young children <3 years of age airway and lung tissue development still occurs. The changes in the developing lung include:

- an increase in airway calibre and length,
- development of the immune system, including the plasticity of T-helper cell response,
- exposure to a range of pathogens and viruses, in particular for the first time.

The interaction of the disease process with normal lung development may have long lasting impact on lung function. It is therefore not surprising that the impact of positive pressure ventilation in addition to the interactions mentioned above further augments the potential for more severe lung injury. Another important factor is that during invasive ventilation, secondary lung infections (ventilator-associated pneumonia (VAP)) and aspiration of saliva and acidic fluids from gastro-oesophageal reflux occur.

Respiratory causes are responsible for ~25% of all admissions to paediatric intensive care units. Bronchiolitis and pneumonia are the most common among respiratory causes but with a relative low mortality (1.9%). All common respiratory viruses, such as RSV, HMV and influenza, can cause ARDS similar to any bacterial infection. Other exogenous causes are fresh water aspiration during drowning, inhalation of toxic fumes in a house fire or aspiration of gastric content in the unconscious or seizing patient (table 1). In cases of smoke inhalation injury, carbon monoxide and cyanide poisoning complicate the care of the patient. Transfusion-related acute lung injury (TRALI) is a potentially fatal side-effect of blood transfusion. It is now considered to be the most frequent cause of transfusion-related morbidity and mortality and is under-reported and underdiagnosed. TRALI is thought to develop *via* transfusion of either an anti-leukocyte antibody or a biological response modifier. Transfusion of blood products in a patient with an already existing ALI may aggravate the lung disease. Conservative blood transfusion management in ARDS is suggested.

A few ARDS/ALI-specific treatment options will be briefly discussed. Most evidence is adult-based as there are only a few paediatric ARDS trials. The general concept of a high PEEP (10-15 cmH_2O) and low tidal

Table 1. Causes of lung injury

Exogenous
Sepsis
Pneumonia
Aspiration and drowning
Meconium aspiration syndrome
Inhalation of noxious fumes
Endogenous
TRALI
Pancreatitis
Burns
Poisoning

volume ventilation (6 $mL \cdot kg^{-1}$) strategy is mostly accepted in paediatric intensive care, despite the lack of paediatric-specific data. With the use of low tidal volumes clinicians accept higher $PaCO_2$ levels as long as the pH is >7.2 (permissive hypercapnia). Lung recruitment using either a sustained inflation manoeuvre (*i.e.* maintaining an inspiratory pressure as high as 40 cmH_2O for 20–40 s) or a staircase PEEP trial have shown improved gas exchange and lung compliance in most human and experimental studies, but only a few studies have reported better outcomes. Not all patients with ARDS have recruitable lungs. Patients with a pulmonary cause of ARDS are less likely to benefit from lung recruitment in the early stage of the disease. High-frequency oscillatory ventilation (HFOV) is commonly used in severe paediatric ARDS. There are only a few, and small, controlled trials demonstrating a benefit of HFOV in children. A recent adult trial using HFOV in ARDS has shown a higher morbidity and mortality in the HFOV arm. Like many diseases, early detection and treatment is key to a good outcome. Hence, there is a similar shift in the paradigm to support any acute lung failure. With the use of NIV and CPAP in the very early stage of lung injury we may see a significant reduction in the severity of many patients with ARDS. Some adult and paediatric trials are already reporting a significant reduction in mortality and morbidity in patients with ARDS if they are treated with NIV at an early stage. Further to the appropriate antimicrobial therapy, surfactant replacement has been successfully used in paediatric ARDS. The key to success is to use surfactant in the early stage to keep the lung open for adequate ventilation. Inhaled nitric oxide to treat hypoxaemia and reverse the associated pulmonary hypertension has been widely used but the sobering fact is that nitric oxide has not had any impact on outcome. Currently, nitric oxide should only be offered in desperate cases before transfer to ECMO and if the patient doesn't respond then nitric oxide should be ceased. The use of steroids is also controversial. It is suggested that the use of steroids in a low dose and mainly during the early stage of ARDS may be beneficial. Steroids may have a short-term benefit in improving gas exchange and lung function, and even ventilator-free days in adults but long-term outcome *i.e.* discharge to home, was not necessarily improved in all studies. Prone positioning is one of the simple means to improve gas exchange in children with ARDS and adult studies have shown improved outcomes and reduced mortality. The concept of changing the body position between supine and prone is to redistribute pulmonary fluids, reopening of the collapsed lung regions in the previously dependent lung regions and improving chest wall mechanics. Because of the ease of repositioning an infant or child compared to adults, prone positioning is widely used in paediatric intensive care settings. ECMO is used as a rescue treatment if conventional treatment or HFOV fails. The international ECMO database reports an ~50% ECMO success rate for patients who otherwise would have died on conventional ventilation.

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Acute and chronic respiratory failure

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Acute respiratory failure

Acute respiratory failure occurs when the lungs are unable to adequately deliver oxygen to the arterial blood or clear carbon dioxide from the blood. Although there are no formal definitions, a P_{aO_2} <50 mmHg or a P_{aCO_2} >60 mmHg is generally considered an appropriate threshold. Measurement of arterial blood gas is critical to the determination of respiratory failure. Interpretation and analysis of blood gas results have been covered in this *Handbook* in the Blood gas assessment and oximetry section.

Key points

- There are a wide range of causes of both acute and chronic respiratory failure in children.
- Blood gas analysis remains the central investigation when assessing respiratory failure.
- Methods of support, and particularly noninvasive techniques, have allowed a much greater ability to avoid prolonged intensive care.
- Improvements in technology, intensive care and the provision of home care for children in chronic respiratory failure have led to increasing numbers of these children being cared for in the community.
- Early recognition of chronic respiratory failure should lead to interventions that will correct gas exchange as far as possible before secondary complications develop.

Acute respiratory failure (ARF) can occur as a result of several different causes including hypoxaemia, hypoventilation, diffusion impairment or shunt. Diffusion problems can be observed due to direct impairment of the movement of gas between alveoli and blood (such as is seen in interstitial lung disease), or due to changes in the balance of ventilation/perfusion (V'/Q') in different parts of the lung. Of these, V'/Q' inequality is the most common and important in the majority of clinical conditions.

Definition and physiology *Acute hypoxic (Type I) respiratory failure* is a common presentation in children with severe respiratory disease. It is important, as reduced oxygen delivery to the rest of the body can lead to tissue hypoxia, which can, in turn, cause organ dysfunction or injury. Severe hypoxia is therefore a potentially critical situation and can lead to neurological, renal, cardiac and other organ failure. However, such findings are uncommon, and mild or moderate hypoxia is well tolerated in the short term. Most hypoxic respiratory failure in children will occur as a result of acute parenchymal disease caused by infection.

In most cases the hypoxia is related to abnormalities in V'/Q' matching and in particular to areas of low V'/Q'. If an area of the lung has a blood flow but no ventilation ($V'/Q'=0$) this allows deoxygenated blood to pass directly through to the systemic circulation, and is termed a shunt. In normal circumstances we have an effective (virtual) shunt of 3–4%, but if this increases, S_{aO_2} is

unable to reach 100% and the plateau of the oxygen dissociation curve (ODC) is depressed. Conversely, if there is reduced (but measurable) ventilation to a well perfused area (low V'/Q'), the alveolar gas tends to contain increased levels of carbon dioxide and P_{aO_2} is reduced, as predicted by the alveolar gas equation. This will also tend to reduce the saturation of arterial blood, but (unlike shunt) can be overcome by increasing oxygen concentration. The effect on the ODC is therefore to move the curve to the right (fig. 1). Areas that are well ventilated but poorly perfused will generate well-oxygenated blood, but the reduced flow limits their contribution to the overall blood gases.

In many diseases, such as acute asthma, chronic lung disease and bronchiolitis, there are significant changes to V'/Q' throughout the lung, due to areas of hyperinflation and atelectasis. This causes some shunting as well as significant areas of low V'/Q' matching and it is this that causes S_{aO_2} to fall. This becomes more evident when we consider that children with lung aplasia, or following lobar resection, will have entirely normal blood gases despite the loss of lung volume.

Type I failure can give rise to significant organ dysfunction and injury, but this is not usually an immediate effect (unless the failure is coupled with systemic shock). Blood gas results will therefore tend to show an isolated hypoxia but without much change in pH. The development of a significant acidosis (often seen as a metabolic acidosis) implies that organ perfusion has been compromised, and may indicate the severity of the problem.

Acute hypercarbic (Type II) respiratory failure is less common in paediatric practice. It can be seen in children with underlying neuromuscular disease or major skeletal abnormality such as severe scoliosis. Acute presentation in such cases would be rare but can follow intercurrent infection (acute on chronic). Unusual causes include Guillain–Barré syndrome, acute upper airway obstruction (*e.g.* foreign body) or over sedation, which may be witnessed following administration of anticonvulsants.

Unlike Type I failure, carbon dioxide retention will produce a rapid fall in pH (respiratory acidosis). Measurement of carbon dioxide and pH is more difficult than saturation, and although there are some noninvasive techniques (such as end-tidal or

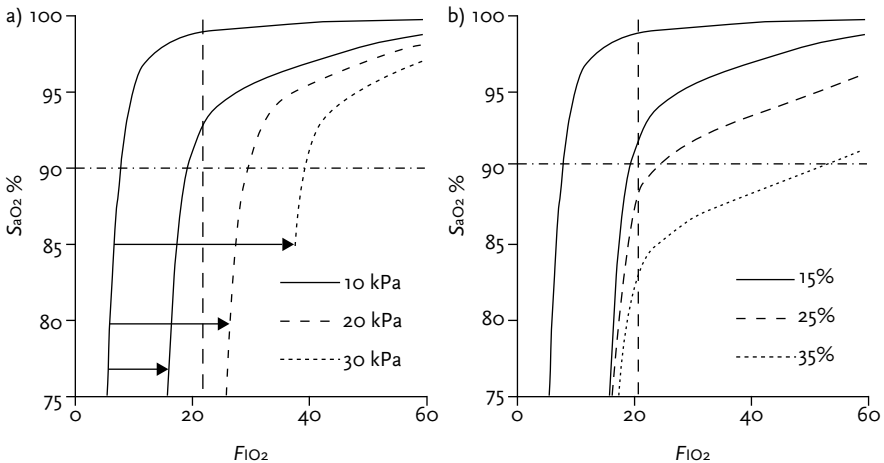

Figure 1. The effect of a) low V'/Q' and b) shunt on the ODC. Note that reduced (but not absent) ventilation will tend to move the curve to the right, and can be overcome with additional inspired oxygen. However, in pure shunt the maximal saturation that can be reached is reduced. F_{IO_2}: inspiratory oxygen fraction.

transcutaneous monitoring), Type II failure can be easily missed or overlooked. Consideration of this possibility in patients at risk is therefore critical and measurement of a blood gas (capillary of arterial) is important. This will show a low pH and raised carbon dioxide, but even pure respiratory acidosis may involve some lowering of the bicarbonate (and hence the base excess) due to the intimate relationship between carbon dioxide and bicarbonate levels.

It is also important to understand the role of muscle fatigue in the presentation of children with ARF. The diaphragm, just like other skeletal muscle within the body, is unable to indefinitely sustain a workload that is >40% of its maximal capacity. When this occurs, the metabolic demands of the muscle result in cellular energy failure and an inability to maintain contraction. This energy failure is usually quite sudden, particularly in children, and so children with significantly increased work of breathing can deteriorate and decompensate very rapidly.

Another clinical situation where respiratory failure can present rapidly is in acute lung injury (sometimes referred to as acute respiratory distress syndrome (ARDS)). In this situation, which may follow sepsis aspiration or trauma amongst other things, interstitial fluid and alveolar oedema develop rapidly causing significant difficulties in oxygenation. It is unusual for this to present *de novo* and usually occurs in a child who is already unwell from one of the underlying causes, such as a severe pneumonia. However, it is a devastating disease with a high mortality. High ventilatory pressures are often required that, in turn, further damage the lung and often lead to interstitial fibrosis and lung scarring.

Clinical effects of respiratory failure: Increasing hypoxaemia stimulates increased respiratory drive and together with the underlying cause of the hypoxia will present clinically as an increase in respiratory effort and distress. Symptoms from other organ involvement become more apparent with increasing hypoxia. Neurological status can be affected with falling consciousness, and urine output may decrease.

Hypoventilation can be much more difficult to assess clinically and measurement of arterial saturations may miss significant problems, particularly if additional oxygen is being administered. In more chronic conditions, headaches and other neurological changes can be seen. If acidosis is significant (<7.25), cellular enzyme systems start to be affected. In particular contraction of myocardial cells starts to decrease, causing reduced cardiac output with implications for organ perfusion.

Investigation of ARF Faced with a child with respiratory problems in whom ARF is possible, the immediate concerns should be to address the ABC of resuscitation:

- oxygen should be administered;
- support summoned and;
- the patient's airway and breathing evaluated in a systematic manner.

However, once the immediate issues have been addressed a more measured assessment can be made. A clear history must be obtained, including the duration of symptoms, previous medical problems, family history, *etc*. A thorough clinical examination aims to determine the cause of the failure and the acute consequences.

The mainstay of investigation in ARF is the measurement of arterial blood gases. Clinical assessment or S_{pO_2} alone are unable to provide a complete picture of the respiratory and metabolic components involved. As an example, a patient with diabetic ketoacidosis may present with tachypnoea, increased work of breathing but normal oxygenation. Immediate physical examination may show dehydration, but may not demonstrate any indication of metabolic acidosis and it may initially appear as though the patient is suffering from a respiratory problem. However, blood gas analysis would rapidly show that the pH was low but so was the carbon dioxide, and that the respiratory effort was a response to a metabolic problem and not the underlying cause of distress.

A chest radiograph may be very helpful in the acute setting. In patients with extensive shadowing, consideration of an ultrasound should be made as pulmonary effusions can otherwise be missed, and management would be altered if a large effusion were present. The exception to this may be a child with bronchiolitis, where the diagnosis is clinical and chest radiographs are not recommended routinely. Radiographs are of limited value in assessing a child with hypoventilation.

Lung function testing may be useful to document recovery from an acute event or track a slow deterioration. Measurements of flow and volume (peak expiratory flow rate, FEV_1 and FVC) are valuable in asthma, and can help to determine the degree of obstruction. They can also be useful in patients with acutely progressing Guillain–Barré syndrome, as FVC has been used as a marker of disease severity, and as an indication for intubation.

Management of ARF The prerequisites of respiratory support are to improve the oxygenation and the clearance of carbon dioxide. This can be managed through improving oxygen delivery (increasing inspired oxygen concentration, using positive pressure ventilation, relieving obstruction), or by reducing demand (reducing work of breathing and reducing metabolic demand).

Oxygen administration: The simplest way to improve arterial oxygen levels is to increase the partial pressure of inspired oxygen (PiO_2). The rate of gas diffusion across the alveolar basement membrane is directly related to the concentration gradient, and so a higher inspired PiO_2 will lead to greater absorption. The effect that increasing PiO_2 will have on blood gases will depend, to some extent, on the underlying disease. If there is significant shunt, then the effect will be small, but for patients with hypoventilation or with V'/Q' inequality, oxygen administration should be effective at improving the abnormality. This is important, as oxygen administration can readily correct arterial saturation values in a hypoventilating patient, and high carbon dioxide levels can be missed if blood gases are not obtained.

Delivery of additional oxygen can be *via* a mask, nasal cannula or a head box. Masks are easily tolerated but can entrain air at higher inspiratory airflows, and so a reservoir bag is needed to deliver high concentrations. Delivery of oxygen *via* nasal cannula or head box has been shown to be equally effective, and the choice of method is mostly down to tolerability and personal preference.

Maintaining a high level of inspired oxygen is important, but other factors may also affect delivery of oxygen to the tissues. Cardiac output, haemoglobin concentration and local blood flow need to be considered.

Noninvasive pressure support: Applying a flow of gas to the upper airway, often with an increased positive airway pressure, has been used to support ventilation for many years. Pressure can be delivered *via* a mask to the nose or face or with nasal prongs in the small child. There are several mechanisms by which this may help.

- Increased pressure in the airway may be transmitted to the lung. In a lung with reduced compliance this may move the pressure–volume curve to a more compliant phase, allowing better air entry for the same effort, and reducing work of breathing.
- Pressure in the upper airways may help reduce resistance to airflow. This may be especially useful in patients with neuromuscular disease who can develop obstruction due to weak pharyngeal muscles, or in patients with obstructive sleep apnoea.
- High flow nasal oxygen (see below) may also reduce dead space. Normally, air within the oropharynx constitutes part of the anatomical dead space but high flow gas will remove this component of the dead space, which can reduce the work of breathing.

Noninvasive support may be delivered either through a tight fitting mask (nasal mask or full facial mask), or through nasal catheters. Proper sizing and fitting of the mask is

essential. Support may be CPAP, with a single pressure (designed to reduce work of breathing, but not directly contributing to ventilation), or biphasic positive airway pressure (BiPAP), where bilevel support enables direct ventilation.

High flow oxygen, such as the Optiflow (Fisher and Paykel, Auckland, New Zealand) and Vapotherm (Stevensville, MD, USA) systems, are a recent innovation. Heated and humidified gas is passed through nasal cannulae at high flow rates (~5 $L \cdot min^{-1}$ in neonates and up to 70 $L \cdot min^{-1}$ in adults). Although the exact mechanism is uncertain, it is a technique that is simple to use and there is increasing evidence of its effectiveness in neonatal, paediatric and adult practice. Reduction of dead space and airway resistance, or an increase in airway pressure, has been postulated as a potential benefit.

Intubation and ventilation remains the definitive method of supporting respiratory failure. The securing of a clear airway is obtained by passing an endotracheal tube through the vocal cords and into the central trachea. A detailed discussion of the management of ventilated patients is beyond the scope of this *Handbook*, but basic physiological principles apply. The settings used need to allow adequate oxygen delivery and carbon dioxide removal. Oxygen delivery requires adequate pressures to deliver gas to the alveoli, and for the partial pressure of inspired oxygen (PIO_2) to be sufficient that oxygen will diffuse across to the blood. Carbon dioxide removal depends on adequate alveolar ventilation, but diffusion is rarely a problem (carbon dioxide diffuses 20 times more readily than oxygen), and so tidal volume and rate become the critical factors. In simplistic terms, oxygen delivery is often increased by adjusting the airway pressures, whereas carbon dioxide removal is effected by adjusting the rate. Inevitably things are more complex than this, and proper lung expansion is critical to both, but the differing factors involved in determining gas exchange for each gas need to be understood when interpreting and reacting to blood gas results.

Another critical factor when instituting ventilation in patients is the effect that positive pressure ventilation will have on the cardiovascular system. Cardiac output is integrally tied to venous return. Positive pressure ventilation (especially in noncompliant lungs) will lead to a restriction on venous return to the heart, and this can act to reduce cardiac output and organ perfusion. High airway pressure will also affect lung perfusion and affect V'/Q' ratios. Hypoxia and hypercarbia in the pulmonary circulation further contribute to vasoconstriction. Recognising these factors and adjusting cardiorespiratory parameters accordingly usually requires the skills of an anaesthetist or intensivist.

Chronic respiratory failure

There is no satisfactory definition of chronic respiratory failure in children. In practice one encounters chronic respiratory failure in two different scenarios:

- the child with an underlying chronic condition who, as part of the natural history of the disorder, is developing a slow failure of ventilation or oxygenation;
- the child who has been on ventilatory support for an acute respiratory insult and then fails to wean and will require long-term ventilation or supplemental oxygen. For the purposes of audit and census the following definition of long-term ventilation is often accepted: ''Any child who, when medically stable, continues to need a mechanical aid for breathing which may be acknowledged after a failure to wean or a very slow wean, 3 months after the institution of ventilation.'' Some of these children will have had an underlying incipient respiratory failure and represent as ''acute-on-chronic'' respiratory failure.

For children with an evolving underlying disorder, unlike ARF, characterised by life-threatening derangements in arterial blood gases and acid-base status, the manifestations of chronic respiratory failure are less apparent or dramatic. Acute respiratory failure develops over minutes to hours with a commensurate drop in pH.

Chronic respiratory failure develops over a much longer period, allowing time for renal compensation and an increase in bicarbonate concentration with a normal or near normal pH.

Causes of chronic respiratory failure There are many causes of chronic respiratory failure in children. Any aetiological classification results in artificial "lumping" especially where dual pathology exists. However, for epidemiological studies and audit it is useful to consider three main categories:

- a loss of central respiratory drive to breathe;
- ineffective thoracic musculoskeletal function;
- disorders of the respiratory tract.

Examples from each of these broad categories are listed in table 1.

Assessment for chronic respiratory failure For children with an underlying condition who are at risk of developing chronic respiratory failure, assessments should be designed to determine the earliest signs of failure so that appropriate intervention can be introduced before secondary complications develop. As with acute failure there will be those who will predominantly have hypoxic Type I failure (*e.g.* a child with severe CF) and those with hypercapnic Type II failure (*e.g.* a boy with Duchenne muscular dystrophy).

For children with CF, spirometry will give an indication that chronic respiratory failure may be developing. When the FEV_1 falls below 30–40% predicted, oxygen saturation will often begin to decrease with exercise or physiotherapy and additional oxygen may be required. This may progress to overnight decline in oxygen saturation with an eventual rise in carbon dioxide, triggering discussion about the use of overnight NIV. Failure to notice chronic failure can lead to increasing lethargy, failure to clear secretions, increased propensity to chest infections and even cor pulmonale and signs of carbon dioxide retention.

For children with Duchenne muscular dystrophy, and other slowly progressive neuromuscular disorders, it is important to notice early signs of respiratory failure so that additional respiratory support can be introduced in a timely fashion; not too soon

Table 1. Examples of causes of chronic respiratory failure in children

Loss of central respiratory drive to breathe
Congenital central hypoventilation syndrome
Acquired central hypoventilation syndrome
Post-infectious encephalopathy
Non-accidental injury
High spinal injury
Birth injury
Vascular malformations
Post-neurosurgery
Ineffective thoracic musculoskeletal function
Spinal muscular atrophy
Congenital myopathy
Duchenne muscular dystrophy
Kyphoscoliosis
Neurometabolic conditions
Skeletal dysplasia
Mucopolysaccharidosis
Thoracic dystrophy
Phrenic nerve damage
Disorders of the respiratory tract
Conditions of the upper airways
Craniofacial disorders
Achondroplasia
Tracheo-bronchomalacia
Acquired: prematurity, post-surgery to the trachea
Congenital: following repair of tracheo-oesophageal fistula or vascular ring
Disorders of pulmonary parenchyma
Pulmonary hypoplasia
Chronic lung disease of prematurity
Progressive lung diseases such as CF or interstitial lung diseases
Recurrent aspiration

before it is required, but not too late so that complications have developed.

Regular assessments will include a history of decreasing cough efficacy, fatigue, weight loss, poor appetite and morning headaches. Lung function can provide important clues as to the likelihood of impending respiratory failure; an FVC <40%, FEV_1 <40%, a poor peak cough flow and a specialised test of respiratory muscle strength, such as the maximal inspiratory and expiratory efforts.

It is now known that a sleep study is essential in the early assessment for chronic respiratory failure in progressive neuromuscular weakness. Measurement of overnight oxygen and carbon dioxide can allow categorisation of incipient respiratory failure into three levels:

- level I: intermittent rapid eye movement (REM) sleep, hypercapnia and hypoxaemia;
- level II: nocturnal hypoventilation in REM and non-REM sleep;
- level III: hypoventilation during all sleep and wakefulness.

The documentation of these changes during sleep provides early evidence of a need for additional respiratory support. If missed, the neuromuscular patient may lose carbon dioxide sensitivity in their respiratory drive and run carbon dioxide levels at a chronically high level. The patient now has little respiratory reserve and relies entirely on a hypoxic drive to breathe, making them very vulnerable to acute on chronic deterioration.

Conclusion

The number of children using long-term ventilatory support for chronic respiratory failure has increased significantly over the past decade and constitutes a major change in the pattern of work for many respiratory paediatricians. Contributing factors to this change in practice include:

- the development of portable ventilators that can be used in the home setting;
- the use of paediatric noninvasive interfaces to deliver ventilation, either in the form of CPAP or BiPAP;
- increasing acceptance on the use of a tracheostomy in the home setting;
- improvements in intensive care allowing for the survival of children with life-threatening illness but ending in incomplete recovery and a chronic ventilatory need;
- a growing experience (especially in children with neuromuscular conditions) that long-term ventilatory support improves quality of life and even alters the natural history of some conditions;
- enthusiastic internet-based organisations and support groups advocating the value and gain of moving children from the hospital to home setting.

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Home oxygen therapy, invasive ventilation and NIV, and home ventilatory support

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The ability to sustain spontaneous ventilation can be viewed as a balance between neurological mechanisms controlling ventilation together with respiratory muscle strength on the one hand, and the respiratory load, determined by lung, thoracic and airway mechanics, on the other hand.

Chronic respiratory failure is constituted by two different types of respiratory failure, which have a distinct pathophysiological background and therapeutic implication (fig. 1). The first type of respiratory failure, "lung failure", is characterised by an abnormality of the alveolar–capillary membrane, as observed in interstitial lung diseases. In this type of failure, the different components of the ventilatory balance are globally normal, with the main abnormality being the transfer of the gases from the alveoli through the alveolar capillary membrane, resulting primarily in hypoxaemia due to the greater diffusion capacity of carbon dioxide compared to oxygen. The second type of respiratory failure, "ventilatory/pump failure", is the result of an imbalance of the respiratory system. In normal individuals, central respiratory drive and ventilatory muscle power exceed the respiratory load, thus explaining the ability to maintain adequate spontaneous ventilation during different physiological conditions such as wakefulness, sleep and exercise. However, significant dysfunction of any of these three components of the respiratory system may impair the ability to generate spontaneously efficacious breaths. Indeed, if the respiratory load is too high and/or ventilatory muscle power or central respiratory drive is too low or inefficient, ventilation may become insufficient. This type of respiratory failure is characterised by alveolar hypoventilation with hypercapnia and hypoxaemia.

Key points

- The main objective of oxygen therapy and mechanical ventilation is to restore a normal nocturnal and daytime gas exchange and a normal sleep quality.
- LTOT is the treatment of choice of chronic hypoxaemia.
- Mechanical ventilation is the treatment of choice of chronic hypercapnia.

The treatment of respiratory failure is determined by the type of respiratory failure. In the case of an abnormality of the alveolar–capillary membrane, the treatment is oxygen. Oxygen therapy, by increasing the oxygen concentration within the alveolar space, will increase the alveolar–capillary gradient and, as a consequence, the arterial oxygen concentration. While in the case of an imbalance of the ventilatory balance, the aim of the treatment is to correct the disequilibrium, by either unloading the respiratory muscles in the case of an increase in respiratory load (as observed in CF), or by replacing them in the case of respiratory muscle weakness (as observed in neuromuscular diseases). In the rare cases of a failure of central drive (as in Ondine's curse) the aim of the treatment is to replace

the brain. Ventilatory assistance, preferentially by a noninvasive route such as NIV, represents the treatment of choice for this type of respiratory failure, by maintaining sufficient minimal ventilation.

Besides these two types of respiratory failure, children may present with structural or anatomical upper airway obstruction, exposing them to recurrent episodes of upper airway closure, which are responsible for apnoeas or hypopnoeas, especially during sleep. These children do not present with overt respiratory failure as the bypass of the obstruction restores normal breathing. In these patients, CPAP delivered by a noninvasive interface, such as a nasal mask, is the technique of choice, with a tracheostomy being reserved for CPAP failure.

During sleep, the breathing process is less efficient. Indeed central drive, chemoreceptor and mechanoreceptor sensitivity are less performant during sleep than during wakefulness with a relationship to the depth of sleep, with stages 3 and 4 sleep being the least responsive. Sleep is also associated with changes in respiratory mechanics with an increase in ventilation (functional residual capacity). Although the activity of the diaphragm is preserved, those of the intercostal and the upper airway muscles decrease significantly. All these abnormalities explain a physiological degree of nocturnal hypoventilation causing a 2–3% fall in S_{pO_2} and an increase in P_{aCO_2} of up to 3 mmHg (0.4 kPa) in healthy adults. In children with moderate abnormal gas exchange during wakefulness, these physiological modifications may precipitate respiratory failure during sleep, underlining the importance of systematic sleep studies in all children who present with, or who are suspected of, respiratory failure. This worsening of breathing abnormalities during sleep is of major importance for the diagnosis and treatment of all types of respiratory failure. Indeed, the criteria to start long-term oxygen therapy (LTOT) and NIV will be based on overnight parameters such as S_{pO_2} and transcutaneous oxygen and carbon dioxide pressure (P_{tcO_2} and P_{tcCO_2}, respectively).

Oxygen therapy

The aim of LTOT is to prevent or correct the deleterious consequences of chronic hypoxaemia, such as pulmonary hypertension and heart failure. But in children, in the absence of validated markers of end-organ morbidity, the minimal level (and duration) of hypoxaemia that may be safely tolerated is not known. Moreover, it is probable that the consequences of chronic hypoxaemia vary according to age, with younger children being more susceptible, and to the type of underlying disease.

In clinical practice, recommendations for LTOT derive from the normal S_{pO_2} values observed in healthy children. As such, nocturnal S_{pO_2} should not fall below 90% without any desaturation (rapid drops in S_{pO_2} of $\geqslant$3%). Thus, the oxygen flow should be adapted to reach this target, without any excessive correction in order to avoid the potential side-effects of hyperoxia. The harmful consequences of hyperoxia have been well documented in the premature child, with retinopathy being one of the most important side-effects. The deleterious consequences of hyperoxia have not been documented in the older child and in other diseases, but an S_{pO_2} target between 94% and 96% is safe and largely sufficient.

The most common paediatric diseases that may need LTOT are bronchopulmonary dysplasia (BPD), interstitial lung disease and CF. BPD is probably the disease in which the consequences and benefits of LTOT have been studied the most extensively. As such, it has been shown that oxygen therapy decreases central sleep apnoeas and improves sleep quality in infants with BPD. A sleep S_{pO_2} level $>$91–92% is also associated with a better weight gain compared to lower S_{pO_2} levels. In CF, nocturnal desaturation, but not the minimal nocturnal S_{pO_2}, has been shown to be associated with pulmonary hypertension. No information on the deleterious consequences of chronic hypoxaemia is available for children with interstitial lung disease.

The choice of the oxygen source depends on the daily duration of LTOT (sleep only or

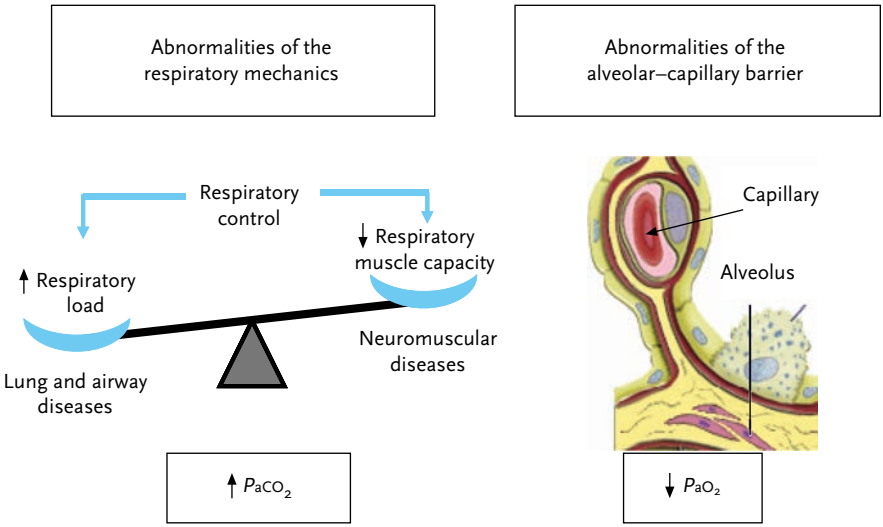

Figure 1. The two different types of respiratory failure: ventilatory imbalance (left) and abnormalities of the alveolar–capillary membrane (right).

also during daily activities), the cost and local facilities. An oxygen concentrator is a cheap and safe source but does not allow ambulation. When LTOT is required during the daytime, and especially during daily activities, gaseous or liquid oxygen is preferred. The efficacy of LTOT should be checked by overnight gas recording to check the SpO_2 but also the carbon dioxide level, in order to detect hypercapnia, especially in patients with lung diseases such as CF, and the possibility of NIV should be discussed.

Noninvasive ventilation

The aim of NIV is to correct alveolar hypoventilation, *i.e.* chronic hypercapnia. Even if the deleterious consequences of chronic hypoxaemia are not well documented in children, our knowledge is even more limited with regard to the consequences of long-term hypercapnia. Besides systemic hypertension, very few side-effects have been objectively reported in children. Again, in clinical practice, the target values are derived from the values observed in healthy children. As such, most authors and experts recommend that the maximal (nocturnal) $PtcCO_2$ should not exceed 50 mmHg.

The most common diseases that may need NIV are neuromuscular disorders, hypercapnic lung diseases, such as advanced CF or COPD, and central hypoventilation if the patient has a minimal respiratory autonomy while awake. The criteria to start NIV are not validated in children but most experts recommend NIV when nocturnal $PtcCO_2$ exceeds 50 mmHg despite optimal medical treatment. The aim of NIV is to maintain the maximal $PtcCO_2$ below 50 mmHg, by providing a sufficient tidal volume and $V'E$.

Numerous ventilators are available for home ventilation but few have been specifically designed for children. However, manufacturers have improved the performances of the most recent devices with some ventilators being as performant as intensive care ventilators. The ventilatory modes have improved significantly over recent years. Initially, two modes were available, a volume-target and a pressure-target mode, with the former being preferentially prescribed for patients with a restrictive lung disease, such as patients with a neuromuscular disease, and the latter being preferentially prescribed for patients

with a lung disease such as CF or COPD. But presently, new "dual control" modes, combining a volume- and a pressure-targeted mode are being increasingly used, even if they have not been validated specifically for the paediatric population. In practice, in the case of chronic alveolar hypoventilation, the main objective is to maintain a sufficient minimal tidal volume to correct chronic hypercapnia. This may be achieved by setting a sufficient tidal volume, inspiratory pressure and inspiratory time, without forgetting a back-up rate for patients at risk for sleep apnoeas or those who are not able to trigger the ventilator, such as patients with neuromuscular disease. As a consequence, the adjustment of the ventilator will thus be based on the combined recording of S_{pO_2} and P_{tcCO_2}.

The NIV interface is as important as the ventilator. Indeed, the patient will not be able to tolerate the NIV if there is discomfort, pain or leaks due to a non-adapted interface. A large number of industrial interfaces are available for long-term NIV in children, even if the range is smaller for children compared to adults. The choice will be guided by the age of the patient, the underlying disease and the ventilatory mode (allowing an interface with or without a manufacturer leak) and, most importantly, the facial physiognomy of the child. The majority of children are ventilated with a nasal mask. A facial mask is reserved for those who have mouth leaks during sleep. Nasal prongs or cannula are relatively new interfaces available for older children that have minimal contact with the patient's face. Of note, because of the cutaneous and facial side-effects, such as facial flattening or maxilla retrusion, which may be observed with all types of interfaces in young children, a systematic and close follow-up by a paediatric maxillofacial team is mandatory.

Continuous positive airway pressure

Obstructive diseases of the upper airways are not rare in children. Apart from nasal obstruction and tonsils and adenoids hypertrophy, children may present with numerous causes of chronic upper airway obstruction. These diseases may be congenital and/or acquired, and may require CPAP in order to prevent airway closure and, thus, the consequent apnoeas and hypopneas. Indeed, by maintaining a normal airway patency during the entire breathing cycle, CPAP may improve alveolar ventilation. CPAP may also prevent the decrease of functional residual capacity by delivering a continuous distending pressure. Common diseases that may cause severe upper airway obstruction are craniofacial malformations, such as Crouzon and Apert disease, Franceschetti syndrome, Pierre Robin syndrome, achondroplasia, and other congenital bone diseases, as well as metabolic disorders such as mucopolysaccharidoses, and Down syndrome. The maintenance of airway patency throughout the entire breathing cycle restores normal ventilation with correction of the OSA. The criteria to start CPAP have not been validated in children. In the absence of reliable markers of end-organ morbidity of OSA, the indication is based on the association of clinical and polysomnographic parameters. Adenotonsillectomy is the treatment of first choice followed, eventually, by an anti-inflammatory treatment in the case of moderate residual OSA. If the OSA persists and is associated with abnormal gas exchange, CPAP should be initiated. If the residual OSA is less severe, without significant abnormalities in gas exchange, a 1-month trial, followed by an objective and subjective sleep evaluation, may be proposed.

Numerous simple CPAP devices are available but most do not have an internal battery and alarms adapted for young children. Numerous new "automatic" CPAP modes are available for adult patients. These new modes are based on the analysis of the flow pattern of the patient with the aim to automatically adapt the level of CPAP to a change in airflow. However, it is not known if these devices are able to detect the changes in airflow in young children and, in a recent clinical study, the use of such a mode was not associated with an increase in CPAP efficacy or compliance.

The CPAP mode requires a vented interface with a manufacturer leak, allowing carbon dioxide clearance through the constant leak. The choice of vented interfaces is much broader than for nonvented interfaces. The side-effects of CPAP interfaces are similar to that of NIV interfaces, justifying the same maxillofacial follow-up.

Tracheotomy

Tracheotomy represents the treatment of last resort for severe airway obstruction that may not be successfully relieved by CPAP, and for persistent nocturnal hypoventilation despite NIV or when NIV is not possible, *e.g.* in patients with advanced neuromuscular disease or in very young infants. In the case of isolated upper airway obstruction, the patient will not need simultaneous ventilatory assistance, whereas in the case of lung or neuromuscular disease, the patient will need ventilatory assistance by means of a tracheostomy.

Tracheotomy is associated with a significant morbidity and discomfort and may impair normal development and, particularly, language development. Discomfort and social life and family disruption are common in patients with a tracheostomy. Indeed, although tracheotomised children may be safely discharged home after careful family education and training, home treatment may be difficult or even unfeasible for some families.

Numerous different tracheostomy tubes are available for children; the size and format should be adapted individually. The aims of a tracheotomy are the same as for the other ventilatory assistance equipment; nocturnal and diurnal gas exchange together with normalised sleep quality.

The necessity to maintain the tracheostomy should be evaluated on a regular basis, in order to decannulate or switch the patient to NIV or CPAP whenever possible.

In conclusion, oxygen therapy, NIV, CPAP and tracheotomy are complementary treatments for children with chronic respiratory failure. The main objective is to restore a normal nocturnal and daytime gas exchange and a normal sleep quality, by means of the least invasive treatment, in order to preserve the best quality of life for the child and their family.

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Primary ciliary dyskinesia

Deborah Snijders, Serena Calgaro, Massimo Pifferi, Giovanni Rossi and Angelo Barbato

Primary ciliary dyskinesia (PCD) is predominantly inherited as an autosomal recessive disorder leading to recurrent and chronic upper and lower respiratory tract infection and, in 40–50% of cases, mirror image organ arrangement and other forms of heterotaxy. Ciliary dysfunction is also implicated in a wider spectrum of diseases, such as polycystic liver and kidney disease, biliary atresia, and central nervous system abnormalities including retinopathy and hydrocephalus.

The prevalence of PCD is very difficult to estimate accurately. In a European survey from a European Respiratory Society Task Force on PCD in children, a prevalence of diagnosed cases in 5–14-year-olds was found to be between one in 10 000 and one in 20 000.

In clinical samples of patients with diffuse bronchiectasis, PCD is naturally more common. It might account for up to 13% of all patients with bronchiectasis, being relatively more common in North African patients than European patients. The average age at diagnosis, in a paediatric case series by Coren *et al.* (2002), was 4.4 years (6 years for those without *situs inversus*). More recent data showed a median age at diagnosis of 5.3 years, lower in those with situs inversus (3.5 *versus* 5.8 years).

Key points

- The gold standard for the diagnosis of PCD is a combination of ciliary beat pattern and frequency analysis and electron microscopy in patients with upper or lower airway disease.
- Specific ultrastructural defects responsible for PCD result in specific abnormalities in beat frequency and pattern; however, a small number of milder phenotypes may appear with subtle or no apparent structural defects or ciliary dysfunction.
- When diagnosis by ultrastructural analysis or beating patterns analysis is not conclusive, but the suspicion of PCD is high, further testing should be performed in order to find the right diagnosis, such as nasal nitric oxide, immunofluorescent microscopy and genetic analysis.

Cilia structure

Normal cilia structure The epithelial lining of the large airways and contiguous structures, including the paranasal sinuses, middle ears and Eustachian tubes, consists of ciliated pseudostratified columnar epithelium. Ciliated cells are also found in the ependymal lining of the brain and fallopian tubes. In addition, the spermatozoal flagella (tail of spermatozoa) has a core structure that is identical to cilia.

Each matured ciliated cell has up to 200 cilia. Each cilium has an array of longitudinal microtubules arranged as nine doublets formed in an outer circle around a central pair. The main structural protein of these doublets is tubulin. The microtubules are anchored by a basal body in the apical cytoplasm of the cell. Radial spokes connect the outer microtubular doublets with a

central sheath of proteins around the central tubules.

Cross-section of the cilia (fig. 1) reveals inner and outer dynein arms (IDA and ODA, respectively), which are attached to a subunit A of each microtubule doublet. The microtubules are interconnected by nexin links, radial spokes and dynein arms. Cilia beating originates from the sliding of microtubule doublets, which is generated by the ATPase activity of the dynein arms.

The dynein arms are periodically distributed along the axoneme; ODAs with a 24-nm periodicity and IDAs with a 96-nm periodicity. The dynein arms are multiprotein complexes that project from the microtubule A of every outer doublet. The outer arms face towards the boundary of the axoneme and the inner arms face the central sheath.

Ciliary movement involves two phases:

- an effective stroke phase that sweeps forward,
- a recovery phase during which the cilia bend backward and extend into the starting position for the stroke phase.

The mucous lining present on the respiratory epithelium has an inner serous layer called the sol phase, in which the cilia recover from their active beat, and an outer, more viscous layer, the gel phase. The tips of the cilia are in contact with the gel layer during the stroke phase in order to propel the secretions forward. During the recovery phase the cilia lose contact with the mucus layer, reinforcing the forward thrust of the mucus.

Normal ciliary beat frequency is 1000–1500 beats·min^{-1}. The frequency is slower in the peripheral airways (*e.g.* bronchioles) compared to the larger airways (*e.g.* trachea). The ciliary motility is maintained in the same plane along the length of the airways and results in mucociliary transport rates up to 20–30 mm·min^{-1}.

Whenever there is an alteration in ciliary structure or function, there will be an alteration in mucociliary clearance, with stasis of the respiratory tract secretions, which will be responsible for the clinical manifestations of the disease.

Genetics of PCD

Inheritance PCD (MIM#242650) is a genetically heterogeneous disorder, which is predominantly inherited as an autosomal recessive trait. To date, the majority of the genes identified for autosomal recessive PCD variants (*DNAI1*, *DNAI2*, *DNAH5*, *DNAH11* and *TXNDC3*) encode ODA components while *KTU* and *LRRC50* are required for cytoplasmic pre-assembly of axonemal dyneins (table 1). In addition, mutations in the two genes *RSPH9* and *RSPH4A* have been reported in PCD patients with abnormalities of the central microtubular pair. Molecular defects affecting dynein regulatory complexes (DRC) and IDAs are characterised by the absence of GAS11 (a DRC component) and the IDA component DNALI1 from the ciliary axoneme (*CCDC38* and *CCDC40*). In a minority of cases, other inheritance patterns have been recognised.

Genetic analyses may help to assess the carrier status of family members and provide tools for informed reproductive choices, although this is only currently possible for a minority of families. They may also become more important diagnostically as ~35% of PCD patients carry either *DNAH5* or *DNAI1* mutations (hot spots and founder mutations are worthy of analysis in patients with ODA).

Clinical aspects of PCD

Children with PCD often have a clinical history of lower airway disease, manifested by a chronic "wet" sounding cough and occasionally wheeze or shortness of breath.

Moreover, >75% of full-term neonates with PCD have neonatal respiratory distress requiring supplemental oxygen for days to weeks.

Complications of chronic lower airway infections, such as bronchiectasis, can be a sign of detoriation of lung function and are more frequent in adults.

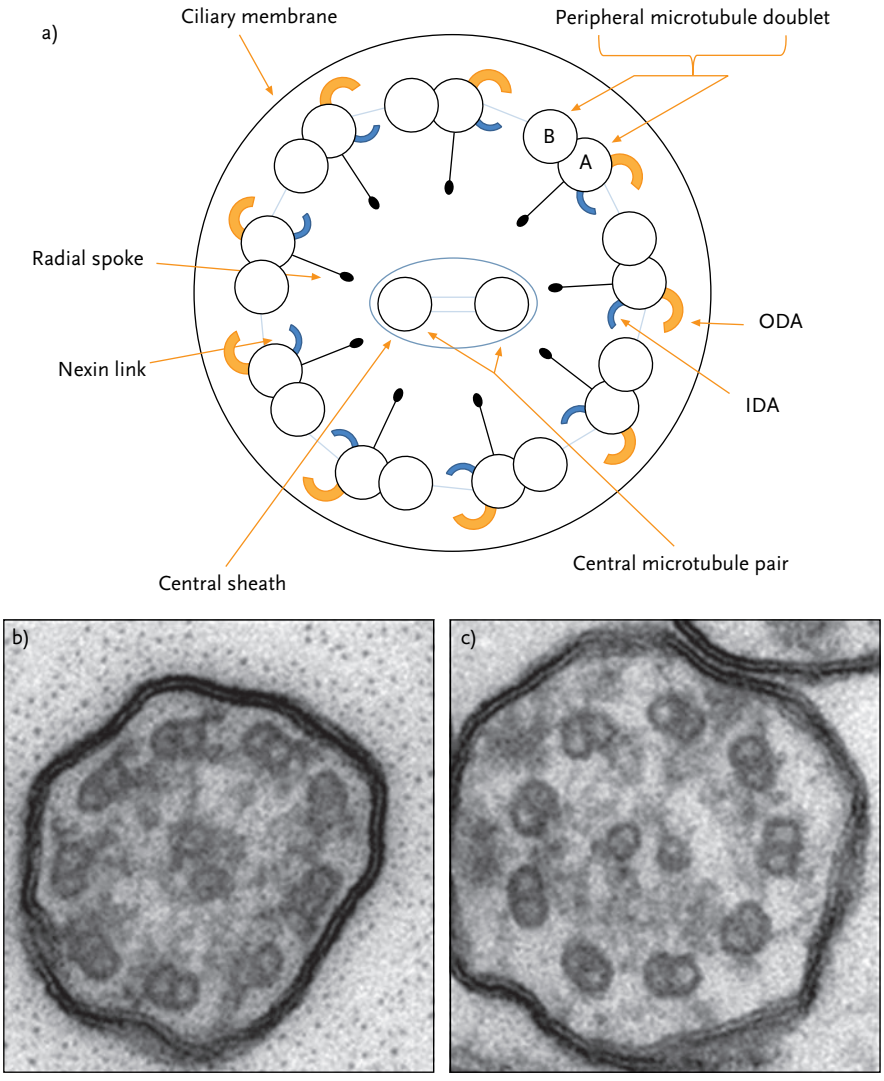

Figure 1. Cross section of the cilia. a) Schematic diagram of a cilium revealing 9+2 arrangement of nine peripheral microtubule doublets surrounding a central microtubule pair. b, c) Transmission electron microscopy of normal cilia (b) and absent IDA and ODA (c). Reproduced from Becker-Heck (2012).

In addition, virtually all subjects have evidence of chronic upper airway symptoms such as chronic rhinitis (nasal discharge, episodic facial pain and anosmia). This may be confirmed by either physical examination and/or sinus imaging. Continuous rhinorrhoea can be present from the first day of life.

Ear symptoms (recurrent otitis media and glue ear) are a frequent complication that can require multiple interventions, including repeated courses of antibiotics.

PCD should be suspected in cases of *situs inversus totalis* or heterotaxy; ~25% of

Table 1. Description of the genes involved in PCD

Gene	Locus	Defective structure	Exons	Hot spot	Founder mutations	Phenotype
DNAH5	5p15	ODA	79+1	Exons 34, 50, 63, 76 and 77	c.10815delT	PCD+KS
DNAI1	9p21-p13	ODA	20	Exons 13, 16 and 17	IVS1 + 3insT	PCD+KS
DNAH11	7p15.3-21	Normal	82	Not known	Not known	PCD+KS
TXNDC3	7p14.1	ODA	18	Not known	Not known	KS
DNAI2	17q25.1	ODA	14	Not known	Not known	PCD+KS
KTU	14q21.3	ODA+IDA	3	Not known	Not known	PCD+KS
LRRC50	16q24.1	ODA+IDA	12	Not known	Not known	PCD+KS
RPGR	Xp21.1	Variable	~25	Not known	Not known	PCD with RP
OFD1	Xp22	Not known	23	Not known	Not known	PCD with MR
RSPH9	6p21	Central pair	5	Exon 5	c.801_803delGAA	PCD
RSPH4A	6q22	Central pair	6	Not known	Not known	PCD
CCDC39	3q26.33	IDA, central pair	20	Not known	Not known	PCD+KS
CCDC40	17q25.3	IDA, central pair	20	Not known	Not known	PCD+KS

KS: Kartagener syndrome; RP: retinitis pigmentosa; MR: mental retardation.

individuals with *situs inversus* totalis have PCD. Prevalence of PCD within the heterotaxy subclass is unknown. In PCD patients, 40–50% present with *situs inversus totalis* (Kartagener's syndrome) and 6% have heterotaxy (*situs ambiguus*).

Adult males with PCD may be infertile due to impaired sperm motility because the flagella of the sperm and cilia often, but not always, have the same ultrastructural and functional defects. Some females with PCD have normal fertility, but others have impaired fertility and an increased risk for ectopic pregnancy because of impaired ciliary function in the oviduct.

The clinical aspects of PCD are shown according to the different age groups in table 2. A positive family history of PCD is an indication to undergo diagnostics, as this accounted for 10% of cases in one series. Also siblings of probands should have PCD excluded.

Diagnosis of PCD is frequently delayed, in part, because it presents with symptoms (rhinitis, secretory otitis media, cough and recurrent bronchitis) that are common in healthy children.

PCD as an associated diagnosis Beside the classical signs and symptoms, we recommend that PCD should be at least considered when the following diagnoses are made, in particular if there is a family history of more than one of these conditions, or if the patient has other features of PCD.

- Complex congenital heart disease, especially with disorders of laterality, such as atrial isomerism, transposition of the great vessels, double outlet right ventricle, anomalous venous return, interrupted inferior vena cava and bilateral superior vena cava.
- Asplenia (predominant bilateral right-sidedness (right isomerism)), or polysplenia (predominant bilateral left-sidedness (left isomerism)). This is present in at least 6% of individuals with PCD.
- Polycystic kidney or liver disease.

Table 2. Clinical presentation of symptoms

Antenatal period	*Situs inversus totalis* or heterotaxy on antenatal ultrasound scanning
	Mild fetal cerebral ventriculomegaly
Newborn period	Neonatal respiratory distress in full-term neonates
	Continuous rhinorrhoea from the first day of life
	Mirror image organ arrangement and other forms of heterotaxy
	Hydrocephalus may occur in some individuals with PCD and may reflect dysfunctional ependymal cilia
Childhood	Chronic productive or wet sounding cough, associated or not with recurrent atelectasis or pneumonia
	Atypical asthma
	Idiopathic bronchiectasis
	Daily rhinitis, without remission
	Severe chronic sinusitis in older children
	Otitis media with effusion/hearing loss
Adolescence and adulthood	Same as for childhood
	Bronchiectasis, more evident in adulthood
	Chronic mucopurulent sputum production
	Digital clubbing
	Pulmonary function tests with progressive obstructive or mixed pattern
	Nasal polyposis and halitosis
	Infertility

- Hydrocephalus.
- Biliary atresia.
- Severe oesophageal disease (oesophageal atresia or severe reflux).
- Retinal degeneration, including *retinitis pigmentosa*.
- Oral-facial-digital syndrome type 1.

Diagnostic testing

The diagnosis of PCD should be based on the presence of a typical clinical phenotype and appropriate diagnostic testing. PCD is a rare disease and diagnostic analysis and interpretation is difficult. There is no one gold standard test, a combination of ciliary function and ultrastructural analysis is recommended. Screening tests may precede ciliary analysis, such as nasal nitric oxide measurement, saccharin test and radioaerosol mucociliary clearance tests

Samples of ciliated cells can be obtained by nasal brushing or bronchoscopic samples. With the only notion that patients should be free from an acute upper respiratory tract infection for 4–6 weeks to help minimise poorly ciliated samples or secondary dyskinesia, avoiding complication of the analysis.

Ciliary beat pattern and frequency analysis

Analysis of ciliary beat pattern using a slow motion replay videotape recorder and a digital high speed video camera is recommended as part of the diagnostic testing for PCD. Ciliated samples at 37°C are observed using a ×100 objective. A digital high speed video camera mounted on a conventional microscope allows over 500 frames per second to be recorded. These are played back in slow motion allowing ciliary beat pattern to be assessed. A permanent

recording can be made for audit purposes and beat frequency can also be measured by directly observing the beating cilia in slow motion. In PCD, all of the cilia are seen to be dyskinetic on slow motion replay. Analysis also allows measurement of ciliary beat frequency. Specific beat patterns have been shown to be related to particular ultrastructural defects. This analysis is particularly useful in identifying patients who have ciliary dyskinesia due to an ultrastructural defect where beat frequency is normal: for example, in those with a central microtubular defect such as ciliary transposition or central microtubular agenesis. A major advantage is that videos may be stored as a permanent record, allowing reassessment if the clinical picture changes.

Until recently, prior to advances in high-speed video analysis, ciliary beat frequency without assessment of beat pattern was common. When the beat frequency is low, suspicion of PCD is high. It had been recommended that if the ciliary beat frequency was above a certain threshold further tests, such as electron microscopy, were not indicated. However, in the experience of some ciliary diagnostic centres, using ciliary beat frequency readings to reject the diagnosis of PCD will result in 10–15% of patients with the disease being missed, since these have beat pattern abnormalities despite normal beat frequency.

Electron microscopy is important in the diagnosis of PCD, and is always performed when there is any suspicion of the diagnosis. However, specialist knowledge is required to interpret the various ultrastructural defects responsible for PCD and it is acknowledged that ultrastructural analysis has limitations. In particular, IDA defects are difficult to determine because they are less electron dense and less frequent along the ciliary axoneme. In addition, it has been shown that the dynein motor protein composition varies along the ciliary length meaning that ultrastructural defects depending on the site of the ciliary cross-section can be missed by electron microscopy. Obtaining samples that do not have significant secondary damage can be difficult. This may lead to erroneous reports of new cases of PCD. Various methods to improve analysis of images from electron microscopy have been suggested. Some patients with PCD may not have an obvious ultrastructural defect; however, normal ciliary ultrastructure should always prompt a full diagnostic review.

Other techniques to assist diagnosis are ciliated cell culture to improve diagnostic certainty of PCD and to confirm less common phenotypes, such as ciliary disorientation, ciliary aplasia, central microtubular agenesis and IDA defects.

In addition, the analysis of dynein protein localisation by immunofluorescent microscopy may help in the clinical diagnosis of PCD. Not only can it diagnose ODA but it can also diagnose IDA abnormalities in the various genetic mutations. In addition, the immunofluorescent microscopy method is not altered by secondary ciliary abnormalities.

Genetic analysis for some cases of PCD is possible, but it is not recommend as part of initial diagnostic testing. After a clinical diagnosis has been ascertained genetic testing may be directed according to the specific PCD variant (*i.e. DNAH5* and *DNAI1* testing in PCD patients with ODA defects or *DNAH11* testing in a special functional defect).

Respiratory treatment

As with all chronic respiratory diseases, the aim of therapy for PCD is to prevent bronchiectasis and to restore or maintain normal lung function for as long as possible, based on early detection and vigorous treatment of complications. There are no randomised trials of PCD treatment and consequently all treatment recommendations are based on very low level evidence, or extrapolated from CF guidelines.

Management of PCD involves aggressive treatment of upper and lower airways

infections and airway clearance by combinations of physiotherapy and physical exercise.

Antibiotics Airway infection with *Haemophilus influenzae*, *Staphylococcus aureus* and *Streptococcus pneumoniae* frequently occur, but *Pseudomonas aeruginosa* and non-tuberculous mycobacteria have also been reported, usually in adults. The use of antibiotic prophylaxis should be considered when repeated courses of antibiotics are necessary. At the first sign of worsening respiratory symptoms or deterioration in lung function, high-dose oral antibiotics should be administered, even better if the evidence is based on sputum or cough swab culture.

If *P. aeruginosa* is isolated, an eradication regime similar to CF should be used, although evidence of efficacy has yet to be obtained in PCD patients.

Other inhaled medications Regular bronchodilators do not seem to be very effective. The role of nebulised recombinant human DNase (Pulmozyme; Genentech Inc., San Francisco, CA, USA) in PCD patients remains unproven. However, anecdotally some patients show an improvement in respiratory symptoms. As for the use of nebulised normal or hypertonic saline, it may theoretically be effective in increasing mucus clearance. *N*-acetylcysteine has been shown not to be useful.

Anti-inflammatory strategies There are no data on which to recommend or avoid inhaled corticosteroids; although the neutrophillic profile of sputum is similar to CF. Corticosteroids are probably best avoided unless they can be shown to be of definite benefit in an individual patient.

Airway clearance techniques Airway clearance is widely used in PCD patients. Since cough clearance is intact, techniques promoting cough seem helpful. Physiotherapy varies with age, the changing clinical state and local expertise and resources.

The effect of physical exercise on airway clearance in PCD may help sputum clearance. Exercise has been shown to be a better bronchodilator than the use of a β_2-agonist in PCD. Exercise is encouraged at all ages to promote general health and wellbeing.

Surgical procedures Complications of bronchiectasis and chronic lung disease become more prominent with age. The role of lobectomy in advanced bronchiectasis is similar to that in other aetiologies, and can rarely be recommended. Although stabilisation or improvement of lung disease is expected with institution of modern treatment, there are reports of PCD patients going on to lung transplantation, both living related and cadaveric. This underlines that PCD is a serious condition, from which adults die, and that paediatricians are mandated to treat children aggressively to retard later lung deterioration.

Environmental exposures Preventive counselling should include:

- the avoidance of active and passive smoking;
- minimisation of exposure to respiratory pathogens;
- minimisation of exposure to indoor and environmental pollutants.

Cough suppressant medications must be avoided.

Immunisations PCD patients should receive all childhood immunisations, as well as pneumococcal and influenza immunisation.

Outpatient follow-up

PCD patients should be managed in specialised centres, in which they have regular access to respiratory paediatricians, audiology, ENT specialists and respiratory physiotherapists. Some patients need access to clinical psychology and social work services.

In addition to general paediatric care, each patient should have regular visits to a tertiary centre to check growth, lung function (including pulse oximetry) and hearing function. Regular sputum or cough swab cultures should be performed. Chest radiographs are probably relatively insensitive. HRCT of the lungs is used to define the extent of bronchiectasis, and can

be repeated to monitor the progression of the disease when necessary.

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Gastro-oesophageal reflux-associated lung disease and aspiration syndrome

Osvaldo Borrelli, Efstratios Saliakellis, Fernanda Cristofori and Keith J. Lindley

Chronic pulmonary aspiration (CPA) syndrome is defined as the entry of food materials, gastric contents and/or saliva into the subglottic airways in a manner sufficient to induce chronic or recurrent respiratory symptoms (Boesch *et al.*, 2006). These symptoms include:

- cough,
- asthma and wheezing,
- recurrent pneumonia,
- choking, failure to thrive,
- apnoea of prematurity,
- acute life-threatening events,
- bronchiectasis/pulmonary fibrosis, and
- delayed resolution of chronic neonatal lung disease.

CPA constitutes one of the most serious threats to the normal development of the respiratory tract and, although more common in pre-term infants, it remains a major health risk throughout infancy and childhood.

Key points

- CPA constitutes one of the most serious challenges to the normal development of the respiratory tract, and it represents a major health risk throughout infancy and childhood.
- Several studies have reported an association between GOR and CPA.
- Both acid and nonacid reflux are implicated in the pathophysiology of parenchymal lung disease.
- The diagnosis of GOR-related aspiration remains challenging because of the absence of sensitive and specific tests.

Different physiological mechanisms have been suggested to be involved in the pathogenesis of CPA, including swallowing dysfunction, salivary aspiration and gastro-oesophageal reflux (GOR). Swallowing dysfunction during feeding commonly occurs in neurologically impaired children as the different phases of the swallowing process require complex coordination between voluntary and involuntary actions, although it should be also considered in neurologically normal infants with recurrent pneumonia, wheezing, chronic cough and stridor. Chronic aspiration of saliva is the least commonly recognised form of aspiration and is usually diagnosed after the development of significant lung injury. It generally occurs in children with neurological impairment as a consequence of their swallowing dysfunction and abnormal laryngeal sensation rather than abnormal production of saliva. Finally, GOR has been implicated in the pathogenesis of CPA, although their relationship is still matter of debate.

GOR is a physiological phenomenon occurring in healthy infants and children several times daily. In contrast, gastro-oesophageal reflux disease (GORD) is defined as a condition in which the reflux of gastric contents causes troublesome symptoms and/or complication, and represents one of the most common causes of foregut symptoms in children (Sherman *et al.*, 2009). Although several studies in children have emphasised the role of GOR in the pathogenesis of upper and lower

airway respiratory disorders, the likelihood of interactions between GOR and the respiratory system remains an area of controversy in paediatric GORD (Tolia *et al.*, 2009). It is now generally agreed that certain underlying disorders predispose children to higher risk of severe GORD, and thus to higher risk of GOR-induced respiratory manifestations. These include neurological disorders, such as cerebral palsy, metabolic or genetic diseases (*e.g.* Pierre Robin syndrome), congenital abnormalities, (*e.g.* oesophageal atresia with tracheo-oesophageal fistula), chronic lung disease (*e.g.* CF), and anatomical abnormalities characterised by a direct connection between the oesophagus and airway. For instance, while type III tracheo-oesophageal fistulas are often apparent at birth, H-type fistulas may be more difficult to detect.

The relationship between GORD and CPA has been the subject of a number of epidemiological and clinical studies. In children with severe neurodisability, severe lower respiratory infections are associated with severe GOR only with coexistence of swallowing dysfunction (Morton *et al.*, 1999). GOR seems to be involved in the pathogenesis of recurrent pneumonia in ~6% of cases (Owayed *et al.*, 2000). However, the prevalence of pneumonia and bronchiectasis among children with GORD without neurological disability or congenital oesophageal anomalies is also increased between three and six times over that among controls (El-Serag *et al.*, 2001; Piccione *et al.*, 2012). Finally, several studies have reported an association between GORD and CF. The prevalence of GORD in children with CF ranges between 25% and 100%, which is six to eight times the rate of GORD in the non-CF population. One-fifth of newly diagnosed infants and 25–55% of CF children older than 1 year show pathological reflux when investigated (Mousa *et al.*, 2012). GOR may contribute to poor CF control at the end stage of disease, and may cause bronchiolitis obliterans syndrome (BOS) after lung transplantation (D'Ovidio *et al.*, 2006).

Although a significant body of literature in children has emphasised the role of GOR in the pathogenesis of lower airway respiratory disorders, it should be stressed that the range of methodologies used hampers the interpretation of the results. Examples include the lack of standardised definitions for respiratory symptoms and/or diseases, and the lack of temporal relationships between the onset of respiratory symptoms and/or signs and GORD symptoms and/or signs. Moreover, it is difficult to evaluate whether GORD children are at increased risk of respiratory disorders in studies that do not assess the prevalence of same disorders in a representative control group. Similarly, the estimation of the prevalence of GORD in children with respiratory disorders using investigational tools cannot be extrapolated to the general population, as the children are investigated by a paediatric gastroenterologist after the failure of conventional therapy. Finally, although it is now generally agreed that the presence of abnormal GOR extending into the proximal oesophagus and cricopharyngeal region is a risk factor for aspiration, its finding does not inevitably imply aspiration.

Pathophysiology of GOR-induced CPA

Proximal reflux episodes followed by direct irritation of the airway epithelium are the pathophysiological mechanism of GOR-related CPA. Through elaborate reflex mechanisms, a close functional relationship exists between the oesophagus and the airway, which ensures the safety of the airway against aspiration of material during an episode of GOR. For instance, microaspiration of gastric contents into the lung can be prevented by protective mechanisms such as oesophageal clearance and reflex closure of the upper oesophageal sphincter and/or vocal cords. However, even if aspiration occurs, gastric aspirate may be rapidly cleared from the lung. In experimental animals, acute instillation of gastric contents into the main bronchi leads to a wide array of histopathological changes both in areas directly in contact with acid as well as in distant areas, including alveolar haemorrhage and pulmonary oedema

(Sherrington, 2006). These changes seem not to be related to direct tissue damage induced by acid, but to the inflammatory cascade triggered by release of preformed cytokines from damaged cells, such as leukotriene B_4 and thromboxane A_2. These in turn stimulate the synthesis of other cytokines, including interleukin (IL)-1, tumour necrosis factor (TNF)-α and IL-8, followed by neutrophil recruitment. Repetitive chronic aspiration induces loss of parenchymal architecture, collagen deposition with fibrosis, bronchiectasis and obliterative bronchiolitis.

Several experimental and clinical data have suggested the role of acid microaspiration in the pathophysiology of bronchial inflammation and bronchoconstriction. However, recent studies also emphasise the role of nonacid reflux in the pathophysiology of some parenchymal lung diseases in both adult and children. Bile acids and pepsin from patients on antisecretory therapy stimulate the production of transforming growth factor (TGF)-β *via* a p38 mitogen-activated protein (MAP) kinase-dependent pathway, connective tissue growth factor and IL-8 secreted by bronchial epithelial cells, suggesting their ability to provoke a significant bronchial reaction (Mertens *et al.*, 2010). Moreover, it has been recently shown that nonphysiological levels of pepsin and acid are able to induce inflammation and death of airway epithelial cells with an effect inversely related to the acid concentration.

Diagnosis

Before considering GOR as cause of CPA, the clinician needs to rule out the presence of swallowing dysfunction and, consequently, a direct aspiration of fluid/food with swallowing. The following steps are to determine whether pathological GOR is occurring, with gastric contents entering the lungs, and to assess the likelihood of an association between GOR and respiratory symptoms and/or signs. Unfortunately, at the present time, there is no sensitive, specific test for GOR-related aspiration, and the diagnosis is made combining clinical, laboratory and radiological tests.

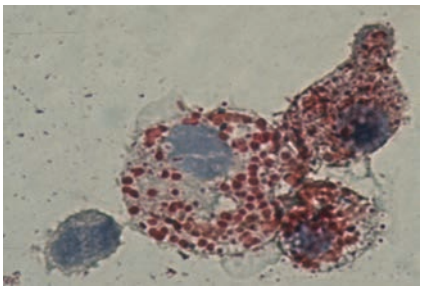

Figure 1. Fluid from BAL stained with Oil Red O. The lipid is seen within the cytoplasm of alveolar macrophages. Image courtesy of F. Midulla (Paediatric Emergency Department, Policlinico Umberto I, Sapenzia University of Rome, Rome, Italy; personal communication).

Biomarkers Ideally, a biomarker for aspiration should be a noninvasive measure of a quantifiable marker within the lung, specific for reflux aspiration and reliably detectable over a sustained period after aspiration.

Lipid-laden macrophages (LLMs) in the bronchoalveolar lavage (BAL) have been reported as useful markers of GOR-related pulmonary aspiration. The amount of lipid per single macrophage is determined after Oil Red O staining of BAL using a semiquantitative method, which assigns to each cell a score ranging from 0 to 4 according to the amount of lipid in the cytoplasm (fig. 1). The number of cells graded 0, 1, 2, 3 and 4 is calculated for each patient, and the final LLM index (LLMI) is determined by evaluating 100 cells, with the highest possible score being 400 (Corwin *et al.*, 1985). A LLMI of 165 is considered to be consistent with aspiration (Furuya *et al.*, 2007). A rapid increase in LLMs occurs after intratracheal milk instillation, lasting for ⩾2 days after a single instillation and longer with recurrent instillation. LLMI seems to correlate with total number of nonacid reflux episodes and the number of nonacid reflux episodes reaching the proximal oesophagus (Borrelli *et al.*, 2010). However, these findings are highly debated. The role of LLMI as a standard test for aspiration is widely disputed, as studies have shown significant

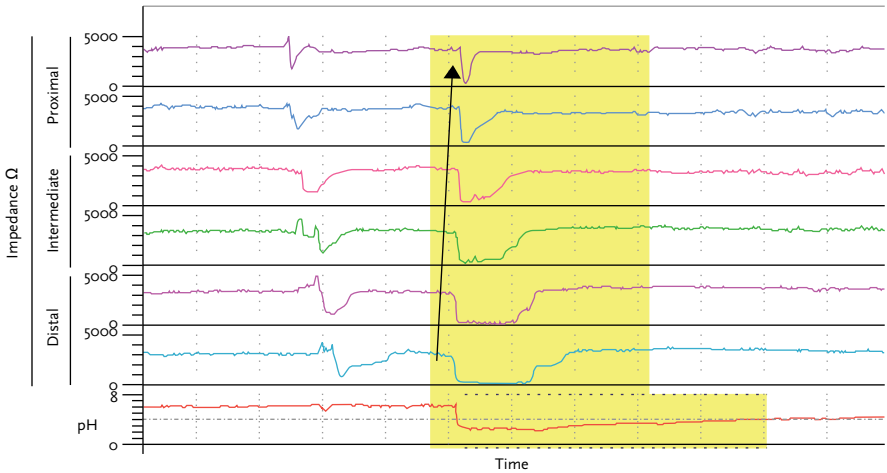

Figure 2. Example of acid reflux episodes reaching the proximal oesophagus. Impedance measurements from the proximal, intermediate and distal oesophagus, and pH are shown. The episode is categorised as acid because of the presence of a pH drop to <4 during the impedance-detected episode (arrow and shaded area).

variation in its sensitivity (57–100%) and specificity (57–89%) (Colombo *et al.*, 2012). An increase in LLMs has been described in pulmonary conditions other than aspiration, such as CF, infections, use of intravenous lipid infusion and pulmonary fat embolism in sickle cell disease, suggesting that any pulmonary insult severe enough to cause tissue destruction may result in an increase in LLMs by releasing lipids from cell membranes (Knauer-Fischer *et al.*, 1999). However, despite these significant limitations, an elevated LLMI may provide supporting evidence of aspiration in a selected group of children.

Pepsin is a proteolytic enzyme of gastric origin and should not be detectable in the lower respiratory tract. Therefore, its detection in the BAL fluid should be a highly sensitive and specific marker for GOR-related aspiration. The presence of pepsin in the BAL is detected in a high percentage of children with GORD and chronic respiratory symptoms (83%) and its level correlates with proximal acid GOR (Starosta *et al.*, 2007). Pepsin has been used as a marker of aspiration in both preterm infants and children ventilated in the intensive care setting. Finally, increased BAL pepsin has been found in adults and children with CF, before and after lung transplantation (Blondeau *et al.*, 2008). Though a promising investigative measure, the detection of pepsin in BAL fluid as a marker of gastric aspiration has a number of concerns. Firstly, early cross-sectional studies only provide a snapshot in time of its presence, and there are no data on how pepsin concentrations change over time following aspiration or with frequency of aspiration events. Secondly, alterations in content and concentrations may be dependent on BAL technique. However, based on current data, the specificity of the pepsin makes this biomarker highly appealing.

Radiology An upper gastrointestinal contrast study is not a reliable test for discriminating between physiological and pathological GOR. However, it is useful to confirm or rule out anatomical abnormalities of the upper gastrointestinal tract that may predispose to GOR-related aspiration. Scintigraphy has been widely used for the evaluation of GOR in children. However, its low sensitivity and specificity compared with 24-h oesophageal pH monitoring makes this test unsuitable for the routine diagnosis and management of GOR in infants and children. Evidence of pulmonary aspiration during the test is usually assessed through images obtained

up to 24 h after administration of the radionuclide. However, a negative test does not exclude the possibility of infrequent aspiration. Furthermore, even in the presence of aspiration, the technique is not able to discriminate between aspiration due to swallowing dysfunction and GOR-related aspiration.

Oesophageal studies Although oesophageal pH monitoring has been regarded for many years as the most sensitive and specific diagnostic tool for diagnosing GORD, its sensitivity and specificity are not well established. In fact, pH monitoring has significant limitations because of its inability to detect nonacidic retrograde bolus movement in the oesophagus, and in particular in infants who are frequently fed milk and/or milk-based formulas. Multichannel intraluminal impedance (MII) monitoring is a new clinically available tool able to detect anterograde or retrograde bolus movement into the oesophagus in a pH-independent fashion. MII and pH (MII-pH) monitoring combined can characterise the reflux episodes as acid or nonacid (figs 2 and 3) and determine the composition (liquid, gas or mixed) and height reached by the refluxate. However, there are some limitations of MII-pH monitoring. First, there is a degree of subjectivity in the interpretation of the results, but improvements in automated software analysis will help to overcome this pitfall. Secondly, a positive test in a child with symptoms and signs of aspiration does not inevitably imply a cause–effect relationship, and negative test does not exclude the possibility of GOR-related aspiration. Finally, the results of MII-pH monitoring are still difficult to interpret given the absence of normal paediatric reference values.

Treatment

Medical and conservative therapies are the initial choice for children with GORD and features of aspiration, including thickened feeds, prokinetics and acid secretion inhibitors. Proton pump inhibitors (PPIs) have been widely used to decrease acid reflux and the perceived risks of PPIs are low. Although the efficacy of PPIs has been shown for the treatment of patients with oesophageal symptoms and signs, no data are available for GORD-related respiratory symptoms. This is especially true in children with chronic pulmonary aspiration due to GORD who do not seem to benefit from medical therapy in terms of improving lower respiratory tract injury. Moreover, it is important to point out that although PPIs

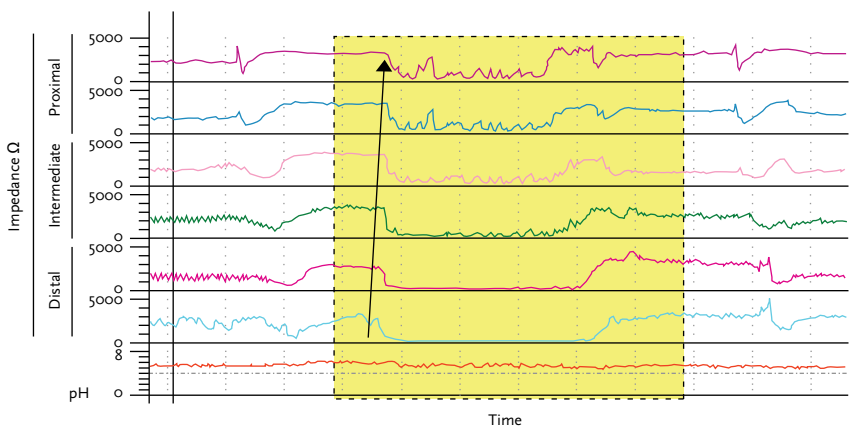

Figure 3. Example of nonacid reflux episode reaching the proximal oesophagus. Impedance measurements from the proximal, intermediate and distal oesophagus, and pH are shown. The episode is categorised as nonacid on the absence of a pH drop to <4 during the impedance-detected episode (arrow and shaded area).

change the gastric pH, they do not prevent episodes of reflux-related microaspiration.

Naso- or gastrojejunal feeding provides an approach to prevent reflux-related pneumonia, especially in children with severe neurological impairment; sometimes, it needs to be combined with fundoplication.

Fundoplication has become the surgical antireflux procedure of choice in children with severe and persistent respiratory symptoms due to GOR refractory to the medical treatment. It represents one of the three most commonly performed major operations in childhood. Resolution or improvement of respiratory symptoms after fundoplication occurs in 48–92% of patients. It has been demonstrated that fundoplication could reverse bronchiolitis obliterans syndrome in some lung transplant recipients with pathological reflux. Unfortunately, in children with neurological impairment, who represent the group with greatest incidence of GOR-related aspiration, symptom relapse has been reported in up to 60% of them following the first antireflux surgery and a high failure rate even after redo Nissen (Pacilli *et al.*, 2007). For this reason, the selection of patients to undergo Nissen fundoplication needs to be accurate and alternative surgical strategies, such as jejunostomy feeding, need to be considered. The insertion of a gastrojejunostomy has the advantage of allowing gastric venting as well as establishing jejunal feeding. However, the tendency for accidental displacement renders this option impractical for long-term use, and surgical jejunostomy represents a more permanent solution. Although with either type of jejunal feeding, aspiration of gastric juice may still occur, they show a similar rate of aspiration pneumonia and mortality compared with fundoplication (Srivastava *et al.*, 2009). Finally, in children with severe, irreversible neurological impairment and intractable aspiration despite medical and surgical treatments previously described, a more aggressive surgical approach, such as oesophagogastric disconnection with oesophagojejunal anastomosis, may be required.

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Foreign body aspiration

Iolo Doull

Foreign body aspiration (FBA) is a serious and potentially fatal condition in infants and children. Choking may occur due to an obstruction in the oral cavity, and insertion injuries may occur when foreign objects are present in either the nose or nasopharynx. Ingestion injuries occur due to foreign bodies in the oesophagus or stomach. Depending on the age of the child and the size of the foreign body, airway obstruction and aspiration can occur anywhere in the respiratory tract. Large airway obstruction preventing adequate ventilation can be fatal, while more distal obstruction can lead to emphysema, atelectasis and subsequent chronic changes including bronchiectasis.

Aetiology and predisposing factors

Children <3 years of age are at greatest risk. Infants have smaller airways than adults. Flow through an airway is inversely proportional to the radius to the fourth power, thus small changes in airway radius lead to proportionately greater changes in airflow, so even small foreign bodies can be dangerous. Compared to adults the larynx is in a relatively high position in infants with the epiglottis close to the root of the tongue, increasing the risk of aspiration. Infants have gag, cough and glottic closure reflexes to protect against aspiration, but they may not always be fully developed from birth, and swallowing, in particular, may be delayed. Children with developmental delay are at increased risk of aspiration.

Key points

- Children <3 years of age are at greatest risk of FBA.
- FBA must be suspected for any witnessed choking episodes.
- FBA cannot be excluded on either normal physical examination or chest radiograph.
- Removal of the foreign body is the primary objective and mainstay of treatment.

Incisors are necessary to bite through food, and molars are necessary to masticate the food in preparation for swallowing. However, incisors erupt approximately 6 months before molars and so food may not be appropriately pulped, remaining as a small smooth or rounded mass, the ideal shape to obstruct an airway if aspirated. Infants and children are less able to cough out foreign bodies aspirated into the airway; peak cough flows at 4 years of age are approximately a quarter of that of adults. Once lodged in an airway, mucus and local inflammation will quickly result in complete airway obstruction, thus diminishing the possibility of forced clearance. Finally infants are easily distracted and often inattentive, are more likely to talk and run around while chewing, and more likely to put a small non-organic foreign body in their mouth while playing.

Epidemiology

The exact incidence of fatal and non-fatal FBA and choking-related injuries in children is unclear; the available data are probably an under-representation, and international comparisons are difficult. Analysis of the US National Electronic Injury Surveillance

System in 2001 identified 17 537 children aged ⩽14 years treated in emergency departments for choking related episodes (rate 29.9 per 100 000 population). Rates were highest for infants (140.4 per 100 000) decreasing with each successive age cohort to a rate of 4.6 per 100 000 for those aged 10–14 years. Many choking-related episodes were mild and included minor pharyngeal irritation without FBA, but ~10% required hospitalisation and for every 110 children treated there was one death. The commonest food substance was sweets/chewing gum (19%) while the commonest non-food item was coins (12.7%). In Italy there are about 400 children admitted per year who require removal of a foreign body.

A review of 13 266 cases (91 reports) of FBA from high-income countries and 24 731 cases (83 reports) from low-/medium-income countries (total 37 997) demonstrated similar demographics in both populations. 60% of subjects were male and 40% were female, and the majority were aged ⩽3 years (high-income countries 75%, low-/middle-income countries 60%). The diagnosis of inhaled foreign bodies was delayed by more than 24 h in approximately 60% of the cases.

In a review of 30 reports comprising 12 979 children with suspected FBA; of whom 11 145 had aspirated an object (14% false negative rate), over 80% of foreign bodies were organic materials, with nuts and seeds being the most common. Approximately 90% were lodged in the bronchial tree, with the remainder in the larynx or trachea. Foreign bodies were more likely to lodge on the right side (52%) than the left (33%), while a small number of objects fragmented and lodged in different parts of the airways.

Presentation

A history of a witnessed choking event is very suggestive of FBA, a child aged <3 years is rarely able to give a clear history, and an adult is present in over half of such cases.

The clinical findings will depend on the level at which obstruction has occurred, although most patients will have a paroxysmal cough. Respiratory distress and/or cyanosis suggest obstruction to a large airway and warrants emergency treatment. Laryngeal obstruction may cause a hoarse voice or aphonia, drooling, stridor and/or wheezing and respiratory distress. Tracheal obstruction may present with biphasic or monophonic wheeze and bilaterally decreased breath sounds and respiratory distress. More distal obstruction may result in unilateral monophonic wheeze and unilateral decreased breath sounds. Cough and wheeze are the most sensitive signs, while stridor and cyanosis are the most specific.

Late presentations may be misdiagnosed as pneumonia, asthma or laryngitis presenting with decreased chest movement, decreased breath sounds, wheezing and possibly crackles and pyrexia.

Investigations

A chest radiograph is mandatory for all cases of suspected FBA to localise potential foreign bodies and assess chest asymmetry, but also to exclude other causes for respiratory distress. Flat objects such as coins tend to align in the sagittal plane in the trachea whereas objects in the oesophagus tend to align in the coronal plane. Lateral chest radiographs can sometimes be helpful.

Chest radiograph abnormalities may include asymmetry, such as air trapping and emphysema, infiltrates and possibly mediastinal shift. For older children who are able to co-operate, a combination of inspiratory and expiratory films should be obtained. Partial airway obstruction may cause a valve-like effect resulting in air trapping and mediastinal shift being more prominent on expiratory films. The majority of foreign bodies are organic materials and are not usually radio opaque. Only 10% of foreign bodies will be visible on a chest radiograph. Pneumothorax and pneumomediastinum are infrequent findings. Chest radiographs may be normal in approximately 17% of children subsequently shown to have FBA. Later radiographic features include segmental collapse, consolidation or atelectasis.

CT and generation of virtual bronchoscopy can be useful in assessment of FBA in stable children, offering greater sensitivity than plain radiographs.

Treatment

Immediate treatment of FBA by parents or carers may dislodge the foreign body. In infants, back slaps in a head down position with or without chest thrusts are the treatment of choice. Abdominal thrusts including the Heimlich manoeuvre appear more appropriate for older children.

Foreign body aspiration must be suspected for any witnessed choking episodes. Although a history of inhalation can be elicited from the parent in many cases, FBA cannot be excluded on either normal physical examination or chest radiograph.

Removal of the foreign body is the primary objective and mainstay of treatment. Rigid bronchoscopy is the classical investigation and treatment of choice, although a common strategy is to use rigid bronchoscopy for children with convincing evidence of FBA, while children with a less clear-cut history or findings undergo flexible bronchoscopy. The majority of cases of FBA in Europe are treated in ENT departments. A number of negative bronchoscopies are required, with the reported incidence varying between 9% and 16.5%.

Rigid bronchoscopy requires general anaesthesia but allows control of the airway at the same time, as instruments can be advanced to remove the foreign body in a safe way, while also facilitating removal of mucous plugging and installation of saline or mucolytics to areas of lung collapse. Removal is completed most often either with an alligator jaw or cup forceps. Balloon tipped catheters can be used, particularly for round foreign bodies, to dislodge foreign bodies that may be lodged with surrounding granulation tissue. For organic material in particular, considerable care is required to prevent disintegration of the foreign body resulting in multiple smaller foreign bodies. Once manoeuvred to the larynx it should be removed *via* the lower triangle of the glottis to avoid trauma to the vocal cords. In the rare circumstance where the foreign body is too large to pass through the subglottic space (the so-called monkey trap phenomenon) a temporary tracheostomy may be required.

Although the vast majority of foreign bodies are removed with rigid bronchoscope, there is increasing evidence for the use of flexible bronchoscopy. In a study of >1000 children, foreign bodies were successfully removed by flexible bronchoscopy in >90%. Flexible bronchoscopy may be superior to rigid bronchoscopy in the removal of foreign bodies from distal airways and, particularly, the upper lobe bronchi.

There is lack of consensus on the best anaesthetic regime with some authors advocating paralysis, while others advocate spontaneous ventilation. Positive airway pressure during the procedure and particularly afterwards is useful for re-inflation of atelectatic lung areas. It is important that after removal of a foreign body the rest of the airways are checked to ensure there are no smaller objects. If there is significant bleeding during the procedure, dilute (100 $mg \cdot L^{-1}$) adrenaline can be administered topically. Pre-operative antibiotics are usually administered and continued for a 5-day course. Corticosteroids may be beneficial following removal of a foreign body to decrease airway oedema.

For patients presenting with respiratory distress or cyanosis, emergency bronchoscopy is essential. However for patients who are clinically stable without respiratory compromise, it is reasonable to take the child to theatre in a planned manner during normal working hours, even if this incurs a delay. It is unlikely that a delay of <24 h in removal of the foreign body will have any significant long-term effects on the lung. A review of over 3000 FBAs suggested that sequelae were more common where a foreign body had been present for >1 week: 27.2% *versus* 6.7% for those <1 week.

Complications

In a meta-analysis of 26 studies where major complications were specified, deaths

occurred in 43 (0.42%) out of 10 236 cases. Death rates in individual studies varied between 0.21% and 0.94% with approximately a third presenting with hypoxic arrest and a third arresting during the procedure. Major non-fatal complications occurred in 0.96% and included severe laryngospasm or bronchospasm requiring tracheostomy or intubation, pneumothorax or pneumomediastinum. Approximately a third required thoracotomy to remove the foreign body.

Prevention

Public health strategies can reduce the risk of FBA in children. There are European and US recommendations about the types of food that are inappropriate for younger children, and choking hazard warnings on small toys that pose particular risks of FBA. Parents can receive education and basic instructions on what to do in an emergency situation.

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Bronchiolitis obliterans

Francesca Santamaria, Silvia Montella and Salvatore Cazzato

Key points

- Bronchiolitis obliterans is a rare paediatric chronic obstructive lung disease, which follows a severe insult to the respiratory tract and results in narrowing and/or complete obliteration of the small airways.
- The most common cause is severe lower airway infection, followed by bone marrow or lung transplantation, drug toxicity, noxious inhalation injury, vasculitis and autoimmune disorders.
- Open lung biopsy for histological confirmation of the diagnosis is rarely necessary. In the appropriate setting, after the exclusion of other chronic obstructive lung disease, HRCT provides adequate evidence for a correct diagnosis.
- Lung function is characterised by a moderate-to-severe fixed airflow obstruction unresponsive to bronchodilators that may slowly progress to fatal deterioration even a few months after diagnosis. Mortality rates range from 3.2% to 16.7%, depending on bronchiolitis obliterans severity.
- The treatment of bronchiolitis obliterans is often unsuccessful because patients are referred to specialised centres when irreversible fibrotic changes and airway obliteration have already occurred.

Bronchiolitis obliterans, or constrictive bronchiolitis, is a rare chronic obstructive lung disease, which follows a severe insult to the respiratory tract and results in narrowing and/or complete obliteration of the small airways. Although the term describes a pathology confined to small airways, inflammation and fibrosis may extend to the alveoli and interstitium.

In children, bronchiolitis obliterans is a long-term sequela of severe infections occurring most commonly after acute pneumonia or bronchiolitis. Other causes include transplantation of bone marrow or lung, drug toxicity, noxious inhalation injury, vasculitis and autoimmune disorders.

The onset of bronchiolitis obliterans is frequently insidious and symptoms may be misinterpreted, thus resulting in delayed diagnosis. Mortality remains high and most patients die of respiratory failure complicated by additional infections.

Epidemiology

Although childhood post-infectious bronchiolitis obliterans is rare, its prevalence seems greater than previously thought, particularly in South America, Europe, USA, India, East Asia, New Zealand and Australia. Although the prevalence of post-infectious bronchiolitis obliterans is unknown, its epidemiology is directly related to severe viral respiratory infections in young children, mainly adenovirus. Race has also been suggested as a predisposing factor for post-infectious bronchiolitis obliterans. However, while an Argentinean group found that their post-infectious bronchiolitis obliterans patients had an increased frequency of an allele highly expressed in an

Amerindian population, 70% of the post-infectious bronchiolitis obliterans children followed up by a Brazilian centre were Caucasian. This suggests that a different distribution may be found among centres according to the local racial composition.

In long-term lung transplant survivors, bronchiolitis obliterans represents the leading cause of morbidity and mortality, and occurs in 60–70% of patients surviving at 5 years, whereas in allogeneic haematopoietic stem-cell transplantation (HSCT) incidence ranges from 0% to 48%.

Pathology

Bronchiolitis obliterans is primarily a lesion of the membranous and respiratory bronchioles with fibrosing inflammatory process surrounding the lumen, which results in progressive airways narrowing, distortion and obliteration. Histological features have a wide spectrum from chronic inflammation to bronchiolar scarring without extensive changes in alveolar ducts or walls, and show a patchy distribution.

The term bronchiolitis obliterans organising pneumonia (BOOP) identifies an airspace filling process with granulation tissue plugs extending to small airways, and is distinguished from bronchiolitis obliterans on the basis of clinical, functional and radiographic features, including response to corticosteroids and prognosis. It was long considered a small airways disease, but current classification lists BOOP among interstitial pneumonias.

Clinical entities

Post-infectious bronchiolitis obliterans Post-infectious bronchiolitis obliterans should always be suspected in previously healthy children who develop chronic respiratory symptoms lasting for longer than 4–8 weeks after an episode of acute, usually severe, infection at preschool age.

Several pathogens are associated with paediatric post-infectious bronchiolitis obliterans, and adenovirus (serotypes 3, 7, 11 and 21) is most frequently implicated. Other microorganisms include:

- Influenza virus,
- Parainfluenza virus,
- Measles virus,
- Varicella virus,
- *Mycoplasma pneumoniae*,
- *Chlamydophilia pneumoniae*,
- *Staphylococcus aureus*,
- *Streptococcus pneumoniae*,
- *Bordetella pertussis*.

Although respiratory syncytial virus (RSV) is frequently associated with bronchiolitis, evidence for a causative role of it in determining post-infectious bronchiolitis obliterans is lacking. Increased serum interleukin (IL)-6, IL-8 and tumour necrosis factor (TNF)-α in children with adenovirus infection suggest that the host immunological response may play an important role in the development of post-infectious bronchiolitis obliterans.

The acute infection leading to post-infectious bronchiolitis obliterans usually requires hospital admission for oxygen therapy and sometimes requires mechanical ventilation. Despite appropriate initial treatment, hypoxaemia, cough, breathlessness, wheezing, tachypnoea, exercise intolerance and crackles on auscultation are common clinical findings. Oxygen may be required for months or years after the acute infection. Failure to thrive, clubbing, chest deformity and pulmonary arterial hypertension are reported in severe cases.

Bronchiolitis obliterans following bone marrow transplant Bronchiolitis obliterans is the most common late, non-infectious pulmonary complication of allogeneic HSCT. Generally, bronchiolitis obliterans does not develop after autologous HSCT. Although there are reports of bronchiolitis obliterans as early as 30 days following HSCT, 80% of cases present 6–12 months post-transplantation.

The presentation is usually insidious, and main symptoms include dry cough (60–100% of cases) and dyspnoea (50–70% of patients). Wheezing and sinusitis are also frequent, while fever is rare unless there is a concomitant infection. Approximately 20%

of patients are asymptomatic, and diagnosis may be suspected based on lung function. In the advanced stages, patients are physically limited because of severe airway obstruction and may require home oxygen. Some patients may develop bronchiectasis with recurrent respiratory infections and colonisation by *Pseudomonas* spp., *S. aureus* and, occasionally, *Aspergillus* spp. Usual examination features are decreased breath sounds, wheezing, inspiratory squeaks and signs of hyperinflation, while basal crackles are rare. However, thoracic examination may be normal in early stages. Almost all patients also have symptoms and signs of chronic graft *versus* host disease (GVHD), especially skin changes and sicca syndrome, with dryness in the eyes and mouth.

Bronchiolitis obliterans following lung transplantation Lung transplantation recipients often have a variable period of good graft function, followed by insidious onset of symptoms. Clinical presentation of bronchiolitis obliterans may vary from asymptomatic disease to nonspecific symptoms as dyspnoea, cough and exercise intolerance, while wheezing and chest pain are less common. Chest auscultation includes expiratory wheezing and occasional crackles, as well as distant breath sounds with only mild expiratory prolongation. Digital clubbing rarely occurs.

Compared to deceased donor transplant, the incidence of bronchiolitis obliterans is lower in living donor lobar transplant recipients, probably due to less frequent and less severe rejection episodes. Moreover, children aged <3 years undergoing lung transplantation show lower risk of bronchiolitis obliterans, probably because of decreased incidence of acute rejection.

Bronchiolitis obliterans following autoimmune disorders or vasculitis The majority of described cases with collagen-vascular diseases and associated bronchiolitis obliterans (*i.e.* rheumatoid arthritis, scleroderma, systemic lupus erythematosus, Crohn's disease and Stevens–Johnson syndrome) are adults. It remains unclear whether this association is due to the disease process or the medication used as treatment.

Risk factors

Pathogen load, immunological response, and genetic and environmental factors may be associated with bronchiolitis obliterans. However, it is still unknown why some children, but not all, develop bronchiolitis obliterans.

Possible risk factors for post-infectious bronchiolitis obliterans are prolonged hospitalisation, multifocal pneumonia, need for mechanical ventilation and hypercapnia. It remains unclear whether the need for mechanical ventilation is an indicator of disease severity or is responsible for the direct induction of airway injury. Moreover, bilateral pulmonary involvement is associated with more severe post-infectious bronchiolitis obliterans.

Recurrent acute cellular rejection (ACR) episodes following lung transplantation, as well as high-grade ACR, are primary risk factors for bronchiolitis obliterans. However, a single episode of minimal ACR without recurrence or progression to rejection is also a significant independent predictor of bronchiolitis obliterans. As a result, early and aggressive treatment of ACR represents an important preventive strategy. Indeed, recognition and treatment of ACR are often delayed, as patients may be stable. Moreover, ischaemia–reperfusion injury after transplantation or primary graft dysfunction are associated with bronchiolitis obliterans, and the risk depends on the severity of graft dysfunction. Ischaemia and reperfusion, or other insults, may damage the respiratory epithelium with resulting exposure of hidden epitopes of collagen type V, which may result in bronchiolitis obliterans secondary to autoimmune injury. Furthermore, leukocyte antigen mismatches following lung transplantation might promote bronchiolitis obliterans, but this is controversial.

The presence of chronic GVHD is the most important, but not the 9 unique, risk factor for bronchiolitis obliterans in HSCT. Other frequent risk factors include:

- airflow obstruction (FEV_1/FVC ratio <0.7) prior to HSCT;
- recipient's age >20 years;
- viral infections (*e.g.* influenza, parainfluenza and RSV) within 100 days following HSCT;
- busulfan-based conditioning regimen;
- mismatched or unrelated donor;
- hypogammaglobulinaemia (especially IgG and IgA);
- methotrexate prophylaxis against GVHD;
- older age of the donor;
- HSCT for chronic myelogenous leukaemia;
- blood-derived stem cells;
- interval from diagnosis of leukaemia to transplantation >14 months;
- female donor to male recipient;
- prior interstitial pneumonitis;
- low pre-transplant serum surfactant protein D levels;
- nucleotide-binding oligomerisation domain 2/caspase recruitment domain 15 variants.

In lung or bone marrow graft recipients, nonimmunological factors leading to bronchiolitis obliterans include Epstein–Barr virus reactivation and infection of the lung allograft by cytomegalovirus, adenovirus, influenza and parainfluenza viruses, RSV, fungi and bacteria. The lung transplantation type may also be a risk factor, with single transplant recipients being at higher risk than bilateral. Gastro-oesophageal reflux may contribute to allograft rejection, and bile acids and pepsin in bronchoalveolar lavage fluid (BALF) from lung transplant recipients indicate aspiration.

Diagnosis

Although diagnosis is based on clinical, functional and radiographic criteria, lung biopsy remains the gold standard to diagnose bronchiolitis obliterans. Since parenchymal involvement is patchy, transbronchial biopsy has a small yield. Transthoracic biopsy from two sites is recommended. One of the major challenges for paediatricians is the search less invasive diagnostic methods for bronchiolitis obliterans.

Pulmonary function tests (PFTs) provide information about disease severity and progression over time. Infant PFTs, when available, indicate severe obstruction, diminished lung distensibility and increased airway resistance since a few months after the disease onset. Older children exhibit severe and irreversible airflow obstruction and the greater the air-trapping, the greater the compromise during exercise. The decrease in forced expiratory flow at 25–75% of FVC (FEF_{25-75}) is the typical functional marker of the disease, often associated with reduced FEV_1 and FVC. Increased residual volume (RV) and RV/TLC ratio indicate hyperdistension. A positive methacholine challenge test following transplant is a risk to developing bronchiolitis obliterans at an accelerated rate. Single-breath nitrogen washout may reveal heterogeneous ventilation and alteration in expiratory flow rates 6–12 months before conventional PFTs. The lung clearance index (LCI) is increasingly used to detect the earliest bronchiolitis obliterans abnormalities. The first evidence of its effectiveness in detecting post-bone marrow transplant bronchiolitis obliterans in adults and children was reported by Khalid *et al.* (2007). In that study, paediatric patients demonstrated an increased LCI from an early stage of bronchiolitis obliterans compared to healthy controls. This finding has been recently confirmed in Australian adults who underwent repeated LCI measurements after HSCT (Lahzami *et al.*, 2011). Finally, in children with post-infectious bronchiolitis obliterans the impairment of T_{LCO} related to poorly ventilated lung units with marked small airways obstruction may be helpful in the differential diagnosis with severe asthma, which often shows normal or even increased T_{LCO} due to hypervascularity.

Chest radiographs are often unspecific or even normal, but may reveal bilateral peribronchial thickening and/or hyperinflation with or without opacities, sometimes with associated pneumothorax or pneumomediastinum. Rarely there is predominant unilateral hyperlucency (Swyer–James or McLeod's syndrome), with the affected lung being smaller on

inspiration and the mediastinum shifted on expiration towards the controlateral lung because of air-trapping.

HRCT is extremely helpful for diagnosis, and structural changes include:

- mosaic perfusion,
- air-trapping,
- bronchial wall thickening,
- bronchiectasis,
- thickening of septal lines,
- narrowing of the pulmonary vessels due to reflex vasoconstriction secondary to tissue hypoxia,
- tree-in-bud pattern (fig. 1).

Expiratory scans are helpful in identifying air-trapping that may be missed on an inspiratory scan. Indeed, the extent of air-trapping may correlate with bronchiolitis obliterans severity. The severity of HRCT within the first 2 years after the acute event seems to predict the subsequent lung function evolution. Furthermore, the characteristic mosaic perfusion on HRCT, due to areas of attenuated density alternating with areas of increased attenuation with a patchy distribution, may be useful in discriminating between patients with bronchiolitis obliterans and those with severe asthma and irreversible obstruction. For all the above mentioned reasons and given the relative risk of lung biopsy, it has been emphasised that in the appropriate setting, once other congenital or acquired disorders have been excluded (*e.g.* CF, primary ciliary dyskinesia, immunodeficiency, bronchopulmonary dysplasia, congenital heart disease, severe asthma, inhaled foreign body, extrinsic bronchial compression and α_1-antitrypsin deficiency), HRCT provides clear evidence for a correct diagnosis without the need for biopsy. Thus, lung biopsy is recommended if HRCT is inconclusive or not available, or when severe progression and gradual deterioration occur despite treatment.

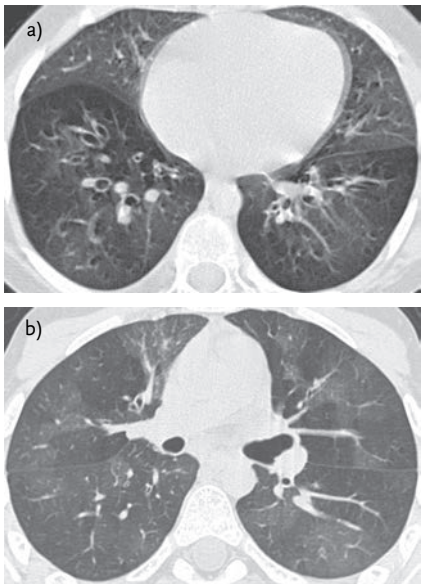

Figure 1. a) HRCT scan of a 4-year-old boy with bronchiolitis obliterans following Mycoplasma pneumoniae *infection. Bilateral areas of increased and decreased parenchymal attenuation (mosaic perfusion), bronchiectasis and air-trapping can be seen. b) Bronchiolitis obliterans in a 13-year-old boy 2 years after bone marrow transplantation for acute lymphoblastic leukaemia. The HRCT scan shows a bilateral mosaic perfusion pattern, air-trapping and bronchial dilatation.*

Ventilation-perfusion scintigraphy with the typical matched ventilation/perfusion defect in one or more pulmonary segments provides a valuable assessment of extension, distribution and severity of lung involvement that correlates with the number of exacerbations.

BALF neutrophilia in the absence of an identifiable pathogen might be a reproducible marker of bronchiolitis obliterans as it increases with the severity of bronchiolitis obliterans stage.

Finally, in severe bronchiolitis obliterans oximetry may reveal overnight hypoxaemia that should prompt a thorough cardiovascular assessment, including electrocardiogram, echocardiogram and cardiac catheterisation, if necessary, to detect pulmonary arterial hypertension.

Treatment

Patients should be treated by a multidisciplinary team with:

- a paediatric pulmonologist,
- a paediatric cardiologist,
- a physical therapist,
- a nutritionist,
- a psychologist,
- a social worker.

Bronchiolitis obliterans treatment for children has not been clearly defined, and pharmacological approaches are often based on the clinical experience of different healthcare workers.

The treatment of bronchiolitis obliterans is often unsuccessful because patients are referred to specialised centres when airway changes are irreversible. It is mainly supportive, including prolonged oxygen supplementation, particularly during the first period of the disease, antibiotics, annual influenza vaccination and chest physiotherapy for cases complicated by bronchiectasis. Adequate nutritional support is fundamental as up to 20% of children with bronchiolitis obliterans may have some degree of malnutrition. Gastro-oesophageal reflux must be adequately treated.

Although frequently used in the clinical practice, corticosteroids in post-infectious bronchiolitis obliterans are controversial because no trials have confirmed their efficacy. There are only clinical reports of beneficial effects of pulse methylprednisolone (25–30 $mg \cdot day^{-1}$ for 3 days) in children with post-infectious bronchiolitis obliterans. Conversely, in GVHD occurring after HSCT high-dose systemic prednisone (1–1.5 $mg \cdot kg^{-1} \cdot day^{-1}$ for 2–6 weeks) or methylprednisolone (10 $mg \cdot kg^{-1} \cdot day^{-1}$ for 3 days on monthly basis for 1–6 cycles) should be prescribed, and immunosuppressive therapy should be reinstituted or augmented. In paediatric lung transplant recipients, the development of bronchiolitis obliterans should lead to augmentation of immunosuppression. Inhaled corticosteroids and/or bronchodilators may be considered in bronchiolitis obliterans, but should be discontinued in the absence of benefits.

In lung transplant and bone marrow transplant recipients, azithromycin may improve bronchiolitis obliterans symptoms, lung function and exercise tolerance, probably because it exerts anti-inflammatory and immunomodulatory activity through neutrophil chemotaxis inhibition and proinflammatory cytokine reduction. Empirical monthly intravenous Ig administration was used in few cases. There are also some anecdotal reports of symptom improvement after chloroquine and hydroxychloroquine in bronchiolitis obliterans, and after TNF-α monoclonal antibodies (infliximab) in bronchiolitis obliterans complicating bone marrow transplantation. Finally, in bronchiolitis obliterans following lung transplantation the addition of montelukast to immunosuppressive drugs was reported to decrease lung function decline over 6 months.

In localised bronchiectasis or atelectasis unresponsive to pharmacological therapy, surgical resection is indicated. Severe cases with oxygen dependency, important physical limitation and extremely impaired lung function should be referred for lung transplantation.

Prognosis

The long-term prognosis of bronchiolitis obliterans is variable and depends on several factors, including the underlying causes and the speed of development. In most cases, post-infectious bronchiolitis obliterans is chronic and nonprogressive, in contrast with bronchiolitis obliterans occurring after Stevens–Johnson syndrome or bone marrow transplantation. Most patients with post-infectious bronchiolitis obliterans improve slowly and progressively, but this may be due to airways growth rather than to resolution of inflammation. Nevertheless, most patients continue to have mild symptoms especially during exercise. Neutrophils, $CD8^+$ T-cell lymphocytes, activated T-cells ($CD_3^+HLA\text{-}DR^+$) and IL-8, a potent chemoattractant and activator for neutrophils, are increased in

the BALF several years after the initial insult, suggesting that lung inflammation persists.

In most bone marrow transplant recipients, bronchiolitis obliterans progressively leads to irreversible airflow obstruction over months to years because of frequent exacerbations. The mortality is 9% at 3 years, 12% at 5 years and 18% at 10 years. Patients with advanced bronchiolitis obliterans usually die from pneumonia. Factors associated with mortality include rapid FEV_1 deterioration (>10% per year), progressive chronic GVHD, underlying disease relapse, respiratory viral infections, airflow obstruction within 150 days following transplantation, and no response to the primary treatment.

Chronic bacterial airway colonisation in lung transplant recipients with bronchiolitis obliterans is commonly associated with poor outcome. Moreover, bronchiolitis obliterans, or its complications, are the single most common cause of death in lung transplant recipients, accounting for 40% of deaths >1 year later.

Morbidity due to frequent obstructive exacerbations and infections requiring hospitalisations is high in bronchiolitis obliterans. Mortality rates range from 3.2% to 16.7%. Fatal course may occur secondary to progressive respiratory failure.

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Plastic bronchitis

Bruce K. Rubin and William B. Moskowitz

Plastic bronchitis is an uncommon disease characterised by the presence of cohesive branching casts filling the airways. This disease has been recognised for thousands of years and was first described by Galen who believed that patients were expectorating pulmonary veins; *venae arteriosae expectoranti*. Plastic bronchitis has had many names through the years although the terms plastic bronchitis, fibrinous bronchitis and cast bronchitis are most commonly used.

Key points

- Plastic bronchitis in children is usually associated with congenital heart disease post-surgery with Fontan physiology.
- Cast formation appears to be related to poor cardiac output, lymphatic abnormalities, inflammation, and tissue factor activation.
- There is no proven therapeutic value in using hypertonic saline, salbutamol, corticosteroids, acetylcysteine, dornase alfa, antibiotics or expectorants.
- There is some evidence to support the use of low-dose azithromycin and aerosol heparin to prevent casts, and tPA can help mobilise casts *in situ* but can be very irritating to the airway. Airway clearance therapy, such as high frequency chest wall compression, is strongly recommended.
- Thoracic duct ligation and cardiac transplantation appear to reduce or eliminate cast formation in some patients.

Diagnosis

Plastic bronchitis is part of the secretory hyperresponsiveness disease spectrum. The diagnosis of plastic bronchitis is confirmed by identifying the cohesive, branching airways casts that are expectorated by the patient or removed bronchoscopically (fig. 1). Bronchoscopic removal is most common in young children with severe, life-threatening respiratory distress due to both the cast and the underlying cardiac disease. These casts contain an abundance of mucin but unlike normal mucin polymers that are linearly joined, there is significant cross-linking between adjacent mucin strands. The casts contain variable amounts of fibrin with many patients having only small amounts of fibrin in expectorated casts.

In patients with bronchiectasis and CF there are large amounts of polymeric DNA and F-actin as the principal polymer gel substance. These mucus (sputum) plugs have low cohesivity and rarely, if ever, develop into solid cohesive complex branching casts diagnostic of plastic bronchitis. There is also no polymeric DNA or F-actin in plastic bronchitis casts further distinguishing them from mucus plugging. Plastic bronchitis also appears to be different from the mucus plugging associated with fungal inflammation of the airway, as noted in allergic bronchopulmonary aspergillosis. It is not clear if plastic bronchitis can be part of the asthma spectrum in patients with severe asthma and secretory

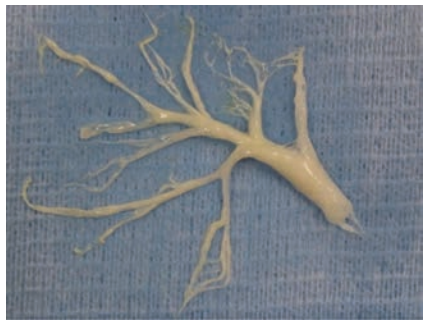

Figure 1. Typical expectorated branching cast from a child with plastic bronchitis and congenital heart disease.

hyperresponsiveness. These patients probably should not be classified as having plastic bronchitis.

We have examined plastic bronchitis casts from more than 50 adults and children with a variety of associated conditions and all show the presence of inflammatory cells. Although plastic bronchitis was once classified as Type 1 or Type 2 (cellular and acellular) the consistent appearance of inflammatory cells, predominantly lymphocytes with a minor component of macrophages, makes this classification of limited therapeutic or prognostic value. Inflammatory cells are more commonly seen in association with asthma and allergy and other non-cardiac associated conditions.

Plastic bronchitis is probably under diagnosed. The diagnosis is often made at autopsy after death from respiratory failure. Patients with milder forms of plastic bronchitis probably undergo spontaneous recovery. Thus, identified patients probably represent the most severe cases with dramatic branching casts, airway obstruction and extensive atelectasis.

Disease associations

Plastic bronchitis in young children is primarily associated with congenital heart disease, particularly in children with single ventricle Fontan physiology (table 1). The occurrence, severity and the frequency of exacerbations of plastic bronchitis varies markedly among patients with congenital heart disease; sometimes first appearing years after surgery. Some patients may have subclinical disease with the expectoration of small casts or resolution of casts between exacerbations. It is not clear which patients with single ventricle physiology are most likely to develop plastic bronchitis, although there are associations with protein losing enteropathy, poor cardiac function, central venous pressure elevation, arrhythmias and low cardiac output. The cardiac and pulmonary interaction leading to plastic bronchitis is not known, but may be associated with abnormalities in tissue factor.

Plastic bronchitis has been associated with lymphatic abnormalities both in patients with congenital heart disease and in patients with primary abnormalities of lymphatic flow. Case reports suggest that thoracic duct ligation can attenuate, or even cure, plastic bronchitis in some patients. A plastic bronchitis-like condition can be triggered by the inhalation of toxic gases such as sulfur mustard. In experimental animals that have inhaled sulfur mustard there is extensive plugging of the airway with fibrin rich casts that appear similar to those seen in humans with plastic bronchitis.

Plastic bronchitis is also associated with sickle cell disease acute chest syndrome. It is not known if development of casts in sickle cell disease leads to areas of hypoxaemic sickling within the lung producing the symptoms of acute chest syndrome, or if the acute chest syndrome itself predisposes to cast formation. Plastic bronchitis is not associated with pulmonary bacterial infection and, in general, antibiotics are not recommended as part of therapy. However, plastic bronchitis has been shown to be associated with influenza A infection in children and similar cast formation has been described in birds who have been experimentally infected with avian influenza.

It is controversial as to whether severe asthma and airway plugging should be considered a plastic bronchitis-like disease. Fatal asthma

Table 1. Conditions associated with plastic bronchitis

Proven
Congenital heart disease with Fontan physiology
Sickle cell disease acute chest syndrome
Pulmonary lymphatic abnormalities
Influenza A pulmonary infection
Toxic inhalation
Possible
Other congenital cyanotic cardiac disease
Non-pulmonary lymphatic abnormalities
Hypersecretory and near-fatal asthma (eosinophilic casts)
Allergic bronchopulmonary aspergillosis
Unlikely
CF
COPD
Bronchiectasis
Bacterial pneumonia

secretions are extremely cohesive and when extracted from the airway appear to have a formation of branching casts; and in that respect they more closely resemble plastic bronchitis than mucus plugging.

Therapy

Because plastic bronchitis is an uncommonly reported condition, most reports of "effective" therapy are isolated case reports or small case series. Furthermore, most patients reported in these case studies have received a number of different medications making it difficult to ascertain which of these therapies, if any, are effective (table 2). Evaluation of data from the International Plastic Bronchitis Registry suggests no benefit from the use of asthma medications, such as short-acting β-agonists or inhaled corticosteroids. There is no therapeutic benefit from using inhaled dornase alfa (Pulmozyme; Roche, San Francisco, CA, USA) as plastic bronchitis casts do not contain polymeric DNA. There is no benefit in using expectorants, such as guaifenesin or hypertonic saline, or mucolytics, such as *N*-acetylcysteine. These medications should only be used with caution as some can induce mucus secretion or increase airway inflammation.

There have been several case reports that the inhalation of tissue plasminogen activator (tPA) can improve plastic bronchitis, most probably through fibrin depolymerisation. tPA is extremely expensive and can be irritating to the airway with haemoptysis or dyspnoea being reported after inhalation. In patients with severe plastic bronchitis a trial of aerosol tPA should be considered at a dose of 0.7–1.0 $mg \cdot kg^{-1}$ every 4 h. Inhaled heparin has also been effective in patients with plastic bronchitis. Heparin has no effect on preformed fibrin but has been shown to reduce mucin secretion and prevent tissue factor activation of the fibrin pathway. Heparin also has anti-inflammatory properties and is far less irritating to the airway and dramatically less expensive than some of the other agents. A trial of aerosolised heparin at a dose of 5000 units every 4 h should be considered.

Isolated reports suggest that inhaled anticholinergics may reduce cast formation. Although there has been concern that inhaled anticholinergics may "thicken" secretions, this has not been the case when these have been used to treat asthma, CF or COPD. There is no role for the use of antibiotics to treat bacterial infection in plastic bronchitis. However, low-dose macrolides can decrease mucin production by inhibiting extracellular regulated kinase (ERK)1/2. There are case reports suggesting that low-dose macrolides, similar to their use in CF or diffuse panbronchiolitis, can attenuate the severity of plastic bronchitis.

In patients with documented lymphatic abnormalities, thoracic duct ligation may be of benefit. There is limited evidence that improving cardiac physiology by fenestrated Fontan has a beneficial effect on the severity or resolution of plastic bronchitis. Improving cardiac output, when possible,

Table 2. Recommendations for therapy

Good evidence
Airway clearance including physical therapy and devices such as high-frequency chest compression vest
Aerosol heparin
Aerosol tPA
Cardiac transplantation
Anecdotal or case report evidence
Hyperosmolar saline
Low-dose oral macrolides (clarithromycin or azithromycin)
Oral or inhaled corticosteroids (only for eosinophilic casts)
Thoracic duct ligation
Modifications of Fontan (fenestration or take down)
No evidence
β-agonist aerosol
Dornase alfa (Pulmozyme)
Mucolytics such as *N*-acetylcysteine
Expectorants such as guaifenesin
Non-macrolide antibiotics

can reduce the severity of plastic bronchitis. There are reports that cardiac transplantation in children and young adults with heart failure can cure plastic bronchitis when medical management is ineffective.

Airway clearance appears to be among the safest and most effective therapy. Once plastic bronchitis has been diagnosed, starting the routine with daily use of a high-frequency chest compression vest, for those with an effective cough, or the CoughAssist device (Philips Respironics, France), for those with impaired cough, can prevent cast re-accumulation. We also recommend exercise, if possible, and good nutrition, which can consist of protein repletion in children with protein losing enteropathy or, sometimes, weight loss, especially in obese adults with plastic bronchitis (table 2).

The future

Through the US National Institutes of Health, Office of Rare Diseases we have established an International Plastic Bronchitis Registry to collect data on patients worldwide (www.clinicaltrials.gov identifier NCT01663948). This will help us to generate hypotheses that can be tested clinically and will, potentially, allow us to use genome or inflammasome screening to interrogate potential causes for this devastating disease. Through the Office of Rare Diseases we have also set up a tissue repository of expectorated bronchial casts and, with an approved protocol, we will make these available to investigators interested in studying this devastating disease. Information can be accessed through www.clinicaltrials.gov.

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Haemangiomas, lymphangiomas and papillomatosis

Thomas Nicolai

Haemangiomas

Airway haemangiomas are benign capillary tumours. Generally, benign capillary tumours occur in 1–2% of newborns, usually involving the skin. However, haemangiomas may also occur in the airways and ~25% of these cases also have haemangiomas of the skin.

The most common benign capillary tumours in the paediatric airway are subglottic and glottic haemangiomas, which may be present at birth and usually grow for the next 4–6 months. Haemangiomas of the lower airways have been described but are rare. Laryngeal haemangiomas can also be part of larger haemangiomas that may extend into the intrathoracic cavity.

Clinical signs Sometimes, the haemangioma may be present at birth leading to neonatal inspiratory stridor. However, this early presentation is rare. In a typical case, inspiratory stridor develops over the first 4–12 weeks of life, depending on the size of the haemangioma and its rate of growth. Quite often an acute viral airway infection will acutely increase the pre-existing airway obstruction caused by a haemangioma. The most common differential diagnosis is croup or laryngomalacia. In contrast to croup the symptoms caused by a laryngeal or tracheal haemangioma exacerbated by a viral infection will not disappear fully after the acute phase of the respiratory infection and may actually progress to overt respiratory insufficiency. Often, an expiratory component of the stridor becomes apparent with critical obstruction, and the voice or cry is changed in quality and loudness.

Key points

- Haemangiomas are benign and respond to propranolol.
- Lymphangiomas may need to be resected if they obstruct the airway; the clinical course is less predictable.
- Papillomatosis of the larynx may require repeated surgical resection and often responds to cidofivir.
- Newer therapies are currently being explored for lymphangiomas and papillomas.

Diagnosis The diagnosis is suspected by a typical history and an inspiratory and, sometimes, also expiratory noise. A very useful instrument for diagnosis is ultrasound, which can define the typical subglottic tumour structures. In addition, an MRI scan can show the typical blood filled glottic or subglottic rounded object. However, care must be taken as children may need sedation for MRI scans, and when these children are intubated for this purpose the haemangioma will be compressed by the endotracheal tube and may then be missed. Also, the intubation itself can be quite dangerous with damage to the subglottic area or even bleeding. Therefore, laryngotracheoscopy (usually performed with a flexible endoscope) is often the easiest way to diagnosis when ultrasound has failed to rule out haemangioma. Subglottic haemangiomas have a quite typical appearance and may form a rounded unilateral or bilateral structure in the

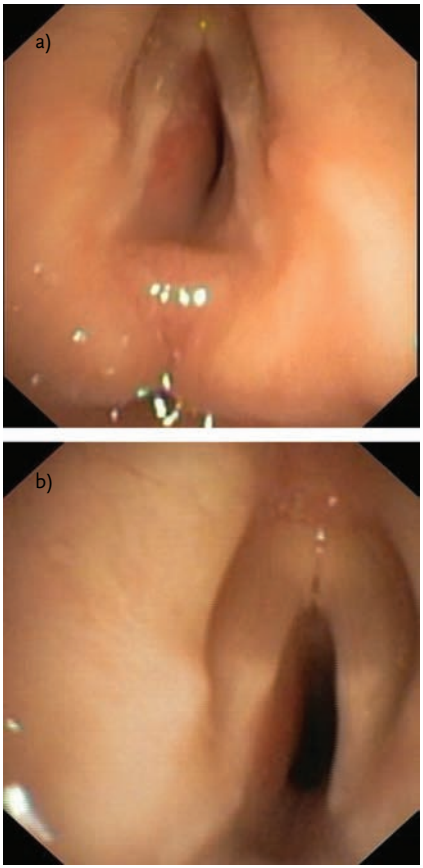

Figure 1. a) Subglottic haemangioma almost totally obstructing the airway. b) Subglottic haemangioma that is reduced in size after 1 week of treatment with propranolol (2 mg·kg^{-1}·day^{-1}).

subglottic area (fig. 1). The surface is smooth and often has a reddish colour. In very rare cases a biopsy may be needed and histology and staining for glucose transporter 1 (GLUT1) will establish the diagnosis.

Therapy Mortality without treatment has been reported to be ~50%. Therapy used to rely on long-term systemic steroids with all their known side-effects. Intra-lesional local application of steroids was also tried, with only limited success; almost two-thirds of the children were eventually tracheotomised. Various methods of surgically removing the haemangioma have been described. Careful endoscopic laser resection has been reported to be quite successful in avoiding tracheotomy in almost all cases, and will, in my view, remain a good option in nonresponders to propranolol. Before these therapeutic options became available many children had to remain tracheotomised for 2–3 years until the size of the malformation had become small enough to allow decannulation.

However, recently it was found, by a serendipitous discovery, that propranolol will shrink haemangiomas and arrest further growth (fig. 1). Therefore, today, therapy consists of the administration of propranolol, sometimes accompanied by initial short-term steroid therapy. With this strategy it is usually possible to avoid tracheotomy, as only about 14% of infants with airway haemangioma are nonresponders. The optimal duration of propranolol therapy has not been established, and it is recommended to treat until the involution phase of the haemangioma is reached (usually at 6–8 months of age but some authors advocate 12 months). Catch-up growth of airway haemangioma in infants after cessation of propranolol has been reported in about 7% of children and may need extended therapy. Refractoriness of the regrowth to propranolol has been described. The long-time prognosis of this tumour is excellent.

Lymphangiomas

Lymphangiomas are not neoplastic growing lesions, but malformations of the lymphoid tissues. It is assumed that these malformations originate from primitive lymphatic sacks formed of mesenchymal or epithelial embryonic tissue. Dysplastic lymph capillaries do not allow normal drainage of interstitial fluid and lead to tissue swelling and cystic transformation of the affected structures. This malformation is usually not confined to specific organs and may involve larger regions of the body. This explains the changeable course of the size with, for example, sudden increases of pharyngeal masses in size during viral

infections or with bleeding into the lymphangioma. It also explains why therapeutic options are sometimes limited: total resection of the affected tissue is not always possible and remaining (often clinically unapparent) malformed regions may later expand in size when drainage of the lymphatic fluid is obstructed. Other manifestations of lymphatic malformations may concern the whole lung and or mediastinum and lead to chylothorax and respiratory failure.

Clinical signs Lymphangiomas can involve the pharynx and larynx and lead to severe airway compromise (fig. 2). Sometimes the lymphangioma may be present at birth, being visible as a cranial, pharyngeal or neck mass, and/or leading to neonatal inspiratory stridor. Clinical manifestations may also occur later in life, *e.g.* with swelling due to an acute viral infection or when bleeding into the lymphangioma leads to an abrupt increase in lesion size.

Diagnosis Airway endoscopy shows an obstructing mass that may have a typical multicystic appearance, and allow for biopsy. MRI scans will delineate the extension of the lymphangioma into adjacent tissues (fig. 3).

Therapy Therapeutic options include:

- surgical resection,
- infiltration with sclerosing agents,

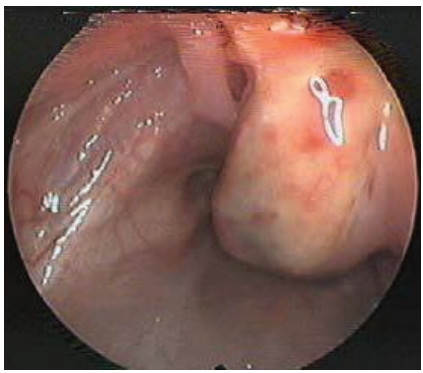

Figure 2. Lymphangioma of the larynx infiltrating the right dorsal aspect.

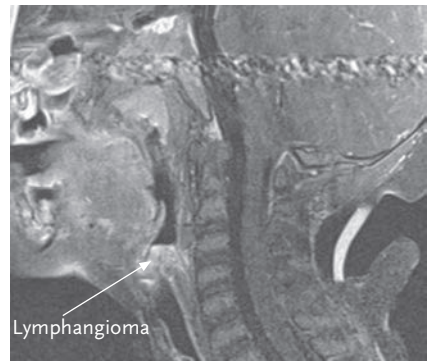

Figure 3. MRI scan of a lymphangioma of the larynx.

- interferon-α2b,
- laser resection.

However, the optimal selection of therapy requires considerable experience. The natural history of lymphangiomas is less benign than that of haemangioma, as involution is not seen regularly.

Future developments Recently, the use of sildenafil has been described in case reports and seems to open up a promising new therapeutic approach, but controlled studies are only currently under way. Another promising therapeutic agent in complicated refractory lymphangioma seems to be sirolimus.

Papillomas

Recurrent respiratory papillomatosis (RRP) of the larynx of children is the most common tumour of the paediatric larynx, and involvement of the lower airways does occur. Its incidence has been estimated to be two to four cases per 100 000. The papilloma viruses most frequently seen in the aetiology are human papilloma virus (HPV) type 6 and 11; however, there are more than 100 types of HPV. The infection is caused by transmission during birth from the mother's genital lesions to the child's airways. Caesarean section can reduce but not totally eliminate the infection risk. However, only very few children born to mothers with genital HPV infections later develop airway papillomatosis; therefore, individual risk

factors have to play a role in disease manifestation. Subtle complex abnormalities of the immune response to HPV in these patients have been found.

Clinical signs The usual time-point of clinical manifestation is 3–4 years of age. Clinical signs include:

- progressive dyspnoea,
- hoarseness,
- stridor.

Papillomas can grow quite large and obstruct the laryngeal opening completely.

Diagnosis Laryngotracheoscopy will show the typical cauliflower-like appearance of growth, usually above the vocal folds, a biopsy will allow the identification of the virus type (fig. 4).

Clinically an aggressive form can be observed with HPV type 6, while the milder course seems to be associated with HPV type 11. Manifestation before the age of 3 years and more than four surgical procedures to remove airway-obstructing papillomas are associated with a more aggressive clinical form, which may not resolve spontaneously.

Therapy Therapy may include resection of the papillomas either surgically or with a microdebrider or laser. However, utmost care must be taken not to cause secondary airways stenosis. It must be kept in mind that papillomatosis itself does not lead to scarring and once overcome will leave a normal larynx. However, surgery sometimes leads to highly dangerous laryngeal scarring at the level of the vocal fold, in particular if the resection of the papillomas has been either too aggressive, including more than one vocal cord during one session, or resection was close to the anterior commissure of the vocal folds. The use of laser surgery may lead to heating structures below the level of the papillomas, such as the vocal fold, and thereby cause damage with scar formation. These scars can lead to complete airway obstruction and tracheostomy. Children with airway papillomatosis and tracheostomy are at risk of generalisation of the papillomatosis to the lower airways (trachea and bronchi) where an eradication of the papillomas is usually impossible.

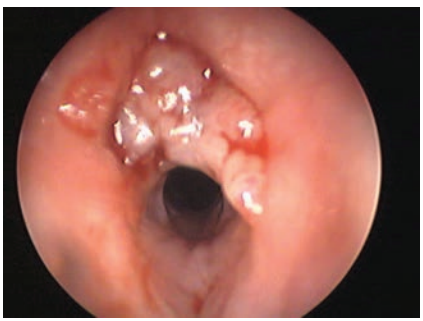

Figure 4. Papillomatosis of the larynx with obscured vocal folds.

A therapeutic modality used widely is the virustatic cidofovir. This antiviral has shown clinical effectiveness in treating adults with AIDS and systemic HPV infection, and is also widely used to infiltrate papillomas locally. At present there are no good randomised studies, but well-documented case series in children and adults with aggressive papillomatosis show that ~60–80% of patients will respond, with the therapy either leading to less frequent interventions for papilloma resection or even disappearance of the lesions.

From experiments in cell cultures and marker expression studies some concern has been voiced that cidofovir may increase the risk for laryngeal cancer. However, such cancer has never been clearly attributed to cidofovir use, and papillomatosis itself can lead to airway cancer when it is present for many years. A recent paper assessing its safety in a large number of patients found no increased laryngeal malignancies. Therefore, in cases with aggressive diseases, cidofovir may be useful and sometimes the only option available. However, parents have to be informed about their choices and the conceivable side-effects of the drug and the infection itself.

In rare cases, a generalised HPV infection of the lung follows tracheobronchial dissemination, resulting in cavitation.

This is more frequent in adult patients and it may be difficult to differentiate this from carcinoma formation.

Future developments Recent research has elucidated that in many people HPV is present in the airway mucosa without overt papillomatosis and that the oncogene Rac1 is overexpressed in the epithelium of these individuals. The downstream product of Rac1, COX-2, can be blocked with a COX-2 inhibitor, which leads to diminished HPV transcription in cell culture. One study has treated three patients with the COX-2 inhibitor celecoxib and achieved disease remission in all. A prospective study has been initiated. Other agents tried for papillomatosis, but for which no clear benefit has as yet been demonstrated convincingly include avastin, artemisinin and propranolol, while interferon seems effective but has had unacceptable side-effects in some children.

Vaccination programmes against HPV will hopefully reduce the frequency of this worrisome disease. In established disease the currently available vaccinations cannot be expected to be effective, but a therapeutic DNA vaccine is currently being developed.

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Interstitial lung diseases

Annick Clement, Guillaume Thouvenin, Harriet Corvol and Nadia Nathan

Key points

- ILD in children represents a heterogeneous group of respiratory disorders that are mostly chronic and impair the respiratory function of the lung.
- The term ILD has been replaced by the term DPLD, thus covering all pathological entities affecting lung homeostasis and remodelling following injury.
- The mechanisms underlying disease development are dependent on the type of DPLD; the common basis is the interaction between injurious environmental triggers and genetic predisposition.
- The presenting clinical manifestations are often subtle and nonspecific, therefore, a two-step diagnosis approach is required: 1) diagnosis of DPLD syndrome; 2) diagnosis of specific DPLD.
- Treatment protocols remain difficult to produce but the overall strategies include general measures and pharmacological therapy, mainly anti-inflammatory and immunosuppressive molecules.
- A favourable response to anti-inflammatory therapy can be expected in almost two-thirds of cases, although significant sequelae are often observed.

Interstitial lung disease (ILD) in infants and children represents a heterogeneous group of respiratory disorders that are mostly chronic and impair the respiratory function of the lung. In pathology, the term ILD describes structural alterations of the lung interstitium. However, in clinical practice, it refers to processes that affect the lung parenchyma, which include the alveolar structure (*i.e.* the alveolar epithelium, the interstitium and the pulmonary capillary endothelium), as well as the terminal bronchioles. Based on these anatomic and functional considerations, a new term diffuse parenchymal lung diseases (DPLD) has recently been introduced to more accurately describe these diseases. Therefore, the term DPLD will be used in this chapter instead of ILD.

DPLD covers a large number of disorders characterised by inflammation and/or remodelling of the lung parenchyma. They include rare diseases with established diagnosis criteria (such as genetic disorders of the surfactant system), as well as pathological conditions with uncertain diagnosis and/or unknown causes. This explains the fact that the estimated incidences of the various forms of DPLD are difficult to establish, especially in children. Indeed, in the paediatric population, disease expressions are dynamically influenced by the ongoing process of lung growth and maturation. Several reports in the literature have provided information on a national survey of paediatric DPLD. An estimated prevalence of 3.6 per million cases was reported in immunocompetent children in the UK and Ireland. In Germany, a rate of 1.32 new cases per 1 million children per

year has been observed. These numbers are certainly underestimated due to the lack of standardised definitions, the absence of organised reporting systems and the variety of pathological conditions. In addition, clinical presentation is nonspecific, contributing to a poor recognition of the disorders that may be confused with other diseases. Nevertheless, it seems that DPLD is more frequently observed in the younger age and in males. In addition, nearly 10% of cases appear to be familial.

Pathophysiology

DPLD can be caused by a number of factors with distinct prognosis and natural history. Agents responsible for initiation of the pathological process can be introduced through the airways and the circulation, or can occur as a result of sensitisation. Consequently, the mechanisms underlying disease progression will be influenced by the causative event, as well as by the host and the environment. These mechanisms are developed through interactions of multiple pathways.

Based on results from experimental models and patient lung tissue analysis, it is proposed that injury of the respiratory epithelium is the key determinant of the disorders. Repeated multi-focal epithelial micro-injury and/or delayed surface regeneration lead to epithelial cell apoptosis and altered epithelial–mesenchymal interactions, with consequently disturbed epithelium homeostasis, dysregulated inflammatory response and lung remodelling.

The mechanisms underlying disease development are dependent on the type of DPLD, with the common basis being the interaction between injurious environmental triggers (which include oxidants and toxic agents, immune complexes, viruses and gastro-oesophageal reflux) and genetic predisposition.

Genetic defects of the surfactant system are increasingly described in paediatric DPLD. They include variations in genes encoding the surfactant protein (SP)-B (*SFTPB*), SP-C (*SFTPC*), ATP-binding cassette, sub-family A, member 3 (ABCA3) and the thyroid transcription factor (TTF)-1. More than 30 *SFTPB* mutations have been identified among patients with a congenital deficiency in SP-B. For *SFTPC*, at least 35 mutations have been reported, localised primarily in the COOH- terminal Brichos domain. Alterations in this domain can lead to diseases *via* mechanisms related to abnormal protein processing and cell toxicity. Recently, several studies have described genetic variations of *ABCA3* in DPLD, with the information that ABCA3 plays an important role in the transport of surfactant lipids into lamellar bodies. Another molecular contributor of surfactant homeostasis is TTF-1, a regulator of transcription for SP-B and SP-C. Other genetic factors/predispositions currently being discussed include genes associated with lung development and embryonic pathways, and those involved in the telomerase system. Telomerases are important regulators of the re-population of the damaged epithelium, partly through activation and proliferation of tissue-resident stem cells and their differentiation leading to replacement of the injured cells. Telomere shortening has been linked to decreased activity of telomerase and a reduced capacity for stem cell renewal. Several studies have also indicated that telomerase is mainly expressed during lung development with a peak expression before birth followed by a decrease to nearly undetectable levels in mature alveolar epithelium. Interestingly, exposure of normal quiescent alveolar cells to injury induces induction of telomerase expression and activity. The contribution of telomerase mutation and/or dysfunction in the progression of paediatric DPLD remains to be explored.

DPLD seems to be observed less frequently in children than in adults. In addition, the overall outcome and prognosis of the disease are thought to be less severe in paediatric patients. These differences may be explained by the types of initial injury (which might not be similar due to changes in the host environment), as well as modifications of the process of wound

healing after injury with age. Recent experimental studies have shown that a single episode of lung injury by either bleomycin or virus can induce pulmonary fibrosis only in aged wild-type mice and not in young animals, supporting the view that age-related physiological changes contribute to distinct disease expressions. Several factors may participate in the altered response to wound with ageing. One of these is the progressive modification in cell renewal capacity due to increased epithelial cell apoptosis and accumulation of senescent stem cells. Apoptosis is necessary for the removal of inflammatory cells following injury, but this process requires a complex balance between the various parenchyma cell types. In several models of lung fibrosis, an abnormal pattern of enhanced apoptosis of alveolar epithelial cells in combination with a decreased capacity of fibroblast to apoptosis has been documented, leading to insufficient surface re-population and fibrotic tissue development. Studies of the molecular mechanisms have recently led to targeting of the endoplasmic reticulum and the transforming growth factor (TGF)-β pathways. Dysregulation of these pathways is increasingly observed in ageing tissues with abnormal scar formation. Among the other contributors to altered healing with ageing are the increased burden of oxidative stress and epigenetic changes. Several recent studies tend to suggest that ageing is associated with a general relaxation of epigenetic control, including progressive changes in DNA methylation and histone modifications, with consequently impaired renewal capacity of the stem/progenitor cells of the lung parenchyma.

Clinical approach and diagnosis

The number of separate disorders under the DPLD umbrella implicates selected investigation strategies. However, despite the differences in causes and outcomes, the clinical presentation of the majority of DPLD is globally similar. Therefore, a two-step diagnosis approach is required:

- Step 1: diagnosis of DPLD "syndrome",
- Step 2: diagnosis of specific DPLD.

Diagnosis of DPLD "syndrome"

The diagnosis of DPLD is established on presenting history and clinical, radiological and functional findings. Major criteria include dyspnoea, diffuse infiltrates on chest radiographs and abnormal pulmonary function tests (PFTs) with restrictive ventilatory defect and/or impaired gas exchange with hypoxaemia.

The presenting clinical manifestations are often subtle and nonspecific. The onset of symptoms is, in most cases, insidious and many children may have had symptoms for months before the diagnosis of DPLD is confirmed. Common symptoms at presentation include:

- tachypnoea/dyspnoea (observed in 80% of patients),
- cough (present in almost 75% of the patients),
- exercise limitation,
- frequent respiratory infections.

Failure to thrive (37%), tiring during feeding and weight loss are also common symptoms, mainly in young patients. Unexplained fever is also reported in infants.

The past medical history should be deeply reviewed for precipitating factors such as feeding history, infections or exposure to environmental agents and drugs. In addition, family history needs to be investigated for relatives or siblings with similar lung conditions.

The frequent clinical findings are inspiratory crackles, tachypnoea and retraction. In a child with a normal birth history, these are strongly suggestive of DPLD. Other findings observed in older patients include finger clubbing and cyanosis during exercise or at rest. Depending on the types of DPLD, associated nonrespiratory symptoms may be observed, such as cutaneous rashes, joint manifestations, uveitis and recurrent fever in situations of collagen–vascular disorders.

Chest imaging is an essential contributor for the diagnosis. Plain radiographs are usually performed at first presentation. In almost all

cases, abnormalities are documented but the information provided is often limited and the key chest imaging tool for diagnosis is HRCT. The most common HRCT feature of paediatric DPLD is widespread ground-glass attenuation, with some observations of intralobular lines and irregular interlobular septal thickening. Large subpleural air cysts in the upper lobes adjacent to areas of ground-glass opacities are also reported in young patients (fig. 1). These cysts are interpreted as paraseptal or irregular emphysema. HRCT is useful not only for diagnosis, but also for selection of lung area to be biopsied.

PFT represents a useful investigation for both the diagnosis and the management of DPLD in children and adolescents. In preschool children, the techniques currently available are limited. Common pulmonary function abnormalities reflect a restrictive ventilatory defect with reduced lung compliance and decreased lung volumes. Vital capacity (VC) is variably diminished and the decrease in TLC in general is relatively less than in VC. Functional residual capacity (FRC) is also reduced but relatively less than VC and TLC, and residual volume (RV) is generally preserved; thus, the ratios of FRC/TLC and RV/TLC are often increased. Airway involvement is observed in only a minority of patients. T_{LCO} is often markedly reduced and may be abnormal before any radiological findings. However, T_{LCO} corrected for lung volume may also be normal in many children. Hypoxaemia,

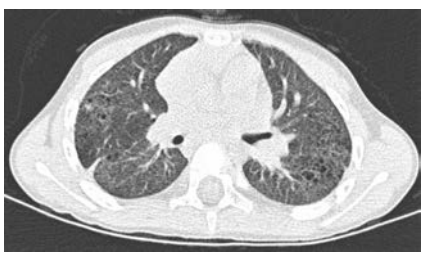

Figure 1. HRCT scan of a 2-year-old girl with surfactant protein C deficiency (I73T mutation in SFTPC *gene). The scan shows diffuse ground-glass attenuations with parenchymal cysts and interlobular septal thickening.*

defined by a reduced resting S_{aO_2} or a reduced resting P_{aO_2}, is often present. Hypercapnia occurs only late in the disease course. During exercise the previously described dysfunctions become even more pronounced, and gas exchange during exercise might be a more consistent and sensitive indicator of early disease.

Bronchoalveolar lavage (BAL) and lung tissue analysis are not commonly proposed in the first-step diagnostic approach. Besides infections, BAL can be of diagnostic value in specific situations, which include pulmonary alveolar haemorrhage, Langerhans cell histiocytosis, lipid disorders with lung involvement, or alveolar proteinosis. In other pathological situations, BAL can usefully serve to direct further investigations, by providing specimens for cytological examination, microbial cultures and molecular analysis.

Histological evaluation of lung tissue usually represents the final step in a series of diagnostic approaches. Different methods of biopsy are reported, based on expertise of the surgical teams and the balance between procedure invasiveness and the potential for obtaining adequate and sufficient tissue material for diagnosis. The techniques of choice are open lung biopsy and video-assisted thoracoscopy biopsy. The other methods, such as transbronchial lung biopsy, are less frequently proposed. The lung histological patterns observed in various forms of DPLD have been reviewed in several reports. The most common abnormalities include thickening of alveolar interstitial walls, accumulation of inflammatory cells, fibrotic components, epithelial cell hyperplasia, and alveolar spaces filled with inflammatory cells, hyaline membranes containing surfactant proteins or cellular debris.

Specific diagnosis of DPLD and classification

There have been many different approaches to the classification of paediatric DPLD; several of them are now being reconsidered. It is believed that some forms are more prevalent in very young children. However,

increasing reports in older patients and adults have documented genetic causes previously documented in infants, such as mutations in the genes encoding proteins of the surfactant system. In addition, along with the continuous improvement of investigation procedures, diseases associated with lung parenchyma structural abnormalities have been reported in patients beyond infancy. Another important issue relates to the inclusion of some forms of bronchopulmonary dysplasia (BPD) in the list of causes. The debate, with the expertise of clinicians and pathologists, is still ongoing. Indeed, BPD may favour repeated insults of the lung parenchyma with delayed surface regeneration early in life. Also, the question of the role of chronic aspiration syndromes as a causal or precipiting factor is increasingly being addressed and will require further prospective studies.

From a clinical point of view, a step-by-step aetiological search is critical, starting with a clinical evaluation requiring careful attention to exposure and environment, systemic manifestations and family disorders. This clinical approach will lead to determining the specific investigations, which will be performed according to the following grouping:

- exposure-related DPLD;
- systemic disease-associated DPLD;
- lung-restricted DPLD;
- DPLD specific to infancy (table 1).

Exposure-related disease refers to diseases caused by a sufficient level of exposure (dose) to components with target organ contact, and subsequent biologic changes and clinical expression. Many agents have been associated with pulmonary complications of various types, including DPLD. In children, this diagnosis is certainly underestimated, as paediatricians do not usually have the expertise necessary to obtain an environmental history. The diagnoses most commonly reported include hypersensitivity pneumonitis, a cell-mediated immune reaction to inhaled antigens in susceptible persons, *e.g.* bird fancier's diseases, humidifier lung diseases and chemical lung diseases. Laboratory tests focus on the search for serum-precipitating IgG antibodies against the offending antigen. Other exposure-related diseases are those caused by radiation and drugs including anti-inflammatory agents (*e.g.* aspirin and etanercept), immunosuppressive and chemotherapeutic agents (*e.g.* azathioprine, methotrexate and cyclophosphamide), and illicit drugs in teenagers.

Systemic disease-associated DPLD comprises a complex group of disorders requiring specific investigations oriented by the clinical expression. They mainly include:

- granulomatous diseases,
- metabolic disorders,
- connective tissues disorders (CTD),
- pulmonary vasculitis,
- Langerhans cell histiocytosis.

In situations of granulomatous diseases, the discussed diagnoses are mainly sarcoidosis, infections and disorders of neutrophil function. Sarcoidosis is relatively uncommon among children. Its diagnosis is based on a combination of suggestive clinical features, with histologically documented noncaseating granuloma, in the absence of other known causes of granuloma formation. Its incidence seems to be influenced by age, race and geographic localisation. Most of the cases in children occur in pre-adolescents and adolescents, with more observations documented in Black children than Caucasian children. DPLD in metabolic disorders are reported in lysosomal diseases such as Gaucher's disease, Niemann–Pick diseases and Hermansky–Pudlak syndrome. CTD refers to any disease that has the connective tissues of the body as a primary target of pathology and whose development implicates genetic, constitutional and environmental elements. The main disorders to be considered during childhood are rheumatoid arthritis, systemic sclerosis and systemic lupus erythematosus. Pulmonary vasculitis is observed in vasculitic syndromes that preferentially affect small vessels (arterioles, venules, and capillaries): anti-neutrophil cytoplasmic antibody-associated vasculitis (granulomatosis with polyangiitis

Table 1. DPLD diagnosis in children

Exposure-related DPLD
Hypersensitivity pneumonitis
Radiation exposure
Drugs
Systemic disease-associated DPLD
Granulomatous diseases
Metabolic disorders
Connective tissue disorders
Pulmonary vasculitis
Langerhans cell histiocytosis
DPLD-associated with other organ diseases
Lung-restricted DPLD
Infections
Surfactant disorders
Pulmonary alveolar proteinosis
Diffuse alveolar haemorrhage
Eosinophilic lung diseases
Diffuse developmental disorders
Lymphatic system disorders
DPLD specific to infancy
Neuroendocrine cell hyperplasia
Pulmonary interstitial glycogenosis
Chronic pneumonitis in infancy

(Wegener's granulomatosis), Churg–Strauss syndrome and microscopic polyangitis); anti-glomerular basement membrane disease; Henoch–Schönlein purpura and cryoglobulinemia vasculitis.

In addition to Langerhans cell histiocytosis, other causes of systemic disease-associated DPLD include inflammatory bowel diseases (Crohn's disease), liver and neurocutaneous disorders, and amyloidosis.

Lung-restricted DPLD include disorders primarily affecting the components of the distal parenchyma. The main diagnosis is infections, surfactant disorders, pulmonary alveolar proteinosis, diffuse alveolar haemorrhage and eosinophilic lung diseases, as well as diffuse developmental disorders and lymphatic system dysfunction. As mentioned previously, some forms of chronic neonatal lung diseases associated with BPD and pulmonary hypertension may also be discussed.

The role of infections, mainly viral, in DPLD is sustained by a number of human and experimental studies documenting targeted injury of the alveolar epithelium. The list of viruses comprises adenovirus, members of the herpes virus family (Epstein–Barrr virus and cytomegalovirus) and respiratory syncytial virus. Among the other pathogens, *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* are currently drawing increasing consideration.

Surfactant disorders include genetic surfactant protein disorders and pulmonary alveolar proteinosis. Mutations in *SFTPC* are currently the main reported genetic disorders with the most prevalent mutation being I73T (c.218 T>C). The phenotype associated with *SFTPC* mutations is extremely heterogeneous, from neonatal fatal respiratory failure to DPLD children and adults. The deficiency in SP-B is a rare autosomal recessive condition known to be mainly responsible for lethal neonatal respiratory distress. Recessive mutations in the *ABCA3* gene were first attributed to fatal respiratory failure in term neonates but are increasingly being recognised as a cause of DPLD in older children and young adults. Mutations in the *TTF-1* gene are associated with "brain-lung-thyroid syndrome" which combines congenital hypothyridism, neurological symptoms (hypotonia and chorea) and lung diseases.

Pulmonary alveolar proteinosis is a rare lung disorder characterised by alveolar filling with floccular material derived from surfactant phospholipids and protein components. Pulmonary alveolar proteinosis is described as primary or secondary to lung infections, haematological malignancies and inhalation of mineral dusts. Abnormalities in granulocyte/macrophage colony-stimulating factor are increasingly reported in pulmonary alveolar proteinosis pathogenesis.

Diffuse alveolar haemorrhage syndromes are caused by the disruption of alveolar–capillary basement membrane as a consequence of injury to the alveolar septal capillaries, and less commonly to the arterioles and veinules. The hallmarks are intra-alveolar accumulation of red blood cells, fibrin and haemosiderin-laden macrophages. In approximately one-third of patients, diffuse alveolar haemorrhage does not manifest haemoptysis, and BAL can be extremely helpful by documenting the presence of siderophages or red blood cells within the alveoli. Diffuse alveolar haemorrhage can be observed in the absence of systemic diseases or in the context of other diseases, which include pulmonary hypertension, congenital heart diseases, pulmonary veno-occlusive disease, arteriovenous malformations, hereditary haemorrhagic telangiectasia, coagulation disorders and coeliac disease.

Eosinophilic lung diseases constitute a diverse group of disorders of various origins. The diagnosis is suggested by increased peripheral eosinophilia and confirmed by the presence of eosinophils in BAL and/or lung tissue. Eosinophilic lung diseases of known cause in children mainly include allergic bronchopulmonary aspergillosis, parasitic infections and drug reactions. Eosinophilic lung diseases of unknown cause comprise Loeffler syndrome (characterised by migrating pulmonary opacities), acute eosinophilic pneumonia and chronic eosinophilic pneumonia.

Among the diffuse developmental disorders is alveolar capillary dysplasia, a rare disorder presenting with persistent pulmonary hypertension of the newborn. A definitive diagnosis can only be made by histological examination, documenting poor capillary apposition and density, allied with medial arterial hypertrophy and misalignment of pulmonary vessels. Interestingly, capillary proliferation in the alveolar wall has been reported in hereditary haemorrhagic telangiectasia.

DPLD specific to infancy includes neuroendocrine cell hyperplasia, pulmonary interstitial glycogenosis and chronic pneumonitis in infancy. Neuroendocrine cell hyperplasia of infancy is a non-lethal disease characterised by tachypnoea without respiratory failure. On lung biopsy, the histological abnormality is hyperplasia of neuroendocrine cells within bronchioles documented by bombesin immunohistochemistry. In some cases, the follow-up reveals the persistence of tachypnoea and oxygen requirement for several months. Usually, there is a good prognosis. Pulmonary interstitial glycogenosis is also a non-lethal disease reported in neonates with respiratory distress syndrome that develops shortly after birth. The histological hallmark is the accumulation of monoparticulate glycogen in the interstitial cells on lung biopsy. It is thought to represent a maturation defect of interstitial cells that causes them to accumulate glycogen within their cytoplasm.

Treatment strategies and outcome

The diversity of DPLD conditions and the lack of randomised clinical trials in groups of well-phenotyped paediatric patients explain the difficulty to propose treatment strategies. Longitudinal care of these children needs to be organised in specialised centres. In this section, general management with the most usual pharmacological therapies is indicated.

General measures are essential and mainly include administration of oxygen for chronic hypoxaemia and maintenance of nutrition with an adequate energy intake. Immunisation with the influenza vaccine on an annual basis is recommended along with other routine immunisations against major respiratory pathogens. In addition, aggressive treatment of intercurrent infections and strict avoidance of tobacco smoke and other air pollutants are strongly recommended.

Pharmacological therapy includes anti-inflammatory and immunosuppressive molecules. Steroids are the preferred choice, administered orally and/or intravenously. Oral prednisolone is most commonly administered at a dose of 1–2 $mg \cdot kg^{-1} \cdot day^{-1}$. Children with significant disease are best treated with pulsed methylprednisolone, at least initially. This is usually given at a dose

of 10–30 mg·kg^{-1}·day^{-1} for 3 consecutive days at monthly intervals. When the disease is under control, the dosage of methylprednisolone can be reduced or the time between cycles can be spaced out. An alternative to steroids is hydroxychloroquine with a recommended dose of 6–10 mg·kg^{-1}·day^{-1}. Individual case reports have described a response to hydroxychloroquine, even in the presence of steroid resistance. Some groups have proposed to base the decision as to which agent to use on the lung biopsy findings, with a preference for steroids in the case of large amounts of desquamation and inflammation, but for hydroxychloroquine if increased amounts of collagen representing pre-fibrotic change are found. However, as documented in the European Respiratory Society Task Force on paediatric ILD, the preferred choice between steroids or hydroxychloroquine in children is highly dependent on the expertise of the centre in charge of the patient, and does not seem to be oriented by the histopathological pattern. In the case of severe disease, steroids and hydroxychloroquine may be associated. In situations of inefficiency of steroids and hydroxychloroquine, other immunosuppressive or cytotoxic agents, such as azathioprine, cyclophosphamide, cyclosporine, or methotrexate, may be used.

Other therapeutic options include macrolides. Indeed, these antibiotics have been shown to display a number of anti-inflammatory and immunomodulatory actions. Of interest is the ability of macrolides to accumulate in parenchymal cells including epithelial cells and phagocytes. New therapeutic strategies currently proposed in adult patients target fibrogenic cytokines. Antagonists to TGF-β include pirfenidone and decorin. The use of molecules directed against tumour necrosis factor (TNF)-α, such as the soluble TNF-α receptor agent etanercept, is also under investigation. In the future, it is probable that an expanding number of molecules aimed at favouring alveolar surface regeneration and repair through activation and proliferation of tissue-resident (progenitor) cells will be discovered.

Lung transplantation is a viable option in children of all ages, even in young infants, and lung or heart–lung transplantation may be offered as an ultimate therapy for end-stage DPLD. The outcome and survival do not seem to be different from those reported in other pulmonary conditions. Among other specific treatments is whole lung lavage in situations of pulmonary alveolar proteinosis.

The prognosis of children with DPLD is extremely variable. It is highly dependent on the cause, the expertise and environment of the patient care system, and the individual response to treatment. It is also very difficult to predict: some children with relatively severe fibrosis on lung biopsy make good progress, whereas others with mild desquamation have a poor outcome. Overall, a favourable response to anti-inflammatory therapy can be expected in almost two-thirds of cases, although significant sequelae, such as limited exercise tolerance or the need for long-term oxygen therapy, are often observed. Reported mortality rates are approximately 15%.

Conclusion

DPLD in children comprises a large spectrum of disorders, resulting from interactions between injurious environmental triggers and genetic predisposition. Although much effort has been made in the clinical approach, there is still a lack in disease characterisation, identification of specific phenotypes linked to documented molecular mechanisms, and proposals of novel therapeutic interventions. The current development of international collaborations, including European and North American teams, with the aim of sharing cohorts of well-phenotyped paediatric patients is a major opportunity to efficiently progress in DPLD understanding and management.

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Surfactant dysfunction and alveolar proteinosis

Armin Irnstetter, Carolin Kröner, Ralf Zarbock and Matthias Griese

Pulmonary surfactant is a complex mixture of the surfactant proteins (SP)-A, B, C and D and lipids, and a is key component of alveolar integrity and function. These proteins are essential for lowering surface tension (mainly SP-B/C) and play a major role in innate immunity (mainly SP-A/D).

Key points

- Two major groups of disorders are associated with the surfactant system: surfactant dysfunction mutations and PAP.
- Surfactant dysfunction mutations include diseases caused by mutations in the genes coding for SP-B, SP-C, the lipid transporter ABCA3 and the transcription factor TTF1.
- Although these entities may show a PAP-like pattern on histology, the extent of alveolar filling is much less than in PAP and this term should be avoided when naming the surfactant dysfunction mutations.
- Hereditary deficiency of the α-chain of the receptor for GM-CSF is responsible for increased accumulation of surfactant in the alveolar space and resulting PAP.
- Surfactant dysfunction mutations may present at birth as respiratory distress syndrome or later in infancy as chronic dyspnoea and hypoxia (chILD syndrome), whereas mutations in the α-chain of the receptor for GM-CSF present only as chILD syndrome.

Detailed molecular knowledge of these components led to the discovery of primary disorders of the surfactant system. Deficiencies of SP-B and SP-C, the lipid transporter ABCA3 located in type II pneumocytes, and the transcription factor TTF1, which regulates expression of SP-B and SP-C, lead to clinical entities that are summarised here as surfactant dysfunction mutations. On histopathological examination characteristic features include interstitial widening, hyperplasia of type II alveolar epithelial cells and proteinaceous material in the distal airspaces. Of interest, association with a deficiency of surfactant or its components, such as SP-B-deficiency and other surfactant deficiency syndromes, may show a pulmonary alveolar proteinosis (PAP)-like pattern on histology. This accumulation of surfactant is the result of an impaired surfactant metabolism leading to local surfactant accumulation; the extent of alveolar filling is much less than in PAP. In the past this has contributed to some confusion and we suggest not using the term "congenital alveolar proteinosis" to describe newborns with surfactant dysfunction.

In contrast to a deficiency of surfactant and its components, other clinical entities lead to a surplus of surfactant, because its removal from the alveolar space is deficient. Such accumulation of surfactant material in the alveolar space is called PAP. The primary pathomechanism responsible for PAP in children is hereditary deficiency of the α-chain of the receptor for granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF is responsible for the metabolism and degradation of surfactant

by alveolar macrophages. Disruption of its receptor leads to PAP. Several other diseases are known to cause PAP. These, as well as secondary surfactant deficiency syndromes, have to be included in the differential diagnosis of patients with disturbance of the surfactant system.

Surfactant dysfunction mutations

Deficiencies of SP-B and SP-C, the lipid transporter ABCA3 located in type II pneumocytes, and the transcription factor TTF1 are caused by mutations in the *SFTPB*-, *SFTBC*-, *ABCA3*- and *NKX2-1* genes. The resulting diffuse parenchymal lung diseases clinically present with two major phenotypes, although other modes of presentation (*e.g.* as an asthma syndrome) have also been observed.

Clinical presentation At birth children with dysfunction mutations typically manifest with idiopathic respiratory distress syndrome or idiopathic pulmonary hypertension without being preterm or having other explanations for their clinical manifestations (*i.e.* infections, congenital heart defects, blood vessel abnormalities or other anatomic abnormalities). The pulmonary symptoms are often so severe that the children require mechanical ventilation. Depending on the underlying mutation the clinical course is variable, ranging from rapid disease progression and death to mild forms. Transient response to medication, such as systemic steroids or administration of surfactant, may be observed.

The other clinical manifestation, the so-called chILD-syndrome (Children's Interstitial Lung Disease), is characterised by an insidious start of dyspnoea, dry coughing, fine crackles and failure to thrive. Such clinical symptoms together with a familial history of fatal or chronic lung diseases or presence of consanguinity must lead to specific genetic testing for the conditions that are potentially disease causing.

If the diagnosis cannot be established, open or thoracoscopic lung biopsy should be performed. The lung biopsy should be evaluated by an experienced histopathologist.

Clinical course and therapeutic strategies *SP-B deficiency*: Two decades ago Nogee *et al.* (1994), first described a mutation in SP-B causing a severe neonatal respiratory distress syndrome in term infants ultimately leading to death. SP-B deficiency is a very rare disease affecting approximately one child in every 1 000 000 live births. The mode of inheritance is autosomal recessive, the most common mutation is the insertion of two amino acids (121ins2). All mutations lead to an absolute or partial loss of SP-B.

The diagnosis is confirmed by sequencing of SP-B (*SFTPB*). Currently, there are no therapeutic options, except lung transplantation. Experimental therapy with inhaled RNA was shown to be successful in animals. Palliative therapy is indicated for children with classic mutation.

SP-C deficiency: Inheritance of this disease, which occurs more frequently than SP-B deficiency, is autosomal dominant. The clinical syndromes described above will lead to sequencing of the candidate gene. In early stages of the disease the radiological findings are similar to those in PAP with the typical alveolar filling pattern and ground-glass opacities (fig. 1). Further in the disease course increased interstitial markings are seen with distinct triangular shaped subpleural or interlobar septa, which develop into multiple subpleural, interstitial bullae. If biopsy is performed, an experienced paediatric pathologist should evaluate the specimen in order to ensure the correct diagnosis. Therapeutic options may include anti-inflammatory therapy (corticosteroids) or treatment with hydroxychloroquine or azithromycin. Additional treatment with immunosuppressants has anecdotally been described for these and other entities. To date, no controlled trials have been performed; all treatments should be tried and assessed in the framework of a registry for ILD (www.childeu.net) in order to systematically record these rare experiences.

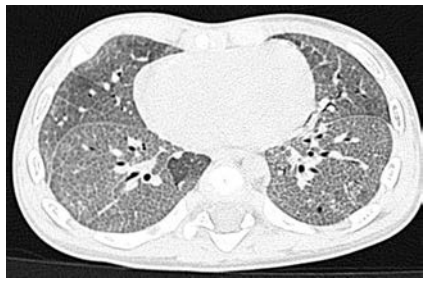

Figure 1. HRCT scan of an infant with SP-C deficiency and presentation of chILD syndrome at 6 months of age. Note the crazy paving pattern in both lower lobes.

ABCA3-transporter deficiency: ABCA3 is a lipid transfer protein which is essential for the biogenesis of lamellar bodies of type 2-pneumocytes. More than 100 different mutations with autosomal recessive inheritance mode have been described. As heterozygous frequency in the population is relatively high, ABCA3-transporter deficiency represents one of the most frequent genetic changes detected in interstitial lung diseases in children and adolescents. The clinical course and prognosis are highly variable depending on the mutations present, may begin at birth or later, and are difficult to foresee. Effective therapeutic interventions should be determined empirically, evaluated systematically and registered prospectively. In addition to diverse systemic steroid therapy regimes, hydroxychloroquine or azithromycin are used.

Brain-thyroid-lung syndrome: this disease, also called thyroid transcription factor-1 deficiency-syndrome or NKX2-1, is caused by haplo-insufficiency of the transcription factor TTF1. This factor modulates the expression of SP-B, SP-C and ABCA3 in the lung and other proteins in the thyroid and basal ganglia. The clinical trials of congenital hypothyroidism, neurological syndromes (muscular hypotonia, which develops to benign hereditary chorea after infancy) and symptoms of chronic respiratory insufficiency represent the full disease spectrum of pulmonary symptoms ranging from neonatal respiratory distress syndrome to typical manifestations of chILD syndrome. Furthermore, recurrent bronchopulmonary infections are seen in childhood. About 40% of the cases present with respiratory symptoms alone. To date there is still relatively little experience concerning the treatment of the disease. Thus, empiric therapy should be evaluated and registered prospectively in order to establish and compare different therapeutic options.

Pulmonary alveolar proteinosis

PAP represents a group of rare diseases that are characterised by an accumulation of periodic acid–Schiff (PAS) reaction-positive granular eosinophilic material in the alveolar space. As mentioned previously, PAP is a histological diagnosis. In paediatrics, the classic form of PAP is due to GM-CSF-receptor-α deficiency. The other forms must be differentiated and include a large number of causes leading to this group of diseases (table 1). An imbalance between the synthesis and secretion of surfactant from type II pneumocytes, its intra-alveolar metabolism and surfactant recycling, and elimination, mainly by macrophages, leads to the accumulation of surfactant material in the alveolar space. GM-CSF is a key regulatory cytokine for the catabolism of surfactant by alveolar macrophages. Although other primary forms of PAP in paediatrics have been described, the underlying mutations have yet to be characterised.

Clinical manifestations and diagnosis The alveolar accumulation of surfactant leads to impaired gas exchange, detected early during exercise. Carbon dioxide transfer is usually not affected. Therefore, the clinical course typically starts insidiously at various ages ranging from infancy to young adulthood. The diagnosis is frequently made in the context of an acute respiratory infection that does not resolve appropriately or has a very severe course. Primary presenting symptoms include exercise-induced non-productive cough, at times developing into coughing with expectoration of whitish surfactant material. Other

Table 1. Conditions associated with PAP due to a reduction in the number and function of alveolar macrophages

Autoimmune PAP due to GM-CSF autoantibodies that block macrophages (overall most frequent form >90%, especially in adults)
Hereditary GM-CSF receptor α/β chain mutations
Inhalation exposure to aluminium, cement, silica, titanium, indium, tin, organic dust, sawdust, fertiliser/agricultural dust, bakery flour, fumes, gasoline, chlorine and petroleum
Infections including *Cytomegalovirus*, *Mycobacterium tuberculosis*, *Nocardia*, *Pneumocystis jirovecii*, HIV
Haematological disorders including myelodysplastic syndrome, acute lymphatic leukaemia, acute myeloid leukaemia, chronic myeloid leukaemia, hairy cell leukaemia, Hodgkin's and non-Hodgkin's lymphoma, multiple myeloma, essential thrombocythemia, polycythemia vera, amyloidosis and Fanconi's anaemia
Other malignancies including adenocarcinoma, glioblastoma and melanoma
Immunological diseases including monoclonal gammopathy, selective IgA deficiency and severe combined immunodeficiency
Metabolic diseases such as Niemann–Pick disease type C2 and type B, and lysinuric protein intolerance
Others including membranous nephropathy, dermatomyositis and lung transplantation

Data from Bonella *et al.* (2012).

symptoms include exercise intolerance, weight loss or failure to thrive. The physical examination may reveal dyspnoea with intercostal retractions, digital clubbing and sometimes fine crackles and reduced breathing sounds. Chest radiographs typically show bilateral alveolar filling pattern, which are often more prominent in the perihilar regions, the so-called bat wing pattern. HRCT initially shows a diffuse distribution of interstitial markings and, subsequently, the so-called crazy paving pattern. The most common abnormalities in pulmonary function tests are significant restrictive patterns and a reduction in the diffusion capacity. Bronchoalveolar lavage (BAL) fluids show typically extracellular PAS-positive material and frequently oval bodies. Diagnosis is made genetically or by open lung biopsy, because in infants and children the typical BAL fluid features are sometimes not as prominent. GM-CSF auto-antibodies are rarely elevated in children, but should be assessed to exclude this condition.

Clinical course and therapeutic strategies *GM-CSF-receptor-α mutations*: The age of diagnosis ranges from 2 to 11 years. Patients may have no clinical symptoms (diagnosed as siblings of affected children) or suffer from dyspnoea and oxygen supplementation, initially during exercise and later at rest. Chest CT scans showed abnormalities in all cases and lavage samples suggest PAP due to whitish recovered fluid in some cases. GM-CSF auto-antibodies are usually not detectable; serum levels of GM-CSF are elevated.

Whole lung lavage represents the most important therapeutic option which has clearly shown to be effective. In older children, a double lumen endotracheal tube is used to ventilate one lung while lavaging the other. In young children, where this procedure is not feasible, other strategies are applied, such as using an inflatable catheter. Lavaging of both lungs is performed sequentially using total volumes of 50–200 $mL \cdot kg^{-1}$ body weight of normal saline.

The time required for lavaging one lung is ~4–6 h. If the child is in a good clinical condition, lavaging the other lung is possible in the same session. It is important to take care to ensure a balanced recovery and avoid electrolyte displacements.

Injection or inhalation of recombinant GM-CSF is ineffective and therefore not recommended. In several cases the patients have to undergo whole lung lavage at regular intervals for long periods in order to enable physiologic gas exchange and development. Such a therapy should be performed in specialised centres to offer a good long-term prognosis.

Differential diagnosis of PAP in children

Niemann–Pick disease type C2: This disease often manifests with respiratory distress during infancy and childhood. The average age of death from respiratory insufficiency is 8 months. The accumulation of PAS-positive lipid material which, in contrast to normal surfactant, also contains high concentrations of ceramids, glucosylceramids and SP-A, is at the centre of the respiratory distress syndrome. Furthermore, the widened interstitium is characterised by progressive fibrosis und lipoid pneumonia. Therapeutically whole lung lavages have been tried without success at late disease stages.

Lysinuric protein intolerance: This is an autosomal recessive disorder caused by defective plasma membrane transport of cationic amino acids in epithelial cells of the gastrointestinal tract and kidneys, due to a mutation in the SLC7A7 gene. So far, most cases have been reported in Finland, Italy and Japan. While major focus is put on renal and gastrointestinal manifestations (*e.g.* pancreas insufficiency), pulmonary affection in the sense of interstitial lung disease is highly variable and can lead to respiratory insufficiency. In these cases, this is often due to PAP, probably caused by reduced expression of SLC7A7 by GM-CSF. A therapeutic approach that has been tried with variable success includes whole lung lavages, inhaled GM-CSF or lung transplantation. However, recurrence of PAP after lung transplantation has been reported.

Many other conditions associated with alveolar proteinosis must be differentiated; almost all are due to a reduced number or function of alveolar macrophages (table 1).

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Pulmonary vascular disorders

Andrea McKee and Andrew Bush

The cardinal manifestation of pulmonary vascular disorders is pulmonary hypertension. The international definition of pulmonary hypertension is a pulmonary arterial pressure (PAP) >25 mmHg. For pre-capillary pulmonary hypertension, pulmonary capillary wedge pressure must be <15 mmHg and cardiac output normal or reduced. Post-capillary pulmonary hypertension (usually due to left heart disease) wedge pressure is >5 mmHg and cardiac output normal or reduced. If the transpulmonary pressure gradient is >12 mmHg with an elevated wedge pressure, then a reactive component is present. There are no data to define pulmonary hypertension on exercise.

Key points

- The symptoms of pulmonary hypertension are nonspecific and the possibility of the condition should always be remembered. Syncope on exercise should never be ignored.
- If pulmonary hypertension is secondary to lung disease, this is usually obvious from the chest radiograph.
- In a child with pulmonary hypertension and a normal chest radiograph, remember OSA and occult interstitial lung disease are possible causes.
- Children with pulmonary hypertension should be referred to specialist centres for consideration of emerging therapies.

Classification of pulmonary hypertension in children

There are significant differences in the pathophysiology of pulmonary hypertension in children and adults. Abnormalities of growth and development are more likely in paediatric cases; so, for example, infants with pulmonary hypertension may have failed to reduce the antenatally physiologically high pulmonary vascular resistance (PVR) during the post-natal period. Abnormalities of vasculogenesis and angiogenesis have increasingly been implicated in paediatric pulmonary hypertension. A recent proposed classification of pulmonary hypertension in children is given in table 1; this differs from the World Health Organization (WHO) classification (table 2), which has been criticised as less applicable to children (*e.g.* pulmonary hypertension secondary to bronchopulmonary dysplasia and congenital diaphragmatic hernia do not fit neatly into the WHO classification). Pulmonary hypertension does not, of itself, mean the child has pulmonary vascular disease; a high pulmonary venous pressure and a high pulmonary blood flow can both elevate PAP without there necessarily being any pulmonary vascular disease. Although the WHO definition does not include measurement of PVR (pulmonary blood flow/transpulmonary vascular pressure gradient; normal range <3 Wood units), in paediatric practice, it is wise to include a PVR >3 Wood units as part of the definition, particularly in children with left-to-right shunts and anaemia. Functional classes of

Table 1. A practical approach to pulmonary hypertension in children: 10 basic categories of paediatric pulmonary hypertensive disease

Pre-natal or developmental pulmonary hypertensive vascular disease
Perinatal pulmonary vascular maladaptation
Paediatric cardiovascular disease
Bronchopulmonary dysplasia
Isolated paediatric pulmonary hypertensive vascular disease (isolated paediatric pulmonary arterial hypertension)
Multifactorial pulmonary vascular disease in congenital malformation syndromes
Paediatric lung disease
Paediatric thromboembolic disease
Paediatric hypobaric hypoxic exposure
Pulmonary vascular disease associated with other system disorders

severity are given in table 3; these are largely adult based and there is a need for a specific paediatric classification.

Epidemiology

Pulmonary hypertension may present at any age. Paediatric pulmonary hypertension is ceasing to be an orphan disease; there are increasing numbers of national and international specifically paediatric registries, which have increased our information base. The incidence and point prevalence of isolated pulmonary hypertension are less than one and five cases per million children, respectively. The number of cases of pulmonary hypertension secondary to congenital heart disease is of a similar order of magnitude. The prevalence of pulmonary hypertension in bronchopulmonary dysplasia is probably underestimated due to ascertainment bias.

Pulmonary hypertension secondary to respiratory disease is usually dominated by obvious features of the underlying cause, for example, very severe bronchiectasis in CF. The underlying mechanism is intermittent or continuous alveolar hypoxia leading to pulmonary vasoconstriction and ultimately vascular remodelling. Systemic arterial hypoxaemia in the absence of alveolar hypoxia (for example, due to multiple pulmonary arteriovenous malformations) does not lead to pulmonary hypertension. Two important ''occult'' respiratory causes of pulmonary hypertension with a normal chest radiograph are interstitial lung disease and sleep disordered breathing, usually OSA. Hence, every case of apparently idiopathic pulmonary hypertension should have these conditions excluded. The management of secondary pulmonary hypertension is largely of the underlying respiratory conditions, and this will not be discussed further. If secondary pulmonary hypertension is thought to be disproportionate to the severity of lung disease, then consideration should be given to the use of therapies used in primary pulmonary hypertension (PPH) (see later), probably best as part of a randomised controlled trial. Any child thought to have primary pulmonary vascular disease should have Eisenmenger's syndrome and other cardiological conditions excluded by a careful cardiological evaluation. The management of this latter group is usually medical in specialist paediatric cardiological centres and discussions of these conditions are beyond the scope of this chapter.

Normal pulmonary vascular development

The pulmonary arteries develop embryologically from the sixth bronchial arches. The pre-acinar vessels follow the airway development and are largely complete by the end of the first 16 weeks of pregnancy, the end of the pseudoglandular phase. Blood vessels form by

Table 2. Updated clinical classification of pulmonary hypertension (PH)

PAH
Idiopathic PAH
Heritable: *BMPR2, ALK1*, endoglin (with or without hereditary haemorrhagic telangiectasia), unknown
Drug and toxin induced
APAH: connective tissue diseases, HIV infection, portal hypertension, congenital heart disease, schistosomiasis, chronic haemolytic anaemia, persistent PH of the newborn
PVOD and/or pulmonary capillary haemangiomatosis
PH due to left heart disease
Systolic dysfunction
Diastolic dysfunction
Valvular disease
PH due to lung diseases and/or hypoxia
COPD
Interstitial lung disease
Other pulmonary diseases with mixed restrictive and obstructive pattern
Sleep disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental abnormalities
CTEPH
PH with unclear and/or multifactorial mechanisms
Haematological disorders: myeloproliferative disorders, splenectomy.
Systemic disorders, sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

PAH: pulmonary arterial hypertension; APAH: associated PAH; CTEPH: chronic thromboembolic PH. Reproduced from Simonneau *et al.* (2009) with permission from the publisher.

Table 3. Functional classes of pulmonary hypertension

Functional class	Status
I	No limitation of physical activity Ordinary activity does not cause dyspnoea, fatigue, chest pain or near syncope
II	Slight limitation of physical activity Comfortable at rest; ordinary physical activity causes undue dyspnoea, fatigue, chest pain or near syncope
III	Marked limitation of physical activity Comfortable at rest; less than ordinary physical activity causes undue dyspnoea, fatigue, chest pain or near syncope
IV	Symptomatic on any physical activity Signs of right heart failure May have dyspnoea and fatigue at rest; discomfort increased by physical activity

This classification may be more appropriate to adults; for example, adults are more prone to right heart failure earlier in the disease.

vasculogenesis (*de novo* formation of vessels in the mesenchyme) with the airways acting as a template for vascular development. Acinar vessels develop in parallel with the terminal bronchioles and alveoli. Alveolar development is largely a post-natal phenomenon and capillaries form by angiogenesis (sprouting from existing vessels). Uniquely, the lung has no function as it develops in the intrauterine environment. It is a fluid-filled, fluid-excreting organ with a very low blood flow and no role in gas exchange. At birth, the most profound adaptations must take place if the baby is to survive. The lung absorbs fluid and becomes "dry"; the alveoli expand, PVR falls and the pulmonary blood flow rises from <5% to equal that of the systemic circulation. The arterial duct and the oval foramen become functionally, and later structurally, closed. In the subsequent weeks, there is thinning of the alveolar capillary membrane and profound increases in the number of alveoli, produced by secondary septation and modulated through elastin and the retinoic acid pathways. Post-natally, alveolar development was thought to be largely complete by 2 years of life, but recent work in rhesus monkeys and also using hyperpolarised helium to measure alveolar size in humans has shown that alveolar size is largely stable during the phase of somatic growth, implying neoalveolarisation, and by implication pulmonary capillary growth, continues to puberty.

Abnormal pulmonary vascular development

Most of these conditions present to the neonatologist and are only briefly discussed here.

Persistent fetal circulation is the most dramatic example of failure of normal developmental homeostasis. Shortly after birth, the baby becomes deeply cyanosed and very difficult to oxygenate. This is a neonatal intensive care unit emergency and will not be discussed further here.

Early-onset "primary" pulmonary hypertension comprises babies presenting at a few weeks of age with very severe pulmonary hypertension for which no underlying cause is found. It is thought to be related to failure of regression of the antenatal physiologically hypertensive pulmonary circulation. Although anecdotally, some cases respond to medical management, generally the prognosis is poor.

Alveolar capillary dysplasia spectrum is an overlapping group of diseases, comprising acinar dysplasia, alveolar capillary dysplasia, and alveolar capillary dysplasia with misalignment of the pulmonary veins, considered by some to be part of the spectrum of paediatric interstitial lung disease. Mutations in the *FOXF1* (forkhead box F1) and *STRA6* (stimulated by retinoic acid 6) genes should be sought. Presentation is usually in a term baby with relentlessly progressive respiratory distress. These conditions should be distinguished from disease due to mutations in *SFTPB* (surfactant protein B), *SFTPC* (surfactant protein C), *ABCA3* (ATP-binding cassette sub-family A member 3) and *TTF1* (thyroid transcription factor 1), which may present in a similar way (see the section on Interstitial lung diseases). Diagnosis is on lung biopsy or at autopsy. There is no treatment and prognosis is poor.

Presentation of pulmonary hypertension due to pulmonary vascular disease

The symptoms of pulmonary hypertension are nonspecific and the condition can be missed initially. Breathlessness may be attributed to airway disease and early cyanosis may be difficult to detect. Syncope, particularly on exercise, is an ominous symptom that should never be ignored. Once suspected, ECG, or better echocardiography, confirms the diagnosis. If there is tricuspid or pulmonary regurgitation, PAP can be estimated reasonably accurately from the Bernoulli equation. The gold standard is right heart catheterisation, which also allows cardiac output and pulmonary capillary wedge pressure to be measured.

Primary pulmonary vascular disease

The three main causes encountered in paediatrics are PPH, pulmonary

veno-occlusive disease (PVOD) and pulmonary embolism (thrombotic and nonthrombotic). Each will be considered in turn.

Primary pulmonary hypertension is a diagnosis of exclusion, requiring the documentation of pulmonary hypertension and an elevated PVR, and the exclusion of any secondary cause of the condition (table 4). Pulmonary hypertension and other vascular disease secondary to liver disease are described in more detail in the section on Systemic disorders with lung involvement.

The pathophysiology of PPH is unclear. Important components are vasoconstriction (which may be related to potassium channel dysfunction), obstructive remodelling of the pulmonary circulation, thrombosis and inflammation. Histopathology reveals combinations of arterial medial hypertrophy, concentric laminar fibroelastosis, plexiform lesions, necrotising vasculitis and fibrosis. There may be increased neuroendocrine cell numbers and positive endothelial staining for endothelin-1 immunoreactivity. Children tend to have more medial hypertrophy, less intimal fibrosis and fewer plexiform lesions than adults. The clinical correlate may be greater pulmonary vascular reactivity and a propensity to sudden death from pulmonary hypertensive crises, especially in infants. Endothelial dysfunction manifests as reduced production of vasodilator and antiproliferative mediators, such as nitric oxide and prostacyclin, and overproduction of vasoconstrictor and pro-proliferative agents, such as endothelin-1 and thromboxane A_2, but multiple other mediators are probably involved.

Table 4. Differential diagnosis of apparent PPH

HIV infection
Substance abuse: smoking crack cocaine, amphetamine ingestion
Liver disease leading to pulmonary hypertension
Connective tissue disease, especially scleroderma
Pulmonary vasculitis
Metabolic: Gaucher disease, Niemann–Pick disease
Sarcoidosis

The most common genetic mutation is in the *BMPR2* (bone morphogenetic protein receptor II) gene, found in ~70% of familial PPH. BMPR2 is part of the transforming growth factor (TGF)-β superfamily and, among other properties, contributes to the modulation of vascular proliferation. Mutations in other receptors for these polypeptides are associated with familial pulmonary hypertension, including activin receptor-like kinase 1 (encoded by the *ALK1* gene) and endoglin, both of which are also associated with hereditary haemorrhagic telangiectasia.

Symptoms are nonspecific but fainting during exercise should always be taken seriously. Infants typically present with right heart failure and cyanosis. There may be suggestive physical signs such as a loud pulmonary component of the second heart sound, the murmurs of pulmonary or tricuspid insufficiency, a parasternal heave or, in advanced cases, the signs of right heart failure. Blood tests should be directed to eliminating any underlying cause of the pulmonary hypertension, as well as excluding thyroid disease, which is not uncommon in PHT. Elevated N-terminal pro-brain natriuretic peptide and brain natriuretic peptide have been reported in children with pulmonary hypertension, and are likely to be increasingly used in the future as biomarkers. Chest radiography may lead to suspicion of the diagnosis if there is peripheral oligaemia and enlarged central pulmonary arteries. The ECG may show signs of right ventricular hypertrophy and strain, and right atrial dilatation and right axis deviation, but these signs should not be relied upon. Echocardiography is mandatory to exclude occult cardiac disease and to estimate PAP, most easily using the Bernoulli equation, if pulmonary or tricuspid insufficiency is present. The 6-min walk test may give useful functional information. The decision to proceed to the definitive diagnostic investigation, right heart

catheterisation and measurement of vascular reactivity, is taken in conjunction with a paediatric cardiologist; the procedure is not without risk, especially in children with suprasystemic PAP. Overall, children appear to have a better preserved cardiac output than adults and go into right ventricular failure later in the course of the disease.

Any underlying condition, such as HIV or connective tissue disease, should be treated as usual. Oxygen should be given to prevent hypoxaemia, even this is of controversial benefit. A single, nonrandomised study of pulmonary hypertension in children with congenital heart disease suggested oxygen had a beneficial effect on survival. Calcium channel antagonists are prescribed only for those children with marked vascular reactivity; the exact definition of this is unclear. Anticoagulation should be considered in selected children, usually those with right heart dysfunction, indwelling lines or a hypercoaguable state, but is used much less often with the advent of advanced therapies (see later). There are no paediatric studies suggesting benefit from anticoagulation. Blade atrial septostomy may help symptomatically by decompressing the right-sided circulation but may be associated with significant mortality. Patients with end-stage disease should be considered for heart–lung transplantation.

There are three groups of compounds that may be used to treat pulmonary hypertension. These are prostacyclin and its derivatives, phosphodiesterase-5 inhibitors (*e.g.* sildenafil), and the endothelin receptor antagonists. Their use has led to enhanced survival.

Continuous intravenous infusion of prostacyclin has been associated with improved survival in children as well as adults but the logistic challenge of this treatment is considerable. The benefit may be not only by vasodilation but also restoration of endothelial function. Inhaled iloprost has also been used but the need for six to eight nebulisations a day has limited its value in children; it may also cause bronchoconstriction when nebulised. Subcutaneous and inhaled treprostinil are other options.

The first ever randomised controlled trial in children with pulmonary hypertension showed that sildenafil reduced PVR and improved survival. Sildenafil is thus the only soundly evidence-based treatment for paediatric patients. There is emerging, but currently less strong, evidence that vardenafil may be a better agent. Tadalafil may also offer further advantages but the evidence base is more flimsy.

Endothelin-1 is a potent vasoconstrictor and mitogen for fibroblasts and smooth muscle cells. There are two isoforms of the endothelin receptor found in pulmonary vascular smooth muscle cells, ET_A and ET_B. ET_B receptors are also found in the endothelium and are involved in endothelin clearance and release of nitric oxide leading to vasodilatation. However, despite these physiological differences, dual-receptor and selective ET_A receptor antagonists are equally effective. Bosentan, a dual-receptor antagonist, is not licensed in children but observational studies suggest it may be beneficial. However, 10–15% of children discontinue therapy because of side-effects, including abnormal liver function tests. There may be additional benefit with the addition of ambrisentan, a specific ET_B antagonist.

Novel innovative therapies may include the use of Rho kinase inhibitors, vasoactive intestinal peptide (VIP), oestrogen derivatives, modulation of the serotonin pathway, L-arginine and therapies (including gene therapy) that may modulate apoptosis to attenuate vascular remodelling.

In general, these new options are expensive and potentially toxic medications that are best utilised in centres accredited for the care of pulmonary hypertension. There is a scarcity of randomised controlled trials in children and treatment algorithms are unfortunately extrapolated from adult studies; this is dangerous, because the pathophysiology of pulmonary hypertension may not be the same. It is likely in the future

that combinations of these medications will be prescribed. They are also increasingly used in pulmonary vascular disease complicating congenital heart disease.

Prognosis is usually poor in children, although the suggestion that it is worse than in adults has not been confirmed. However, children are often sicker at presentation. 5-year survival is of the order of 75%. Factors carrying a poor prognosis include WHO functional class III/IV, poor nutrition and older age at presentation, and lower mixed venous oxygen saturation and higher PVR.

Pulmonary veno-occlusive disease
Presentation is indistinguishable from PPH. Physical examination may reveal digital clubbing (unusual in other forms of PAH than cyanotic congenital heart disease) and crackles. Chest radiograph and HRCT will show signs of pulmonary venous congestion. The diagnostic gold standard is open-lung biopsy but noninvasive testing may obviate the need for this. If lung tissue is obtained, the pulmonary veins and venules contain organised and recanalised thrombi with intimal fibrous pads and medial hypertrophy. The veins may show medial hypertrophy and arterialisation. There may be similar changes in pulmonary capillaries and the pre-capillary circulation, including fibrinoid necrosis in the latter. If cardiac catheterisation is undertaken, wedge pressure is often normal because the large pulmonary veins are not affected and pulmonary vasodilator trials may precipitate pulmonary oedema. There is no medical therapy and referral to the local transplant centre is indicated at diagnosis.

The majority of cases are idiopathic; rare familial cases are described, and cases secondary to chemotherapy, bone marrow transplantation and congenital heart disease have been described. Differential diagnosis includes congenital absence or stenosis of the pulmonary veins and pulmonary venous obstruction due to mediastinal pathology such as fibrosing mediastinitis.

Pulmonary embolic disease Causes of pulmonary embolic disease are summarised in table 5. This is undoubtedly underdiagnosed in children because it is frequently not considered. Presentation may be with acute collapse due to a massive embolism or the more subtle onset of breathlessness due to repeated small emboli. There are four important questions if pulmonary embolic disease is suspected (table 6).

The factors predisposing to thromboembolism are intravascular foreign body (*e.g.* a portacath), a sluggish circulation, coagulopathy and immobility. More than one factor may be operative. Typical causes of a sluggish circulation include the post-Fontan situation and left atrial dilatation secondary to cardiomyopathy. Numerous congenital and acquired prothrombotic disorders have been implicated in pulmonary embolism or *in situ* thrombosis. Membranous glomerulonephritis is a notorious source of pulmonary thromboemboli from the renal veins.

There are numerous causes of nonthrombotic emboli. Tumour emboli originating from Wilm's, hepatoblastoma or testicular teratoma are among the commonest. In tropical regions, schistosomal ova are an important cause of pulmonary hypertension. Talc emboli from injecting crushed up tablets as a form of substance abuse is another cause. The presentation of infected emboli, another complication of intravenous drug abuse, is usually dominated by a septic picture.

Since these conditions are so rare in childhood, there is usually insufficient experience to rely on noninvasive diagnosis, for example with D-dimer. Suspicion may be aroused by a ventilation/perfusion scan, which typically shows normal ventilation but marked perfusion defects. Contrast-enhanced CT scanning will demonstrate filling defects in the proximal pulmonary arteries. If distal disease not visible on CT scanning is suspected and, in particular, if nonthromboembolic disease is a diagnostic consideration, then a lung biopsy may be indicated.

Management is of the underlying cause, for example, removal of the indwelling line.

Table 5. Causes of pulmonary embolic disease

Thromboembolic disease	Nonthrombotic embolic disease
Indwelling venous catheters (>25% cases)	**Tumour emboli**
Low flow states	Right atrial myxoma
Cardiac failure	Liver, renal or testicular tumours
Fontan circulation	**Tropical**
Dilated cardiomyopathy	Schistosomiasis
Coagulopathy	**Fat embolism**
Factor V Leiden	Trauma
Protein C deficiency (congenital or acquired)	Burns
Protein S deficiency (congenital or acquired)	Cardiopulmonary bypass
Antithrombin III	Acute pancreatitis (always consider an underlying diagnosis of CF if no other obvious cause)
Dysfibrinogenaemias	**Adolescent issues**
Miscellaneous, including oral contraception	Pregnancy complications (amniotic fluid embolism)
Immobility	Intravenous drug abuse (talc emboli from injecting crushed up tablets)
Blunt thoracic trauma	
Axillary vein thrombosis	
May be associated with acquired lymphangiectasia and chylothorax	
Renal vein thrombosis	
Membranous nephropathy, may also have a coagulopathy	

More than one cause may be operative in a given child; for example, a boy with Duchenne muscular dystrophy has immobility and cardiomyopathy as predisposing factors.

For an otherwise well child who has had a pulmonary thromboembolism and is clinically stable, anticoagulation with heparin and warfarin is indicated. If there is an underlying coagulopathy, the advice of a paediatric haematologist should be sought. If the child is critically unstable, then consideration should be given to thrombolysis and even embolectomy, in consultation with a paediatric cardiologist and cardiothoracic surgeon.

Table 6. Four clinical questions if pulmonary embolic disease is suspected

Has there been embolic occlusion of part of the pulmonary arterial tree?
Is the child cardiovascularly stable or is urgent intervention required?
What is the material embolised?
What has predisposed to the embolic event?

Given that heritable coagulopathies may present with thromboembolic disease, consideration should be given to screening the child and first-degree relatives for at least for protein C, protein S and antithrombin III deficiency, given the risk of thromboembolic events in these conditions.

Invasive pulmonary capillary haemangiomatosis This rare condition is characterised by proliferating sheets of thin-walled vessels, which infiltrate the pulmonary circulation leading to vascular occlusion. The condition behaves like a low-grade vascular neoplasm. Rarely, there is extrathoracic spread of the abnormal vasculature. Presenting features include dyspnoea, thrombocytopenia and haemoptysis, and symptoms of pulmonary hypertension. There may be digital clubbing and pleural and pericardial effusions. Familial and congenital cases have been described. HRCT differentiates the

condition from other causes of pulmonary hypertension. The distinction is important because vasodilator trials may cause pulmonary oedema in this condition. Typically, there is diffuse bilateral thickening of the interlobular septa and small centrilobular opacities, which are poorly defined. There may also be diffuse ground-glass opacities. Definitive diagnosis is by lung or other tissue biopsy. Occasional children have an associated connective tissue disease or other comorbidity. Localised forms may be treated surgically, disseminated disease with interferon-α2a or heart–lung or bilateral-lung transplant. However, most affected children die quickly.

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Eosinophilic lung diseases and hypersensitivity pneumonitis

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Eosinophilic lung diseases

Eosinophilic lung diseases are a diverse group of disorders characterised by pulmonary opacities associated with tissue or peripheral eosinophilia. The diagnosis of eosinophilic lung disease can be made if any of the following findings is present:

- pulmonary opacities with peripheral eosinophilia,
- tissue eosinophilia confirmed at lung biopsy, and
- increased eosinophils in bronchoalveolar lavage (BAL) fluid.

Eosinophilic lung diseases are generally classified in terms of presentation (clinical or radiological) and aetiology. Clinical and radiological presentations can include simple pulmonary eosinophilia, chronic eosinophilic pneumonia, acute eosinophilic pneumonia, allergic bronchopulmonary aspergillosis (ABPA) and pulmonary eosinophilia associated with a systemic disease, such as Churg–Strauss syndrome and hypereosinophilic syndrome.

Key points

- Eosinophilic lung diseases are a diverse group of disorders characterised by pulmonary opacities associated with tissue or peripheral eosinophilia.
- Hypersensitivity pneumonitis, or extrinsic allergic alveolitis, is a diffuse granulomatous ILD caused by inhalation of various antigenic organic particles or low molecular weight chemicals.

Based on aetiology, eosinophilic lung diseases are generally classified as those of unknown cause (idiopathic hypereosinophilic syndrome) and those of known cause (ABPA, bronchocentric granulomatosis, parasitic infection and drug reactions), as well as eosinophilic vasculitis.

Diagnosis The diagnostic methods consist of a detailed medical history and physical examination. The duration and severity of symptoms are also of critical importance. Testing for potential helminth infections, including stool examination and serology, should be guided by the exposure history. If no inciting drug or infection is identified, a thorough investigation for allergic/atopic or autoimmune disorders, blood cell disorders and other neoplastic conditions should be initiated. A history of asthma may raise suspicion of Churg–Strauss syndrome, ABPA, or bronchocentric granulomatosis.

Pulmonary infiltrates, characterised by foci of air-space consolidation and focal ground-glass opacities, can be seen in pulmonary eosinophilia of all causes. Cavitation can occur in certain cases of ABPA and Churg–Strauss syndrome, as well as in certain parasitic infections.

Important initial parameters that can be obtained from routine laboratory testing include:

- a complete blood count with differential counts (confirmed by microscopy),
- routine chemistries (including tests of hepatic and renal function),

- levels of inflammatory markers and autoantibodies, and
- serum IgE,
- vitamin B_{12} and
- tryptase levels.

Bone marrow investigations should also include a core biopsy with histology and immunohistochemistry, including CD34, CD117, tryptase and CD25. In addition, cytogenetics, FISH (fluorescent *in situ* hybridisation) and molecular analyses should be performed. Bone marrow investigation is warranted in all patients in whom hypereosinophilia remains unexplained or if a haematopoietic neoplasm is suspected. Haematopoietic malignancies typically accompanied by eosinophilia are myeloproliferative neoplasms (MPNs), certain variants of acute myeloid leukaemia (AML), a smaller subset of patients with myelodysplastic syndromes (MDS), some MDS/MPN overlap disorders, several (mostly T-cell derived) lymphoproliferative disorders and (advanced) systemic mastocytosis.

Finally, lymphocyte (T-cell) phenotyping (by flow cytometry) should be performed in patients with hypereosinophilia to identify aberrant populations, most commonly $CD3^-$ $CD4^+$ T-cells, which have been associated with eosinophilopoietic cytokine production.

Peripheral eosinophilia occurs in virtually all cases, either in the initial presentation or during the course of the disease. Eosinophilia is not always severe in blood samples, with eosinophil counts of 500–1000 cells·mm^{-3}, or it can even be absent from the initial clinical presentation, thereby making diagnosis difficult.

Increased eosinophil counts in the air spaces, common to various causes of pulmonary eosinophilia, result in severe eosinophilia in the BAL fluid and are the principal method of confirming the diagnosis of acute and chronic eosinophilic pneumonia. In such cases, eosinophils account for >25% of the cells in the BAL fluid.

Lung biopsy (transbronchial or by thoracotomy) is not a prerequisite for the diagnosis of pulmonary eosinophilia. Biopsy is performed to rule out the hypotheses of infection and neoplasia, as well as to make a differential diagnosis with other interstitial diseases and cryptogenic organising pneumonia, or to confirm Churg–Strauss syndrome. Histopathological findings that are common to virtually all causes include intra-alveolar exudation of histiocytes and eosinophils, also present in the interstitium, and eosinophilic microabscesses, macrophages containing Charcot–Leyden crystals and findings of bronchiolitis obliterans or organising pneumonia. Small focal areas of interstitial fibrosis, as well as intra-alveolar necrosis and even a certain degree of vasculitis, can occur, although without granulomas. Granulomas, as well as being present in ABPA, are indicative of parasitic infections and Churg–Strauss syndrome.

Eosinophilic lung diseases of unknown cause

Simple pulmonary eosinophilia, or Löffler syndrome, was originally reported as a benign acute eosinophilic pneumonia of unknown cause characterised by increased peripheral blood eosinophils, minimal or no pulmonary symptoms, and spontaneous resolution. In some patients, these clinical characteristics may prove to be secondary to the presence of parasites, ABPA or drugs. Pathological specimens show oedema and accumulation of eosinophils in the alveolar septa and interstitium.

The radiographic manifestations consist of transient and migratory areas of consolidation. These consolidations are non-segmental, may be single or multiple, usually have ill-defined margins, and often have a predominantly peripheral distribution. The prognosis is excellent. The use of corticosteroids is rarely necessary, and spontaneous resolution occurs within 30 days.

Acute eosinophilic pneumonia presents frequently in young smokers as acute hypoxaemic respiratory failure. These patients present without peripheral eosinophilia but usually have >25% eosinophils in bronchoalveolar fluid.

Acute eosinophilic pneumonia may be secondary to a number of causes, such as vaccinations (BCG (bacille Calmette–Guérin) vaccination and minocycline) and drugs (fludarabine, progesterone and sertraline), infections (*Aspergillus* and *Coccidioides*) or environmental factors (smoking, tear gas, gasoline and demolition dust). It is important to rule out fungi infection.

The principal histological finding in acute eosinophilic pneumonia is diffuse alveolar damage associated with interstitial eosinophilia. The predominant radiographic findings are bilateral reticular densities (with or without areas of patchy consolidation) and pleural effusion.

Chronic eosinophilic pneumonia is an idiopathic condition characterised by chronic and progressive clinical features and specific pathological findings. The clinical manifestation is usually insidious and the patient experiences symptoms for an average of 7.7 months before the diagnosis is made. Most patients are middle aged and ~50% have asthma. Females are more frequently affected than males. Pulmonary function tests can be normal in mild cases but usually show restrictive defects.

Idiopathic hypereosinophilic syndrome is a rare disorder characterised by marked, prolonged idiopathic eosinophilia and variable organ dysfunction related either to infiltration by eosinophils or secondarily eosinophil-associated tissue damage.

The diagnosis is based on three criteria established by Chusid *et al.* (1975):

- persistent eosinophilia (eosinophil count >1500 cells·mm^{-3}) for $\geqslant 6$ months or death within 6 months due to the signs and symptoms related to eosinophilia;
- eosinophilia-related involvement of at least one organ; and
- absence of a known causes of eosinophilia, such as drugs, parasites, malignancy, vasculitis, chronic eosinophilic pneumonia and Churg–Strauss syndrome.

There are two variants of idiopathic hypereosinophilic syndrome: myeloproliferative and lymphocytic. The myeloproliferative variant is a haematological disorder that belongs to the leukaemia group, and is accompanied by dysplasia, hepatosplenomegaly and increased vitamin B_{12} level. The lymphocytic variant results from a proliferation of T-helper (Th) type 2 cells with overexpression of the cytokines interleukin (IL)-3, granulocyte–macrophage colony-stimulating factor (GM-CSF) and, especially, IL-5. In the lymphocytic variant, as in allergic disorders (IgE levels are usually increased), the three sites most commonly involved are the respiratory tract, gastrointestinal tract and skin. Treatment includes corticosteroids, and other agents, such as anti-IL-5, have been considered.

Eosinophilic lung diseases of known cause

ABPA is a hypersensitivity reaction to *Aspergillus* antigens. ABPA is typically seen in patients with long-standing asthma or CF. It is usually suspected on clinical grounds, and the diagnosis is confirmed by radiology and serological testing. Diagnostic criteria include the presence of:

- asthma,
- peripheral blood eosinophilia,
- an immediate positive skin test for *Aspergillus* antigens,
- increased serum IgE levels, and
- pulmonary opacity on chest radiographs.

The IgE level is probably the most useful laboratory test for ABPA, as it correlates well with disease activity. Lung biopsies are rarely performed for diagnosis.

Bronchocentric granulomatosis is a rare disorder characterised by a necrotising granulomatous inflammation of bronchial and bronchiolar epithelium with chronic inflammatory changes in the surrounding lung parenchyma. Approximately one-third of affected patients have tissue eosinophilia and tend to have asthma, peripheral eosinophilia and positive sputum cultures for *Aspergillus* organisms.

Many *parasites* can cause pulmonary opacities with blood or tissue eosinophilia.

Because the prevalence of individual parasitic infections varies from one geographic region to another, familiarity with the common parasites in one's geographic area of practice is critical to arriving at a correct diagnosis.

A wide variety of *drugs* and toxic substances are important causes of pulmonary eosinophilic infiltrates. Patients with drug-induced eosinophilic lung disease can present with a variety of pathologic conditions ranging from a mild, simple pulmonary eosinophilia-like syndrome to a fulminant, acute pulmonary eosinophilia-like syndrome. Pulmonary involvement by cutaneous adverse drug reactions is rare and is considered to be a severity factor. Many patients with drug-induced eosinophilic lung disease will improve by simply discontinuing the medication; in severe or persistent cases, however, short courses of corticosteroids appear to hasten recovery. The diagnosis is usually made on the basis of clinical history and blood eosinophilia rather than imaging findings.

Churg–Strauss syndrome was first described in 1951 by Churg and Strauss on the basis of the histologic criteria necrotising vasculitis, tissue infiltration by eosinophils and extravascular granulomas.

This syndrome is characterised by three phases.

- Allergic phase: presence of asthma or rhinitis.
- Eosinophilic phase: presence of severe persistent peripheral eosinophilia (eosinophil count >1500 cells·mm^{-3}) for >6 months.
- Vasculitic phase: presence of systemic manifestations and small vessel vasculitis, represented by the involvement of two or more extrapulmonary organs.

However, the three phases can be dissociated and asthma is present in 100% of cases.

In 1990, the American College of Rheumatology established the following criteria for the diagnosis of Churg–Strauss syndrome, confirmation of at least four being necessary: asthma; eosinophilia (eosinophil count >1500 cells·mm^{-3}); paranasal sinus involvement; transient pulmonary infiltrates; mononeuropathy or polyneuropathy; and biopsy findings of vasculitis. Therefore, the histopathological criterion of small vessel biopsy findings of extravascular eosinophils can be dispensed with if the other clinical criteria are present.

With these new criteria, a diagnosis of Churg–Strauss syndrome has come to be more common. Skin, muscle and sural nerve biopsy can reveal perivascular eosinophilic inflammation and confirm the diagnosis. Lung biopsy is considered the gold standard, although transbronchial biopsy is typically insufficient. Chief among biopsy findings is small vessel vasculitis associated with positivity for antineutrophil cytoplasmic antibody (ANCA), perinuclear ANCA test results being positive in 50–70% of cases. The combination of Churg–Strauss syndrome and positive ANCA test results represents a more significant form of vasculitis and has therapeutic implications. A study evaluating the radiological test results of nine patients revealed bilateral foci of non-segmental consolidation in most of the cases.

Currently, the mean survival among Churg–Strauss syndrome patients is 9 years. Doses of prednisone (40–60 mg·day^{-1}) for several weeks are usually necessary in order to control vasculitis and should be followed by a maintenance regimen for 1 year.

Hypersensitivity pneumonitis

Hypersensitivity pneumonitis, or extrinsic allergic alveolitis, is a diffuse granulomatous interstitial lung disease (ILD) caused by inhalation of various antigenic organic particles or low molecular weight chemicals. Because the resulting inflammatory response involves not only the alveoli but the terminal bronchioli and the interstitium, the term "hypersensitivity pneumonitis" may be more correct than "extrinsic allergic alveolitis".

The prevalence and incidence of hypersensitivity pneumonitis vary

considerably depending upon disease definitions, methods used to establish the diagnosis, intensity of exposure, environmental conditions and host/genetic risk factors that remain poorly understood. The disease may also arise in children. Clinical behaviour in children is similar to adult cases.

Occupational and environmental exposures A number of occupations have been associated with the risk of hypersensitivity pneumonitis, including farmers, mushroom and tobacco workers, woodworkers, maple bark strippers, stucco workers, malt workers, millers, machinists, foundry workers, office workers, *etc.*, or hobbyists such as bird fanciers.

Clinical features The spectrum of clinical features varies and has been conventionally classified into acute, subacute and chronic forms. The interval between sensitisation by antigen inhalation and the symptomatic onset of HP is unknown. It seems to be variable and may range from several months to several years after the antigen exposure.

Acute hypersensitivity pneumonitis is characterised by an influenza-like syndrome (fever, chills, malaise, myalgia and headache) and respiratory symptoms (dry cough, dyspnoea, tachypnoea and chest tightness). However, respiratory symptoms in acute hypersensitivity pneumonitis are sometimes absent. The disease onset is abrupt and usually occurs 4–12 h after antigen exposure. In general, acute hypersensitivity pneumonitis is non-progressive and spontaneously improves within a few days after antigen avoidance. The disease often recurs after re-exposure to antigen. Clinical examination shows bibasilar crackles and occasional cyanosis, whereas finger clubbing is rare. Patients with recurrent acute farmer's lung may sometimes develop an obstructive lung disease with centrilobular emphysema instead of fibrosis.

Subacute hypersensitivity pneumonitis may be associated with repeated low-level exposure to inhaled antigens. After recurrent acute episodes, this form may also become chronic, resulting in fibrosis. It is characterised by an insidious onset of dyspnoea, fatigue and cough. Because the respiratory symptoms are usually mild or absent in subacute hypersensitivity pneumonitis, infectious pneumonia or noninfectious ILD is the important differential diagnosis.

Chronic hypersensitivity pneumonitis may result from continuous, low-level exposure to inhaled antigens. Bird antigen exposure is the most common in this form of disease. The onset of chronic hypersensitivity pneumonitis is insidious, with slowly increasing dyspnoea, dry cough, fatigue and weight loss. Digital clubbing may be present in 20–50% of patients and predicts clinical deterioration. Chronic hypersensitivity pneumonitis often develops progressive fibrosis with cor pulmonale and mimics idiopathic pulmonary fibrosis (IPF) or fibrotic nonspecific interstitial pneumonia (NSIP) in the advanced stage. This form of disease, therefore, often leads the physician to mistake the disease for other chronic ILDs. The auscultatory findings include bibasilar crackles and, characteristically, inspiratory squeaks resulting from the coexisting bronchiolitis.

Acute exacerbation of chronic hypersensitivity pneumonitis is an emerging concept showing an accelerated respiratory deterioration with the presence of new bilateral ground-glass opacities on HRCT. The pathogenesis of acute exacerbations in chronic hypersensitivity pneumonitis is unknown.

Diagnosis Several diagnostic criteria for hypersensitivity pneumonitis have been recommended. However, none of these criteria has been validated. The diagnosis of hypersensitivity pneumonitis relies on a high level of clinical suspicion, the recognition of antecedent antigen exposure, and a constellation of clinical, radiological, laboratory and pathological findings.

A large prospective multicentre cohort study (116 patients with hypersensitivity pneumonitis and 284 control subjects with

other ILD) showed that the diagnosis of hypersensitivity pneumonitis could be made with six significant predictors:

- exposure to a known offending antigen;
- positive precipitating antibodies;
- recurrent episodes of symptoms;
- inspiratory crackles;
- symptoms 4–8 h after exposure; and
- weight loss.

If all six predictors are present, the probability of having hypersensitivity pneumonitis is 98%. If none of the six predictors is present, the probability is 0%.

Careful history taking is mandatory. Clinicians should have specific expertise concerning the antigens relevant to hypersensitivity pneumonitis. Important factors are hay feeding, bird keeping, feather duvets and pillows in the home, air conditioning or ventilators in the buildings, and formation of mould on room walls or in cellars.

Important diagnostic tools include BAL, HRCT, provocation tests and lung biopsies.

The most sensitive diagnostic test is *BAL*. In our experience and based on a literature review, a normal BAL widely excludes the diagnosis of hypersensitivity pneumonitis. The characteristic finding is a lymphocytosis in the subacute and chronic forms. In asymptomatic sensitised individuals (subclinical alveolitis), BAL lymphocytosis is also apparent. BAL lymphocytosis >30% is recommended as a discriminative factor of chronic hypersensitivity pneumonitis from IPF, showing usual interstitial pneumonia (UIP) pattern on HRCT.

The radiological manifestations of acute hypersensitivity pneumonitis are those of acute pulmonary oedema. The characteristic *HRCT* manifestations of subacute hypersensitivity pneumonitis consist of patchy or diffuse bilateral ground-glass opacities, poorly defined small centrilobular nodules, and lobular areas of decreased attenuation and vascularity on inspiratory images and of air trapping on expiratory images. The ground-glass opacities primarily reflect the presence of diffuse lymphocytic interstitial pneumonitis; minor degrees of organising pneumonia, when present, also can contribute to this appearance. The poorly defined centrilobular nodules may be caused by cellular bronchiolitis, the predominantly peribronchiolar distribution of interstitial pneumonitis or focal areas of organising pneumonia. The lobular areas of decreased attenuation and air trapping are presumably caused by small-airway obstruction by cellular bronchiolitis or by constrictive bronchiolitis.

Chronic hypersensitivity pneumonitis is characterised by the presence of reticulation and traction bronchiectasis and bronchiolectasis on HRCT, due to fibrosis superimposed on findings of acute or subacute hypersensitivity pneumonitis. The reticulation in chronic hypersensitivity pneumonitis can be patchy or random or have a predominantly subpleural and peribronchovascular distribution but typically tends to spare the lung bases. In a small percentage of cases, chronic hypersensitivity pneumonitis results in subpleural honeycombing.

Acute hypersensitivity pneumonitis is characterised *histologically* by the presence of neutrophilic infiltration of the respiratory bronchioles and alveoli. A pattern of diffuse alveolar damage and temporally uniform, nonspecific, chronic interstitial pneumonitis may also be seen. Subacute hypersensitivity pneumonitis is characterised histologically by the presence of cellular bronchiolitis, noncaseating granulomas and bronchiolocentric interstitial pneumonitis with a predominance of lymphocytes. Areas of organising pneumonia (bronchiolitis obliterans with organising pneumonia) may be identified. These findings, however, are not present in all cases. Furthermore, in some patients, the predominant histologic pattern is NSIP or UIP.

Although *lung function* may be normal in acute hypersensitivity pneumonitis, abnormal lung function is common in most patients with chronic hypersensitivity pneumonitis. The most frequent functional

abnormalities are a restrictive impairment and/or an impaired gas exchange (decreased diffusing capacity or increased alveolar/arterial oxygen gradient). Only a few patients with farmer's lung show obstructive impairment resulting from emphysema. However, these changes are not characteristic of chronic hypersensitivity pneumonitis but are found in any type of ILD. Therefore, these abnormalities are not diagnostic for hypersensitivity pneumonitis. Although hypoxaemia is common in hypersensitivity pneumonitis, patients with mild-to-moderate disease may lack this symptom and only present hypoxaemia with exercise.

The functional impairment is not well correlated with the severity of radiological abnormalities. The importance of pulmonary function tests is to evaluate the severity of the physiological impairment at diagnosis and during follow-up.

Treatment Antigen avoidance is the key element in the treatment of hypersensitivity pneumonitis and complete cessation of exposure to the provoking antigen is the safest advice for these patients.

Although there is often an apparent beneficial response to corticosteroids in hypersensitivity pneumonitis, it is difficult to distinguish between the effects of treatment, the natural course of the disease and the effect of antigen avoidance. A randomised, double-blind, placebo-controlled study of corticosteroids in patients with acute farmer's lung found that patients given prednisolone showed more rapid improvement in lung function, with a significantly higher diffusing capacity at 1 month, compared to the control group, but there was no difference in the long-term outcome between the two groups. Recurrence of acute farmer's lung was more common among corticosteroid-treated patients than among controls if they had continuing antigen exposure, raising the possibility that corticosteroid treatment was also suppressing the counter-regulatory aspects of the immune response in these patients.

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Pulmonary haemorrhage

Robert Dinwiddie

Pulmonary haemorrhage can occur at any age in childhood, from birth through to adolescence. The presentation can be acute or chronic, clinically obvious or covert and subtle over a period of time. Presenting features can vary from the acute and life-threatening to chronic ill health secondary to iron deficiency anaemia. The aetiology is best divided into two age groups: neonatal and childhood.

Neonatal

Neonatal pulmonary haemorrhage most commonly occurs in preterm infants secondary to severe pulmonary oedema in association with respiratory distress syndrome and patency of the arterial duct (patent ductus arteriosus). The incidence is ~1%. The underlying causes are shown in table 1.

The underlying mechanism is thought to be due to capillary leakage into the interstitium. Haemorrhagic fluid can also leak directly into the alveolar spaces and then into the small and large airways. Neonatal pulmonary haemorrhage has also been associated with the administration of exogenous surfactant. Other predisposing factors include birth asphyxia, excessive fluid administration, hypoglycaemia, coagulation defects, intercurrent infection, hypothermia and cardiac failure.

Frothy haemorrhagic fluid appears through the nose and mouth or *via* the endotracheal tube. In its most acute form it is associated with the sudden onset of shock and can be life-threatening. Chest radiographs show diffuse interstitial shadowing throughout both lung fields. Treatment includes the use of high levels of positive end-expiratory pressure (PEEP), replacement of blood loss but with overall fluid restriction and correction of coagulation deficiencies. If there is an associated patent ductus arteriosus then this should be closed as soon as possible.

Key points

- Pulmonary haemorrhage can occur at any age.
- Presentation varies from the acute and life-threatening to "hidden", with no obvious haemoptysis.
- Many cases are idiopathic but a number of clear underlying causes can be recognised by selective investigations.
- Known complications include chronic iron deficiency anaemia and pulmonary fibrosis.
- Systemic corticosteroids are the most effective treatment in the majority of cases.

Infancy and childhood

Pulmonary haemorrhage in infancy and childhood can occur due to a variety of causes. They are best divided into those which result in diffuse or focal areas of bleeding. These are shown in table 2. Consideration should also be given to the possibility that bleeding from the nose or mouth can be due to other causes, such as epistaxis or haematemesis.

Table 1. Causes of pulmonary haemorrhage in the neonatal period

Respiratory distress syndrome
Patent arterial duct (patent ductus arteriosus)
Fluid overload
Cardiac failure, left-to-right shunt
Birth asphyxia
Administration of surfactant
Coagulation disorders
Neonatal sepsis

Clinical presentation

The most obvious clinical presentation of diffuse or focal pulmonary haemorrhage is with clinically apparent bleeding manifesting itself as haemoptysis. However, only a proportion of children present in this way and many present with less specific symptoms such as cough, breathlessness, wheezing and exercise limitation. In some cases, in which the underlying condition has been present over a longer period of time, a faltering growth pattern is seen. A few patients with focal intrapulmonary haemorrhage, such as in CF, complain of a localised "bubbling sensation" within the chest. At the other extreme, major acute cases may present with massive haemoptysis, profound anaemia and shock, which can be life-threatening.

Physical examination may reveal pallor, tachycardia, fever, tachypnoea and dyspnoea, with indrawing of the chest muscles and cyanosis. Localised chest signs include focal or generalised areas of decreased air entry and crackles or wheeze. Finger clubbing is also seen but is uncommon.

Diagnostic work-up

As shown in table 2 the differential diagnosis is extensive. A carefully considered diagnostic work-up exploring known causes is warranted in every case, bearing in mind that a significant proportion are "idiopathic" and no specific underlying condition will be found. A suggested list of diagnostic tests is shown in table 3 and an algorithm for diagnosis is shown in figure 1.

Lung function tests may demonstrate evidence of airflow obstruction, reduced lung volumes and functional residual capacity and associated hypoxaemia with reduced oxygen saturation levels in air. The diffusion of carbon monoxide is also reduced over the longer term if progressive lung damage occurs. This parameter is difficult to measure in young children.

Radiological changes include bilateral patchy interstitial infiltrates throughout one or both lungs. In the longer term the chest radiograph may develop more chronic changes including reticulo-nodular shadowing due to pulmonary fibrosis.

Depending on the severity, a CT scan of the chest will show patchy interstitial infiltrates in one or both lung fields. More generalised areas of consolidation may also be evident (fig. 2). In those with prolonged disease, changes of pulmonary fibrosis can develop. Any associated bronchiectasis will also be seen.

Histopathology

When acute pulmonary haemorrhage occurs red blood cells are seen in large numbers in the alveoli and interstitial spaces. Within 48–72 h many alveolar macrophages are seen which have phagocytosed red blood cells and are in the process of digesting them. These cells are called siderophages and stain positive with Prussian blue. A specific parameter used for reporting alveolar haemorrhage in bronchoalveolar lavage specimens is the Golde score. This gives a ranking score of 0–4 depending on the density of haemosiderin in the cells. 100 cells are counted and the Golde score is reported. In normal individuals this is <20. A score of 20–70 is found in those with significant alveolar haemorrhage. Other pathology groups have used a cut-off of $>20\%$ of siderophages present among the total number of alveolar macrophages as diagnostic for haemorrhage.

Lung biopsy is rarely indicated but if undertaken may show abnormalities of the

Table 2. Causes of pulmonary haemorrhage in infants and children

Diffuse
Haemosiderosis
IPH
Goodpasture syndrome
Cow's milk protein allergy, Heiner syndrome
Systemic vasculitis
Granulomatosis with polyangiitis (Wegener's)
Henoch–Schonlein purpura
Churg–Strauss syndrome
Microscopic angiitis
Collagen vascular
Systemic lupus erythematosis
Cardiac
Left-to-right shunt
Left-sided obstruction
Cardiac failure
Coeliac disease
Alveolar injury
Bleeding diatheses
Focal
Viral or bacterial lung infection
TB
Atypical mycobacterial infection
Bronchiectasis
CF
Non-CF bronchiectasis
Primary ciliary dyskinesia
Immunodeficiency
Foreign body
Vascular
Haemangiomas
Arterio-venous malformations
Neoplasms
Tracheostomy
Fabricated or induced illness

alveolar capillary endothelial basement membrane and, in cases of repeated bleeding episodes, early pulmonary fibrosis.

Diffuse pulmonary haemorrhage

Idiopathic pulmonary haemosiderosis (IPH) is a rare condition in children with a variable and, at times, severe prognosis. It can appear at any age throughout childhood but its onset is more common in the early years. It varies in severity and presents when there is active bleeding into the lung tissue itself. This can take the form of haemoptysis, from small amounts to massive acute life-threatening episodes, or the gradual onset of severe anaemia without any clinically obvious haemoptysis. Patients can become breathless and occasionally wheezy or may be asymptomatic. If haemoptysis does occur it is manifested by cough and small or large amounts of blood which may continue over several days or weeks. The full blood count shows an acute reticulocyte response and evidence of iron deficiency anaemia. Diagnosis is made by the finding of haemosiderin laden macrophages in bronchoalveolar lavage fluid, gastric aspirates or on lung biopsy in the absence of any other known aetiology for pulmonary haemorrhage.

Other associations with pulmonary haemorrhage include acute glomerulonephritis and Goodpasture's syndrome. These patients also present with haematuria and proteinuria. Antibodies to glomerular and alveolar basement membranes can be detected in the blood. Renal biopsy, which is rarely indicated, demonstrates specific antibodies to basement membrane and disruption of the underlying vascular endothelial membrane. Similar changes have been demonstrated in the lung. Chest radiography findings are similar to IPH with patchy interstitial infiltrates seen bilaterally, increasing in severity during episodes of active bleeding. Over the longer term, if this is recurrent, pulmonary fibrosis occurs and the changes, which are initially ground-glass in appearance, become more reticular and nodular.

Table 3. Possible diagnostic tests for cases of pulmonary haemorrhage

Full blood count	ECG
Coagulation studies	Echocardiogram
Erythrocyte sedimentation rate	Pulmonary function tests
C-reactive protein	Chest radiograph
Serum iron and ferritin	CT scan of the chest
Renal function tests	Sputum culture and sensitivity
Immune deficiency screen including HIV/AIDS	Mantoux test
Total IgE	Viral antibodies
Cow's milk protein antibodies	CF mutation analysis
Anti-neutrophil cytoplasmic antibodies	Ciliary biopsy and electron microscopy
Antinuclear antibodies	Bronchoalveolar lavage
Anti-glomerular basement membrane antibodies	Lung biopsy (rarely necessary)
IgA anti-tissue transglutaminase antibodies	

Pulmonary haemorrhage is also associated with allergy to cow's milk protein, *i.e.* Heiner syndrome. Apart from acute episodes of pulmonary haemorrhage it most commonly presents in children under the age of three with clinical signs of cow's milk protein intolerance including vomiting, diarrhoea, gastrointestinal bleeding, rhinorrhoea and faltering growth. Some patients develop significant lymphoid hyperplasia of the upper airway, specifically, adenotonsillar hypertrophy, which in severe cases can lead to cor pulmonale. Chest radiographs show patchy bilateral infiltrates. Blood counts show a marked eosinophilia and elevated levels of IgE. Antibodies to cow's milk protein are diagnostic. A cow's milk-free diet results in the disappearance of symptoms. Pulmonary haemorrhage occurs in cardiac failure, particularly where there is a left-sided obstructive lesion or a large left-to-right shunt. Such conditions are usually evident clinically before a bleeding episode occurs. Diffuse pulmonary haemorrhage is also a

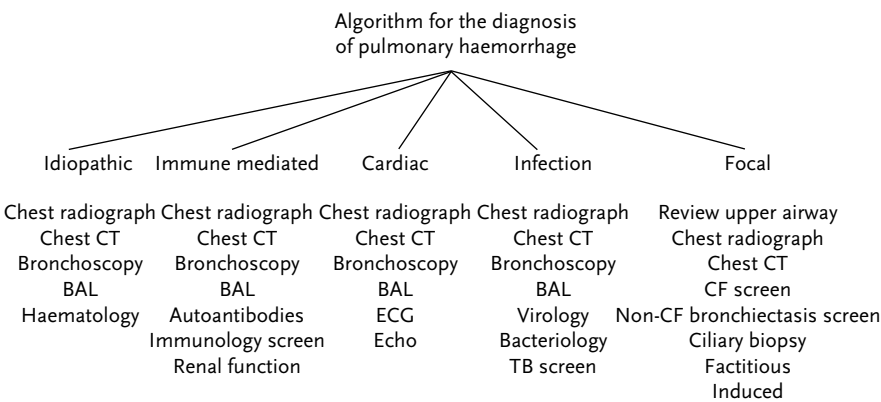

Figure 1. Algorithm for the diagnosis of pulmonary haemorrhage. BAL: bronchoalveolar lavage; Echo: echocardiography.

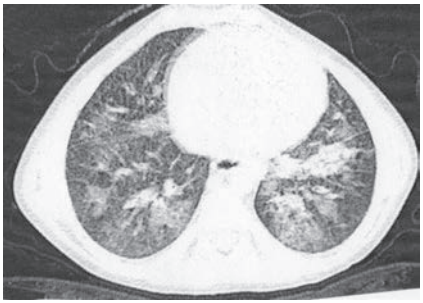

Figure 2. CT scan of 5-year-old boy with diffuse bilateral alveolar haemorrhage.

known complication of systemic lupus erythematosis, Henoch–Schonlein purpura, granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis, coeliac disease and diffuse alveolar injury from exposure to external toxic agents.

Focal pulmonary haemorrhage CF is the most common cause of massive pulmonary haemorrhage in older children. Many episodes are precipitated by an acute exacerbation of long-term infection. Bleeding can be exacerbated in individual cases by the use of over aggressive chest physiotherapy techniques, high-concentration mucolytic agents and, occasionally, as a complication of rhDNase therapy.

Management includes reduction of physical activity, adaptation of chest clearance techniques to less physically stressful methods and appropriate intensification of antibiotic therapy. Should this be unsuccessful then bronchial artery embolisation is indicated. This is not without risk as embolisation of an adjacent anterior spinal artery with paraplegic consequences is a known complication. This procedure is, however, successful in the majority of cases. Limited lung resection is the final option if other procedures fail to control the bleeding.

Pulmonary haemorrhage can occur as a complication of non-CF bronchiectasis, with or without immunodeficiency, TB and primary ciliary dyskinesia. In these conditions heavily blood-stained sputum is more common than the major bleeding episodes which can occur in IPH and CF. Localised lesions such as haemangiomas and arteriovenous malformations can also be the cause of acute bleeding episodes. Bleeding can occur as a complication of an underlying clotting disorder. Pulmonary haemorrhage can be real or imagined as part of the spectrum of factitious or induced illness in childhood.

Management

Major bleeding episodes can occur without warning and may be fatal. Chronic covert haemorrhage also occurs over a period of several weeks and may present only with chronic but sometimes severe anaemia. Management of the acute situation requires oxygen therapy and other respiratory support including bronchodilators, blood transfusion and ventilation in severe cases. Corticosteroids such as pulsed methylprednisolone 10–30 $mg \cdot kg^{-1} \cdot day^{-1}$ for 3 days are given at monthly intervals. In less severe cases oral prednisolone is given at 2 $mg \cdot kg^{-1} \cdot day^{-1}$ for a minimum of 5–7 days following which the dose is titrated to the lowest level that controls symptoms. In a number of cases oral steroids may only be necessary for short periods while in others a continuing dosage on a daily basis or preferably on alternate days is required to control symptoms. Other immunosuppressive agents such as hydroxychloroquine, azathioprine and cyclophosphamide have been used. If there is evidence of cow's milk allergy then a milk free diet is indicated. Inhaled corticosteroids have also been used in an attempt to reduce underlying inflammation. Plasmapheresis has been used in Goodpasture's syndrome.

Prognosis

The natural history of most causes of pulmonary haemorrhage is to wax and wane over a period of time. Because of the rarity of these conditions there are no formal clinical trials of any the above treatments. The overall prognosis is therefore variable, in severe cases of IPH, mortality rates as high as 50% over a 5-year period have been

reported in the past. Results with recent more intensive treatment regimens have reduced this to around 14%. Those who have major haemorrhagic episodes are most at risk. Other patients may show only small episodes of a milder degree and in these cases there is a tendency to improve with age, especially during adolescence and early adult life.

Further reading

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Sickle cell disease

Tobias Ankermann

The term sickle cell disease (SCD) is used to refer to a haemoglobinopathy that results from a genetic variant giving rise to sickle haemoglobin (HbS). This includes the homozygote SCD (HbSS, previously named sickle cell anaemia) and compound heterozygote haemoglobinopathies (HbS-β-thalassaemias, HbSC disease, *etc.*). In Europe, ~1300 children will be born with SCD per year. 60–70% of these children suffer from HbSS.

HbS-haemoglobinopathies cause a chronic haemolytic anaemia and a disease of the blood vessels. HbS is caused by a mutation in the β-globin locus on chromosome 11; HbSS leads to polymerisation and a loss of solubility of the haemoglobin during deoxygenation. The subsequent change in the rheological properties of the erythrocyte leads to dysfunction in the microcirculation with vaso-occlusive crises. Vascular occlusions can occur in almost all organs (*e.g.* skin, lung, liver, spleen, bone, kidney and brain). The clinical consequences of this are acute and chronic pain, hyposplenism (or functional asplenia in older children following splenic infraction and splenic sequestration) with secondary immunodeficiency, osteonecrosis, nephropathy and cerebral infarction. The most common causative organisms of infectious complications following secondary immunodeficiency are *Streptococcus pneumoniae*, *Salmonella*, *Haemophilus influenzae* type b, *Neisseria meningitidis* and *Mycoplasma*. In acute chest syndrome (ACS) of infectious origin, the most commonly identified agents are atypical bacteria and viruses.

Key points

- SCD includes HbS-haemoglobinopathies, which lead to haemoglobin polymerisation with subsequent vaso-occlusion, a chronic haemolytic anaemia and endothelial damage in blood vessels, with consequent chronic organ failure.
- In the lungs and airways, SCD induces acute pulmonary vascular occlusions, ACS, LRTIs, and chronic lung disease with lung fibrosis and pulmonary hypertension.
- Important pulmonary comorbidities of children with SCD are bronchial hyperresponsiveness, atopy and asthma.

The chronic disease of the vessels results in priapism, cerebrovascular disease, hypercoagulability and inflammation of endothelial structures.

In the lungs and airways, SCD leads to acute manifestations (acute pulmonary vascular occlusions, ACS and acute lower respiratory tract infections (LRTIs)), and a chronic lung disease with lung fibrosis and secondary pulmonary hypertension with cor pulmonale. Children with SCD frequently exhibit bronchial hyperresponsiveness and bronchial asthma. The comorbidity of SCD and asthma is associated with a two-fold increased mortality and a reduced life span of patients with asthma and SCD compared to patients with SCD without asthma. The role of OSAS is not yet clearly defined. Pulmonary complications are the most

frequent reason for death in children with SCD.

Keystones of care are:

- protection against infections (*e.g.* vaccination against pneumococci, *H. influenzae* B, *Neisseria*, influenza A, and antibiotics (prophylactic penicillin in small children continued until the immunisation series is complete, with pneumococcal polysaccharide vaccine with HbSS and HbS-β^0-thalassaemia),
- early intervention to prevent disease progression if pain or fever occurs,
- optimal asthma therapy, and
- together with haematologists, hydroxyurea, folic acid and occasionally a transfusion regimen.

In acute vaso-occlusive crisis and ACS, oxygen, hydration, analgesia, antibiotics and incentive spirometry are required.

Acute chest syndrome

ACS is an acute lung injury and is caused by infection, fat embolism, vaso-occlusion or a combination of these factors. It is defined as respiratory signs and/or symptoms (cough, tachypnoea, chest pain, retractions, rales, crackles, wheezing and hypoxaemia) and/or new infiltrates on the chest radiography and fever (>38.5°C) (fig. 1). One-third of children with ACS complain about abdominal pain and pain in their extremities. Figure 2 shows a practical approach to the diagnosis of ACS. The discrimination of ACS from pneumonia or other LRTIs is often difficult but not essential for treatment. Children with suspected or manifest ACS should be admitted to hospital for close observation of their clinical and respiratory status. The treatment should be initiated early and is based on the administration of oxygen to counter the polymerisation of HbS. Furthermore, antibiotic treatment (third-generation cephalosporin or amoxicillin/β-lactamase inhibitor plus a macrolide; if methicillin resistant *Staphylococcus aureus* (MRSA) is suspected, consider vancomycin), inhalation of β_2-sympathomimetics, intravenous hydration, analgesia and incentive spirometry are keystones of the therapy of ACS. If the haemoglobin concentration decreases (<2 g·dL^{-1} of individual baseline) or the PaO_2 decreases <70 mmHg below the normal range during oxygen therapy, then blood transfusion is indicated. One small trial (DeNOVO) suggested that patients with ACS and early transfusion had an improved outcome, when compared with historical data. In very severe cases or when transfusion fails to reduce the HbSS to <30%, an exchange transfusion should be considered. Extracorporeal membrane oxygenation (ECMO) and nitric oxide are therapy options in very severe cases but are not standard therapies.

The application of glucocorticoids is controversial. In mild ACS, positive effects have been described, but there are reports that administration of glucocorticoids in ACS leads to relapse after sudden termination, reactive vaso-occlusive disease and longer hospitalisation. In children with ACS on artificial ventilation, it may be necessary to perform bronchoscopy and to apply DNase to remove mucus and/or bronchial casts. Figure 3 delineates the therapy of ACS.

Chronic lung disease in SCD

Fibrotic remodelling of the lung occurs due to changes in the structure and function of

A new pulmonary infiltrate detected by chest radiograph involving at least one complete lung segment that is not consistent with the appearance of atelectasis

and

one or more of the following signs or symptoms:

- cough
- signs of increased work of breathing (retractions, tachypnoea)
- chest pain
- wheezing
- rales
- body temperature >38.5°C
- hypoxaemia relative to baseline measurement

Figure 1. Clinical criteria for diagnosis of ACS in children with SCD.

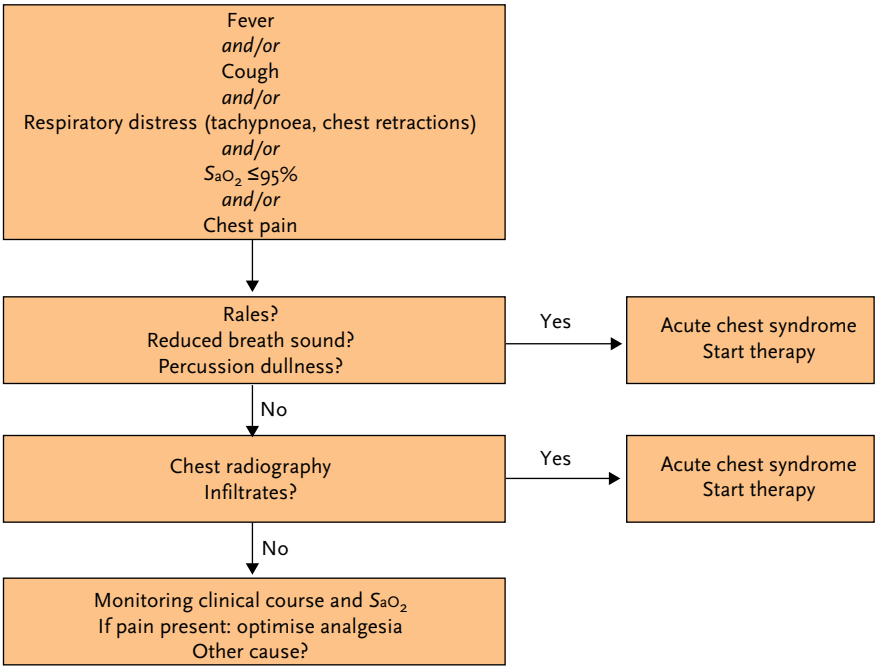

Figure 2. Practical approach if criteria for ACS are met in children with SCD. Reproduced and modified from Miller (2011) with permission from the publisher.

the endothelium and the metabolism of nitric oxide. ACS and asthma are important risk factors for this process. Lung function tests in preschool children mostly demonstrate an obstructive pattern. A restrictive pattern occurs beginning in the second decade. In the third decade, there can be a progressive decline in TLC and diffusion capacity. CT may show interstitial lung disease.

Atopy, asthma and bronchial hyperresponsiveness are important comorbidities in children with SCD. The prevalence of asthma in children with SCD is between 20% and 48%. Children with SCD and asthma and/or specific sensitisation suffer more frequent and earlier episodes of ACS. A possible explanation is the ventilation/perfusion mismatch in asthma with local tissue hypoxia in the lung following sickling and vaso-occlusion, and the higher incidence of LRTIs in children with atopy and asthma. The paediatric pulmonologist should examine children with SCD when they are well on an individual basis (every 4 months in small children; up to 6–12 months in older children with HbSS and HbS-β^0-thalassemia). Integral parts of the consultation are:

- history,
- recording of room-air oxygen saturation,
- lung function testing (according to age, including diffusion capacity in older children),
- allergy tests (skin-prick test or specific IgE), and
- checking for signs and symptoms of OSA.

If, in asthma, a decline in lung function or a specific sensitisation is detected, lung function should be tested every 6 months.

Children with abnormal overnight oxygen saturation (<95%) and/or abnormal lung function test should be screened for OSA, interstitial lung disease and pulmonary

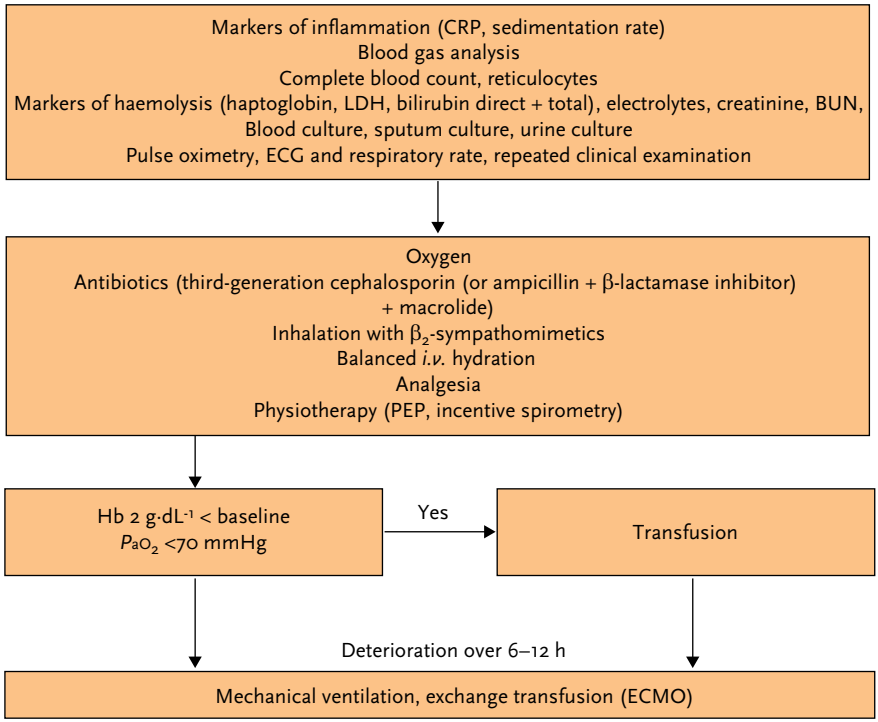

Figure 3. Procedure and therapy if criteria for ACS are met in children with SCD. CRP: C-reactive protein; LDH: lactate dehydrogenase; BUN: blood urea nitrogen; PEP: positive expiratory pressure. Reproduced and modified from Miller (2011) with permission from the publisher.

hypertension. At present, there is no specific therapy for chronic lung disease in SCD. Asthma in SCD is associated with ACS, faster decline in lung function and mortality, and should therefore be managed based on established asthma guidelines. In childhood, pulmonary hypertension is less common. Therefore, evidence-based recommendations for the treatment of pulmonary hypertension in children with SCD are lacking. The application of sildenafil, bosentan and prostacyclins has been reported.

Course of lung disease in SCD

Children with SCD demonstrate a decline in lung function with increasing age, accompanied by decreasing exercise tolerance. The incidence of ACS and comorbidity with asthma are important risk factors for the development of chronic lung disease and early mortality. With optimal care, children with SCD are able to reach the sixth decade of life. Without structured care, many children will not reach adulthood.

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Lung and mediastinal tumours

Amalia Schiavetti

Benign or malignant paediatric chest tumours can originate from the lung parenchyma, mediastinum, pleura or chest wall.

Primary lung tumours

Primary pulmonary neoplasms are rare in children, whilst metastatic disease or inflammatory/congenital diseases are more frequently recognised. The ratio of primary to metastatic to inflammatory/congenital tumours is reported to be 1:5:60. In a published large series of childhood lung tumours, 16.7% were primary and 83.3% reflected metastatic disease or secondary involvement by a haematolymphoid or histiocytic process.

Clinical picture Primary pulmonary tumours in children present with nonspecific symptoms. Some lesions are found incidentally on radiological studies requested for unrelated medical diseases. Common presenting symptoms include cough, chest pain, haemoptysis or shortness of breath and they may mimic common entities. Due to the paucity of primary pulmonary malignancies in paediatric and adolescent patients, delays in diagnosis are common. At least half of these lesions can present with advanced stage disease. Most patients are initially diagnosed as having pneumonia that contributes to a delay in diagnosis.

Diagnosis Initial workup consists of baseline laboratory and chest radiography. Persistent symptoms or persistent radiographic findings despite therapy require a CT scan and/or MRI of the chest, as well as evaluation by a pulmonologist. CT is most useful for parenchyma lesions, whereas MRI provides better visualisation of soft tissue lesions, vascular anatomy and masses of the mediastinum. The presence of a suspicious mass lesion can require bronchoscopy for central lesions and thoracoscopic or image-guided biopsy for peripheral lesions. Bronchoscopic evaluation should consist of gross inspection. Tracheal and endobronchial tumours are most likely to be carcinoid tumours or mucoepidermoid carcinomas; both are malignant processes. Tissue biopsy of endobronchial lesions can be performed, although this procedure is

Key points

- Primary pulmonary neoplasms are rare in childhood; metastatic disease or inflammatory/congenital diseases are more frequently recognised.
- The most common primary lung malignancies in children are pleuropulmonary blastoma and carcinoid tumour; bronchogenic carcinomas are exceptionally rare.
- Symptoms of primary lung tumours in childhood are nonspecific (cough, haemoptysis, chest pain or shortness of breath); persistent symptoms or persistent radiographic findings despite therapy require a CT scan and/or a MRI of the chest.
- Tumours arising in the anterior mediastinum are most commonly due to lymphoma followed by germ cell tumours; large masses present life-threatening airway compromise, especially during anaesthesia.

opposed by some authors because of the risk of fatal haemorrhage. If attempted, endobronchial biopsy should be performed in a setting where thoracic surgery is immediately available. A history of a congenital cystic malformation of the lung has been reported to increase the risk of lung malignancy. It is thought that these malformations may undergo malignant degeneration with time.

Prognosis and treatment The frequency of the various histology types and the outcome for children with pulmonary malignancies is different to adults. In adults, ~80% of the lung tumours are adenocarcinoma, small cell carcinoma or squamous cell carcinoma and the 5-year overall survival for all patients is very poor. In children, pleuropulmonary blastoma, inflammatory myofibroblastic tumour and carcinoid tumour are frequently recognised. The prognosis is dependent on the histology and stage. All patients with localised disease are treated with surgical resection. Some patients with advanced disease can be treated with chemotherapy, radiotherapy and selective surgery either independently or in combination.

Malignant tumours

Primary lung tumours are mostly malignant.

Pleuropulmonary blastoma (PPB) is a rare malignant embryonal mesenchymal neoplasm of the lung and pleura described in 1988 as a unique entity distinct from pulmonary blastoma. This tumour occurs almost exclusively in children <6 years of age. Three subtypes of PPB have been described; defined grossly:

- type I is cystic and lacks solid component,
- type III is solid without a cystic component,
- type II consists of a mixture of solid and cystic components.

PPB has a propensity to metastasis to the brain. The differential diagnosis for type I PPB includes more common benign cystic lung malformations. Treatment is based on aggressive surgery followed by multimodal chemo-radiotherapy. The overall 2-year survival is 63% (type I 80%; type II 73%; type III 48%). Although PPB has not been identified as part of a specific syndrome, it is a strikingly familial cancer with genetic implications for others in the immediate and extended families. In fact, in ~25% of cases, PPB is associated with other extrapulmonary lesions in the same patient or family members.

Carcinoid tumour is considered a low-grade neuroendocrine carcinoma due to its potential for locally aggressive growth and low potential for metastasis. These lesions are typically obstructive endobronchial masses in older children and adolescents and have been reported to account for 50–80% of primary malignant lung tumours in children. These lesions tend to be endobronchial and this probably explains the presentation with haemoptysis. Patients with carcinoid tumours seem to have the best prognosis. No adjuvant therapies are recommended for paediatric pulmonary carcinoid tumours. The outcome is related to the extent of disease at presentation and to the tumour resection.

Mucoepidermoid carcinoma is typically an exophytic polypoid mass that causes bronchial obstruction (80% of cases). Treatment is primarily surgical, with chemotherapy and radiotherapy reserved for those tumours with incomplete resection. The prognosis in children appears to be more favourable than in adults.

Inflammatory myofibroblastic tumour (IMT) has traditionally been considered benign and is known by many names including plasma cell granuloma and inflammatory pseudotumour. More recently, the World Health Organization recognised IMT as a low-grade mesenchymal malignancy. These nodular lesions are rarely endobronchial, and more frequently intraparenchymal. Surgical resection is the treatment of choice, although chemotherapy and radiation have been proposed as adjuvant therapy.

Among the rare epithelial lung cancers most paediatric cases are adenocarcinomas. The actual incidence in children is difficult to determine and is limited to individual case

reports and small case series. These tumours may occur in children at any age, but they are more usually found during adolescence. The adenocarcinomas in these patients are histologically similar to conventional pulmonary adenocarcinomas of adults and should be managed according to reasonable adult guidelines with surgical resection of operable tumours. Radiation therapy and chemotherapy may be of some benefit to patients with unresectable tumours. Delay in diagnosis and metastasis at presentation has led to generally poor survival in the few cases of bronchogenic carcinoma in children.

Benign tumours

Among benign lung tumours, hamartomas may present as large parenchymal masses with respiratory distress. Chest CT classically shows fat and "popcorn" calcifications, which suggest the diagnosis.

Metastatic lung tumours

Metastases to the lung are more common than primary lung malignancies in children, and they may be excised for diagnosis, staging or therapeutic purposes. Most malignant lung lesions are metastases from distant organs or direct invasions from adjacent structures. Metastatic tumours account for ~80% of all lung tumours in children and >95% of malignant tumours of the lung in this population. Wilms tumour, lymphoma, hepatoblastoma, rhabdomyosarcoma, Ewing sarcoma, osteosarcoma and gonadal tumours can produce metastases in the lungs, both isolated and multiple (fig. 1). Although a wide variety of childhood tumours produce lung metastases, Wilms tumour and osteosarcoma are the most frequent. Metastases to the lung can be seen on chest radiography, but CT frequently identifies small pulmonary nodules that are occult on conventional chest radiography. It is difficult to distinguish benign from malignant pulmonary nodules in children based on CT imaging features. Pulmonary metastases often appear as round, sharply marginated nodules, but they may be also ill-defined. While some metastatic lung nodules are excised for diagnosis and staging purposes, others are removed as a part of oncological management to achieve long-term survival and cure. Conversely, surgical management of metastatic disease is not used for chemosensitive and radiosensitive malignancies. Wilms tumour and osteosarcoma are the two most common solid tumours leading to surgical excision of isolated metastatic lung nodules.

Secondary involvement of the lung in systemic diseases

Langerhans cell histiocytosis presents in multiple organs including lungs. The lung is considered a high-risk organ, but is less frequently involved in children than in adults. Chest radiographs may show a nonspecific interstitial infiltrate. A chest CT is needed to visualise the cystic/nodular pattern of the Langerhans cell histiocytosis, which leads to the destruction of lung tissue. Medical treatment following Histiocyte Society clinical trials is recommended.

Leukaemia and lymphoma Leukaemic infiltration of the lung may cause a pattern that is radiographically similar to primary infections. Lung involvement by leukaemia usually manifests as patchy interstitial, septal or pleural infiltrates in contrast to non-Hodgkin and Hodgkin lymphoma, which tend to form larger, well-circumscribed nodules. An associated mediastinal mass or hilar adenopathy are variable features. Leukaemia and lymphoma are closely related and patients with leukaemia may present with an anterior mediastinal mass and pleural effusions. The distinction between the two is arbitrarily based on the degree of bone marrow involvement such that patients with ⩾25% marrow blasts are designated as having leukaemia. The differential diagnosis for lymphoma involving the lung in children primarily includes Hodgkin lymphoma and non-Hodgkin lymphoma. Associated pulmonary nodules and pleural effusions occur in only ~5% of patients with Hodgkin lymphoma, whereas effusions occur in 50–75% of those with non-Hodgkin lymphoma.

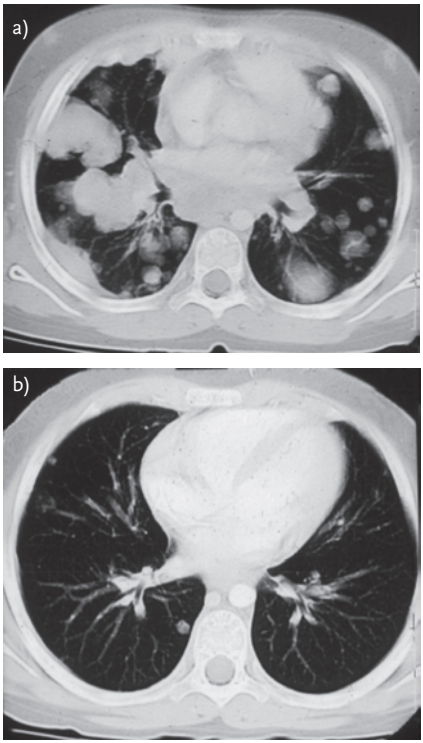

Figure 1. Metastatic Wilms tumour in a 9-year-old girl. a) A chest axial CT scan showing bilateral, large, hilar nodes and multiple round lung lesions with right pleural thickening. b) A chest axial CT scan performed after chemotherapy showing a dramatic decrease in parenchyma lesions and hilar nodes. There is no pleural involvement.

Mediastinal tumours

Tumours in the mediastinum are best characterised by the compartment in which they arise. Malignant tumours arising in the anterior mediastinum are most commonly due to lymphoma followed by germ cell tumours. Tumours of the posterior mediastinum are usually of neurogenic origin with neuroblastoma being most common.

Benign tumours are typically teratomas localised in the anterior mediastinum. About half of mediastinal tumours in childhood occur in the anterior mediastinum .The majority of these are malignant, including metastatic tumours and primary tumours such as lymphomas, germ cell tumours, carcinoid and thymoma.

Lymphoma Lymphoma accounts for ~13% of all childhood cancers and is the most common cause of a mediastinal mass in children. 60% of all lymphomas in this age group are non-Hodgkin lymphomas while Hodgkin lymphoma makes up the remainder (fig. 2).

Diagnosis The growth rate in non-Hodgkin lymphoma is often more rapid than in Hodgkin lymphoma. Non-Hodgkin lymphomas have a rapidly growing tumour mass that can cause life-threatening complications. In particular, children with anterior mediastinal masses are at high risk of life-threatening airway compromise during anaesthesia. Large mediastinal masses can cause compression of surrounding mediastinal structures and patients may have symptoms of airway obstruction or cardiovascular compromise. The additive effects of an anaesthetic with paralysis and positioning during biopsy can lead to acute airway obstruction and death. The least invasive procedure should be used to establish the diagnosis. Lymph nodes in areas outside the mediastinum provide access for tissue diagnosis; in the other cases, a diagnostic and management challenge arises for paediatric surgeons. Some patients at greatest risk require pre-treatment of the mass before tissue diagnosis. Anterior mediastinal masses in children should be approached in a step-wise fashion with multi-disciplinary involvement, starting with the least invasive techniques and progressing cautiously. Biopsy may be obtained by trans-thoracic puncture under CT or ultrasound guidance and it can be considered a viable, safe and accurate method of reaching a diagnosis in the paediatric population. If these children require general anaesthesia for diagnosis, the surgeon should have a well-defined and pre-operatively established contingency plan. Of the many clinical, functional and radiological criteria used to identify the children at greatest risk for anaesthetic complications, the peak expiratory flow rate (PEFR)

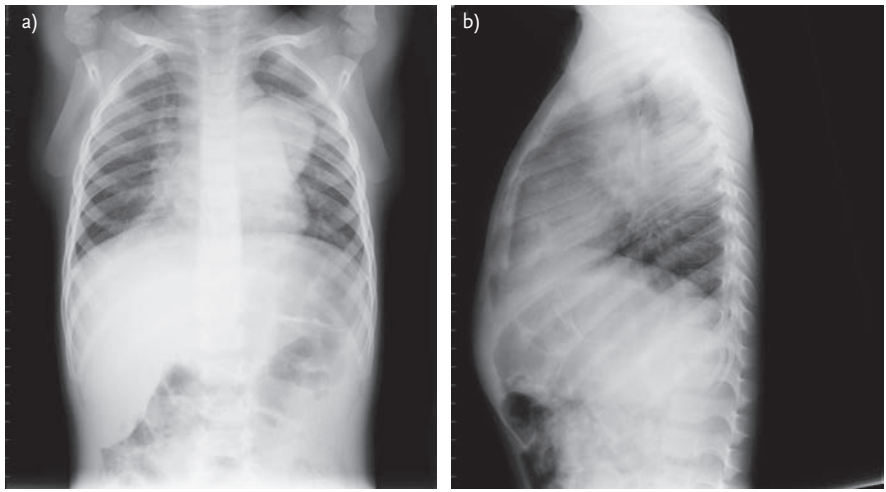

Figure 2 Hodgkin lymphoma in 7-year-old boy. a) Anteroposterior and b) lateral chest radiographs demonstrate a large anterior mediastinal mass lesion.

and the tracheal cross-sectional area seem to be the most reliable. General anaesthesia should not be administered to children if the PEFR and tracheal cross-sectional area are both <50% predicted. If both are >50% pred, general anaesthesia can be administered safely.

Treatment After diagnoses and staging evaluation by imaging, chemotherapy is the main component of treatment for childhood non-Hodgkin lymphoma, while the majority of patients with Hodgkin lymphoma are currently managed with combined modality, incorporating radiotherapy and chemotherapy.

Germ cell tumours/teratomas

About 20% of mediastinal germ cell tumours are malignant and include seminomas and non-seminomatous tumours, such as teratocarcinoma, yolk sac tumour, embryonal carcinoma, choriocarcinoma and mixed types, the others are teratomas. Malignant germ cell tumours are generally a complex tumour, often containing coexisting benign components. There are two age peaks for mediastinal germ cell tumours at about 2 years of age and at adolescence. During infancy and young childhood, the histological subtypes are restricted to benign teratoma and yolk sac tumour. In adolescence, histological subtypes most commonly include yolk sac tumour, seminoma, teratoma and immature teratoma. Seminomas lack serological markers, whereas non-seminomatous tumours are often associated with increased serum β-human chorionic gonadotropin or alpha-fetoprotein levels. Adolescents may be relatively asymptomatic, whereas infants may have severe respiratory symptoms. Surgical excision is the therapy of choice in benign tumours such as teratomas. Malignant germ cell tumours are chemosensitive tumours.

Posterior mediastinum Approximately 90% of posterior mediastinal masses in children are of neurogenic origin. These include ganglion cell tumours and nerve tumours. Most are ganglion cell tumours that arise from sympathetic chain ganglia and form a spectrum of disease ranging from the most aggressive, neuroblastoma, to the less aggressive, ganglioneuroblastoma and benign ganglioneuroma. About 30% of these contain calcifications on radiological imaging.

Tumours of the pleura

Mesothelioma of the pleura is primarily a tumour of the adult, >90% of mesothelioma are diagnosed after the fifth decade of life; the prognosis is dismal. Pleural involvement by malignant tumours in children is typically from metastatic diseases, invasive chest wall neoplasms, lymphoma or pleuropulmonary blastoma.

Chest wall tumours

The most common malignant primary tumours of the chest wall arise from bone or soft tissue. They are mostly commonly of the Ewing types (Askin or primitive neuroectodermal tumour) or rhabdomyosarcoma; others include fibrosarcoma or osteosarcoma. Non-malignant chest wall tumours are neurofibroma, haemangiomas and osteochondromas. Imaging findings that suggest a malignant chest wall mass include rib destruction, pleural extension and large size. The prognosis is dependent on the total resection, as well as on the histology and stage. Small-cell malignant tumours, such as Ewing's sarcoma and Askin's tumour, should be treated with an aggressive multimodality approach combining chemotherapy, radiation therapy and surgery.

Mesenchymal hamartomas of the chest wall are unusual rib lesions most commonly affecting infants. The typical radiographic manifestation of a chest wall mesenchymal hamartoma is that of a large, extrapleural, partially calcified soft-tissue mass arising from one or more ribs, with associated destruction and distortion of the bone. Although these features suggest an aggressive process, mesenchymal hamartomas are benign lesions, with no reports of recurrence or metastasis following complete surgical resection.

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Systemic disorders with lung involvement

Andrew Bush

The lung can be affected by systemic disease in a number of ways, which are not necessarily mutually exclusive.

- The underlying condition has both systemic and pulmonary specific manifestations, for example ciliopathy, in which ciliary disease can cause combinations of upper and lower respiratory disease, complex congenital heart disease, retinitis pigmentosa, and renal, hepatic and pancreatic cystic disease. Only those diseases not covered elsewhere in this *Handbook* will be discussed in this section.

Key points

- Although individual rare diseases are, by definition, rare, taken together, they are sufficiently common that they need to be considered in paediatric respiratory differential diagnosis.
- Respiratory paediatricians need to be aware that multisystem diseases may present with respiratory signs and symptoms.
- Respiratory paediatricians also need to be ready to advise specialists in other fields, especially cardiology, nephrology and hepatology, about respiratory complications of their disease specialities.
- Ciliary dysfunction, far from being a purely respiratory issue, affects multiple organs. The basic science and clinical aspects of ciliopathy are a huge growth area.

- An extrapulmonary disease may itself be a single-organ disease but the consequence of that disease (causing dysfunction of that organ) affects the lung either through relatively specific (*e.g.* hepatopulmonary syndrome) or nonspecific mechanisms (*e.g.* pulmonary oedema secondary to renal or cardiac failure), or by causing dysfunction in an another organ.
- Lung disease or its treatment may affect another organ and dysfunction of that organ may create a positive feedback loop, worsening lung disease. An obvious example is OSA leading to congestive cardiac failure and secondary pulmonary oedema.
- The treatment of a systemic disorder may affect the lungs (*e.g.* chemotherapy with bleomycin leading to pulmonary fibrosis).
- Finally, apparent associations that are in fact artefacts of receiving medical attention for another condition must not be confused with real connections between diseases.

This section will give a brief overview of the lung manifestations of liver, kidney and heart disease; haemoglobinopathy, excluding sickle cell disease, which is discussed elsewhere; connective tissue disorders (both acquired inflammatory (*e.g.* systemic lupus erythematosus (SLE)) and inherited (*e.g.* Ehlers–Danlos syndrome)), metabolic diseases and miscellaneous disorders (*e.g.* familial dysautonomia and lymphangiomatosis). Pulmonary manifestations of congenital and acquired immunodeficiencies are discussed elsewhere.

Table 1. Diseases affecting the liver and lung

Disease	Liver manifestations	Lung manifestations
CF	Fatty liver Biliary cirrhosis Portal hypertension Gall stones	Chronic infection and inflammation Pneumothorax Haemoptysis Allergic bronchopulmonary aspergillosis
α_1-antitrypsin deficiency	Cirrhosis	Bronchiectasis and emphysema
Ciliopathy	Biliary atresia Cystic liver disease	Recurrent infections Bronchiectasis Chest wall deformity (Jeune's and other syndromes)
TB	Granulomas	Granulomas Fibrosis Bronchiectasis Lymphadenopathy Pleural effusion
Sarcoidosis	Hepatosplenomegaly	Granulomas Lymphadenopathy Pulmonary fibrosis
Gaucher disease	Hepatosplenomegaly	Pulmonary infiltration with Gaucher cells
Mucopolysaccharidoses	Hepatosplenomegaly	Upper airway obstruction Skeletal malformations leading to extrapulmonary restrictive lung disease
Niemann–Pick disease	Hepatosplenomegaly	Pulmonary infiltrates Extensive bronchial casts

Lung manifestations of liver disease

Diseases affecting the liver and the lungs The more important of these are summarised in table 1.

Effects of liver dysfunction on the lung The definition of hepatopulmonary syndrome (HPS) in children is the presence of:

- liver disease;
- hypoxaemia (alveolar–arterial oxygen tension gradient >15 mmHg or PaO_2 <80 mmHg while breathing room air);
- evidence of intrapulmonary shunting; and
- no other cause of hypoxaemia.

HPS is manifest by profound hypoxaemia due to intrapulmonary right-to-left shunting, ventilation/perfusion mismatch and, possibly, the creation of a functional diffusion barrier; it must be distinguished from hypoxia as a nonspecific complication of liver disease due to ascites, pulmonary oedema or pleural effusion. Pulmonary angiogenesis may also be a feature. Prevalence is reported as up to 35% in cirrhotic children but the syndrome may be seen even with relatively mild disease. There will be signs of liver disease, especially spider naevi, and platypnoea (worsening hypoxaemia ongoing from the supine to the erect position). Digital clubbing is common. Spirometry and lung volumes are usually normal, with reduced diffusion capacity; in severe disease, restrictive physiology may be seen. Cases have been described in

association with noncirrhotic portal hypertension and otherwise uncomplicated viral hepatitis. The pathophysiology is not known but the physiological abnormality is usually due to dilatation of pulmonary capillaries; occasionally, the syndrome arises as a result of the development of anastomoses between pulmonary and systemic veins, in the portal or paraoesophageal regions. This syndrome should be remembered in children with diseases affecting liver and lung (*e.g.* CF) if there is hypoxaemia disproportionate to the apparent severity of the lung disease. The abnormal shunting may be detected by contrast echocardiography (peripheral injection of saline containing microbubbles, which rapidly appear in the left atrium); a perfusion scan, which will show accumulation of technetium that has bypassed the lungs in the brain and kidneys, and can be used to quantify shunt; and contrast HRCT. Technetium scanning may be the most sensitive test. Contrast echocardiography may be positive even in nonhypoxaemic liver disease, suggesting that subclinical HPS is common. Treatment is of the underlying liver disease, if this is susceptible to medical management, which may resolve HPS. Nonspecific measures include supplemental oxygen but the child is likely eventually to undergo liver transplantation due to rapidly progressive hypoxaemia. Hypoxaemia related to pulmonary angiogenesis (see earlier) may not respond to liver transplantation. The rare cases with large shunts may benefit from coil embolisation. Medical management is anecdotal; for example, case series of the use of methylene blue and antibiotics. Untreated the prognosis is poor (23% 5-year survival *versus* 69% in patients matched for severity of liver disease but without HPS).

Pulmonary hypertension is covered in more detail in the section on Pulmonary vascular diseases; it is far less common than HPS and, rarely, features of both may co-exist. Presentation is as with primary pulmonary hypertension. The reasons why some patients develop HPS while others develop severe pulmonary hypertension are not known.

Hepatocellular failure may lead to ascites and, in theory, large volumes of intra-abdominal fluid may splint the diaphragm causing respiratory impairment. In fact, old studies looking at lung function before and after tapping even huge volumes of ascites (a practice now known to be dangerous) showed remarkably little change in lung function. However, if there are discontinuities in the diaphragm, pleural effusions may result. Hepatorenal syndrome is a serious consequence of advanced ascites, due to systemic and splanchnic vasodilatation, and renal vasoconstriction, leading to multiorgan (including lung) failure. There are two types of HPS. Type 1 presents as acute renal failure, type 2 as reduced glomerular filtration rate and refractory ascites. Pulmonary oedema may be exacerbated by hypoalbuminaemia and cirrhotic cardiomyopathy, the latter of which is characterised by diastolic dysfunction. Treatment of these serious complications should be in a specialist liver unit. Another indirect mechanism of lung disease is pulmonary compression by a hugely involved liver and spleen; partial and total excision of a huge spleen has been reported in CF with at least transient benefit. Finally, there may be dilation of bronchial veins in children with portal hypertension, similar to oesophageal varices. If there is haemoptysis as well as haematemesis complicating portal hypertension, bronchial embolisation may be considered as well as variceal banding.

Lung manifestations of kidney disease

Diseases affecting the kidney and the lungs

The more important of these are summarised in table 2.

Effects of renal dysfunction on the lung

Pulmonary oedema and pleural effusion are the most common pulmonary manifestations of renal disease. ''Uraemic lung'', manifested by pulmonary oedema, is multifactorial in origin and is not a simple transudate. Aetiological factors in a given individual may include fluid overload, hypoproteinaemia, myocardial dysfunction and increased pulmonary capillary permeability. Pleural effusion is also

Table 2. Diseases affecting the kidney and lung

Disease	Kidney manifestations	Lung manifestations
CF	Acute and chronic renal failure Renal stones Renal amyloid	Chronic infection and inflammation Pneumothorax Haemoptysis Allergic bronchopulmonary aspergillosis
Ciliopathy	Cystic kidney disease Nephronophthisis Renal dysplasia	Recurrent infections Bronchiectasis Chest wall deformity (Jeune's and other syndromes)
Wilm's tumour	Renal mass	Pulmonary metastases Pulmonary embolism
Tuberose sclerosis	Angiolipoma Renal cystic disease Renal carcinoma	Lymphangioleiomyomatosis
Goodpasture's syndrome	Glomerulonephritis Renal failure	Pulmonary haemorrhage
Granulomatosis with polyangiitis (Wegener's)	Glomerulonephritis Renal failure	Pulmonary haemorrhage (Upper airway disease)
SLE	Glomerulonephritis Renal failure	Interstitial lung disease Pleuritis and pleural effusion Acute pneumonitis Pulmonary haemorrhage and increased risk of infection
Henoch–Schönlein purpura	Glomerulonephritis Renal failure	Pulmonary haemorrhage
Scleroderma	Renal failure	Pulmonary fibrosis Aspiration Pulmonary vasculopathy and pulmonary hypertension
Glomerulonephritis (especially membranous)	Nephrotic syndrome	Pulmonary embolism
Potter's syndrome	Renal agenesis	Pulmonary hypoplasia

multifactorial, including fluid overload and uraemic pleuritis.

Other indirect effects include opportunistic infection secondary to immune suppression, urinothorax secondary to obstructive uropathy, respiratory muscle dysfunction, and dystrophic calcification secondary to chronic acidosis and abnormal calcium and phosphate homeostasis. Calcification is frequently an asymptomatic finding. Immunosuppression leads to a higher than expected prevalence of TB, for which a high index of suspicion should be maintained because presentation may be atypical.

Side-effects of medications used to treat renal disease may affect the lung, including iatrogenic immunosuppression, the consequences of plasmapheresis, and medications used to treat hypertension, including angiotensin-converting enzyme (ACE) inhibitors causing chronic cough.

Haemodialysis complications include the potential for silicone emboli and activation

of the complement cascade and other immunological issues of dialysis membranes causing hypoxaemia. Hypoventilation secondary to carbon dioxide loss across the dialysis membrane may contribute to hypoxaemia. Peritoneal dialysis may cause pleural effusions if there are diaphragmatic defects. The volumes of fluid used for peritoneal dialysis have little acute effect on lung function.

Lung manifestations of cardiac disease

Respiratory paediatricians inevitably interact with paediatric cardiologists and, often, the debate is whether respiratory issues are primary or secondary to heart disease. In my experience, the clinical scenario "the child has a respiratory problem and it's not the heart" is usually resolved when it is discovered that it *is* the heart.

Diseases affecting the heart and the lungs The more important of these are summarised in table 3.

Effects of cardiac dysfunction on the lung Respiratory diseases may be the first presentation of an underlying cardiovascular abnormality. Steroid-resistant asthma may be the presentation of a vascular ring or pulmonary artery sling; the latter may also be associated with complete cartilage rings, complicating assessment. Diagnosis of vascular compression is with contrast-enhanced CT or MRI. "Exercise-induced asthma" in young adults who have had ligation of the arterial duct as part of the management of lung disease of prematurity may, in fact, be a late complication of recurrent laryngeal nerve damage. The breathless child may have pulmonary oedema secondary to a hitherto unsuspected congenital cardiac lesion (pulmonary venous hypertension or high pulmonary blood flow due to left-to-right shunting), or a congenital or acquired cardiomyopathy. Enlarged cardiac chambers secondary to these conditions may cause airway compression and localised atelectasis or pneumonia. Recurrent multifocal consolidation may be the presentation of increased pulmonary blood flow due to left-to-right shunts.

Primary respiratory disease may have a cardiovascular presentation; for example, apparent dilated cardiomyopathy may be a presentation of OSA, and "primary pulmonary hypertension with a normal chest radiograph" may be the presentation of OSA, interstitial lung disease and pulmonary embolism.

The child in a paediatric intensive care unit (PICU) after cardiac surgery presents particular challenges to the paediatric pulmonologist. Respiratory failure and acute respiratory distress syndrome (ARDS) are well-described complications of cardiopulmonary bypass, and activation of complement and other immunological cascades by the membrane oxygenator is thought to be responsible. Ventilator-acquired pneumonia is an important complication of especially prolonged ventilation and must be distinguished from other causes of new infiltrates, such as atelectasis and pulmonary oedema. Another common referral is the ventilated child who weans to minimal support but then fails extubation. Significant pulmonary parenchymal disease is excluded by a low oxygen requirement. The differential diagnosis lies between upper airway obstruction (usually subglottic stenosis or vocal cord paralysis secondary to recurrent laryngeal nerve damage) and respiratory muscle disease (usually due to phrenic nerve damage, occasionally an intensive care unit myopathy). If upper airway obstruction is suspected, bronchoscopy should be performed with the child being extubated for the purpose, under a formal general anaesthetic. Another common referral is a unilateral, post-cardiac surgical whiteout. Fluid (pleural effusion, chylothorax or haemothorax) is excluded with thoracic ultrasound. The differential diagnosis then lies between extrinsic compression of the airway by an enlarged cardiac chamber, surgically placed shunt or great vessel, airway malacia (which is relatively common in cardiac patients), and airway plugging by mucus or a blood clot. A particularly difficult issue to deal with is the airway compression by the hugely enlarged pulmonary arteries seen in absent pulmonary valve syndrome, usually associated with tetralogy of Fallot.

Table 3. Diseases affecting the heart and lung

Disease	Cardiac manifestations	Lung manifestations
Down syndrome	Congenital heart disease	Gastro-oesophageal reflux Incoordinate swallowing OSA
VATER, VACTER, and VACTERL syndromes	Congenital heart disease, especially ventricular and atrial septal defects Tetralogy of Fallot	Tracheo-oesophageal fistula Vertebral abnormalities leading to scoliosis
William's and Noonan's syndromes	Aortic and pulmonary stenosis Cardiomyopathy	Pulmonary lymphangiectasia Chest wall deformity
Ciliopathy	Complex congenital heart disease, especially with heterotaxic syndromes	Recurrent infections Bronchiectasis Chest wall deformity (Jeune's and other syndromes)
TB	Pericardial effusion Constrictive pericarditis	Ghon focus Pleural effusion Lung cavities and fibrosis
Sarcoidosis	Cardiomyopathy Arrhythmia	Lung granulomas Pulmonary fibrosis
Neurological disease	Cardiomyopathy	Inspiratory and expiratory muscle dysfunction Incoordinate swallowing Upper airway obstruction
CF	Impaired function and tamponade due to air leaks	Chronic infection and inflammation Pneumothorax Haemoptysis Allergic bronchopulmonary aspergillosis
Mucopolysaccharidoses	Cardiomyopathy	Upper airway obstruction Restrictive lung disease Chest wall deformity Recurrent respiratory infections
SLE	Myocarditis Pericarditis Endocarditis	Interstitial lung disease Pleuritis and pleural effusion Acute pneumonitis Pulmonary haemorrhage Increased risk of infection
Scleroderma	Cardiomyopathy	Pulmonary fibrosis Aspiration Pulmonary vasculopathy Pulmonary hypertension

VATER: vertebral anomalies, anal atresia, tracheo-oesophageal fistula, renal and/or radial anomalies; VACTER: vertebral anomalies, anal atresia, cardiovascular anomalies, tracheo-oesophageal fistula, renal and/or radial anomalies; VACTERL: vertebral anomalies, anal atresia, cardiovascular anomalies, tracheo-oesophageal fistula, renal and/or radial anomalies, and limb defects.

Very rarely, a pneumonia involving all lobes of the lung is the cause of a complete whiteout; in such cases, the child is obviously septic.

Other post-surgical respiratory complications include tracheal infarction secondary to unifocalisation procedures, and superior caval vein thrombosis leading to secondary pulmonary lymphangiectasia and chylothorax. An intriguing late complication of the Fontan procedure is hypoxaemia due to microscopic pulmonary arteriovenous malformation, analogous to HPS (see earlier). Exclusion of hepatic blood flow from the affected areas of the lung may be the cause and revision surgery may relieve hypoxaemia.

Among the most feared and difficult-to-treat late pulmonary complications of cardiac disease is type 2 plastic bronchitis, usually seen in association with low-flow circuits such as after the Fontan procedure. The child expectorates branching, mucoid bronchial casts, which may be so large as to be life-threatening. Treatments include nebulised fibrinolytics, macrolides and lymphatic duct ligation. In extreme, treatment-refractory cases, heart transplantation may be indicated.

Medical cardiac treatments may also affect the lungs; for example, ACE inhibitors cause chronic cough. Finally, chemotherapy and mediastinal radiotherapy for malignant disease may have cardiac and respiratory repercussions.

Pulmonary embolism is dealt with in more detail in the section on Pulmonary vascular disorders. Predisposing factors in the context of cardiac disease include the placement of intravascular catheters, low cardiac output, left atrial dilatation, arrhythmia, right-sided endocarditis secondary to valve disease and immobility. Eisenmenger's syndrome is associated both with coagulopathy and a bleeding diathesis.

Lung manifestations of gastrointestinal disease

The most common causes of lung and gastrointestinal disease are gastro-oesophageal reflux disease and CF, which are discussed in detail elsewhere.

Inflammatory bowel disease Pulmonary manifestations are rare. In ulcerative colitis, the commonest parenchymal problem is bronchiolitis obliterans organising pneumonia (BOOP). Other manifestations include pulmonary fibrosis and pulmonary interstitial pneumonia. Pulmonary nodules and pleural disease are rare. Airway disease, including bronchiectasis and chronic airway sepsis, are reported and pulmonary complications can occur after panproctocolectomy for ulcerative colitis. Laryngeal and tracheal granulomatous lesions have been rarely reported. Other issues are a thrombotic tendency leading to pulmonary embolism and the iatrogenic complications of corticosteroids and other immunosuppressants used for treatment.

Acute pancreatitis ARDS and respiratory failure are well-described complications of this condition.

Coeliac disease There are case reports of co-existence of coeliac disease and idiopathic pulmonary haemosiderosis (Lane-Hamilton syndrome). There may also be an increased susceptibility to TB in coeliac disease patients, possibly related to immunodeficiency secondary to malabsorption.

Lung manifestations of haemoglobinopathies

Sickle cell disease (SCD) is the best studied haemoglobinopathy, which has a number of acute and chronic complications. These are discussed in the section on Sickle cell disease and, therefore, are not detailed here.

Other haemoglobinopathies The chronic main pulmonary consequences are related to iatrogenic iron overload, which may affect the liver, kidneys and endocrine systems, with renal and hepatic consequences having indirect effects on the lungs. Direct pulmonary effects are less studied, although pulmonary iron deposition has been documented. Other findings include restrictive lung disease suggestive of either or both of pulmonary fibrosis and interstitial

pulmonary oedema, abnormal lung mechanics and haemosiderin-laden macrophages in bronchoalveolar lavage (BAL) fluid. Pulmonary hypertension may also occur.

Lung manifestations of inherited connective tissue disorders

Ehlers–Danlos syndrome is a heterogeneous group of conditions, characterised by skin hyperextensibility and tissue fragility, and joint hypermobility. It is inherited as an autosomal dominant mutation. Pulmonary manifestations are seen in types IV and VI, and include emphysema, bullae and pneumothorax, tracheobronchomegaly and haemoptysis.

Marfan's syndrome is autosomal dominant with an incidence of one in 5000. It is caused by mutations in the *FBN1* gene, which encodes fibrillin, an important structural molecule, which also is pivotal in the control of transforming growth factor (TGF)-β signalling. Systemic features of Marfan's syndrome include aortic root dilatation and aneurysm, mitral valve prolapse, joint hypermotility, and a high-arched palate. The respiratory manifestations, which are usually a minor feature of the condition, include scoliosis, pectus excavatum and carinatum, and pneumothorax. Bronchiectasis, tracheobronchomegaly and histological changes of distal acinar emphysema have been reported.

Lung manifestations of acquired inflammatory connective tissue disorders

These are rare in childhood and, in most cases, do not affect the lungs. Space precludes describing many rarer entities.

Systemic lupus erythematosus Pulmonary manifestations may be the presenting feature in children and eventually occur in 20–40%. These include pleuritis and pleural effusion (the commonest manifestation), interstitial lung disease, acute lupus pneumonitis that may progress rapidly to respiratory failure, pulmonary haemorrhage, and increased risk of infection, including *Pneumocystis jirovecii* pneumonia. Indirect pulmonary effects may arise from renal and cardiac disease and coagulopathy, including pulmonary embolism. Pulmonary hypertension may be asymptomatic until late on and has an ominous prognosis. Lung function testing usually shows a restrictive pattern. Airway disease is rare in SLE.

Dermatomyositis Respiratory problems are usually secondary to muscle dysfunction. Oropharyngeal muscle problems may lead to incoordinate swallowing and recurrent aspiration. Inspiratory and expiratory muscle weakness may lead to respiratory failure initially during sleep, and a weak cough and recurrent infections respectively. Direct lung involvement is rare in children but may include vasculitis and pulmonary alveolar proteinosis.

Scleroderma Lung involvement is present in the majority (90%) of children afflicted by this very rare disease and is the leading cause of death. Manifestations include pulmonary fibrosis, aspiration secondary to oesophageal problems and pulmonary vasculopathy leading to pulmonary hypertension.

Granulomatosis with polyangiitis (Wegener's) and other pulmonary vasculitides A classification of systemic vasculitides affecting the lung is given in table 4. Pulmonary involvement in vasculitides is common in granulomatosis with polyangiitis and Kawasaki disease, and less common in Churg–Strauss syndrome, polyarteritis nodosa, Henoch–Schönlein purpura and Takayasu's arteritis. Vasculitis may be complicate connective tissue disorders such as dermatomyositis (see earlier) and Behçet's disease. Manifestations depend on the size of the vessels involved: medium-to-large artery involvement leads to pulmonary infarction and necrosis, sometimes with granulomas; small-vessel arteritis causes pulmonary haemorrhage. There may be clues as to the underlying aetiology from systemic features, such as upper airway and renal disease in granulomatosis with polyangiitis, and the typical oropharyngeal appearances and lymphadenopathy in Kawasaki disease. A positive cytoplasmic anti-neutrophil

cytoplasmic antibody (c-ANCA) test is reasonably specific for granulomatosis with polyangiitis; perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) elevation is also seen in other vasculitides. Pulmonary vasculitis enters the differential diagnosis of pulmonary haemosiderosis and should be excluded by lung biopsy if necessary because this may affect treatment decisions, for example the use of pulsed cyclophosphamide.

Lung manifestations of storage disorders

Gaucher disease is an autosomal recessive condition characterised by accumulation of glucosylceramide in macrophages. Type 1 commonly presents in childhood. Clinical lung disease is unusual, being seen in <10% of cases (usually those presenting early with severe systemic disease), but subclinical respiratory issues may be present in 70%. These include both airway obstruction and restrictive lung disease. Respiratory problems may be due to infiltration of the interstitium and alveolar spaces by Gaucher cells, or indirectly as a consequence of lung compression by massive hepatosplenomegaly, or the consequences of liver disease, including HPS (see earlier). Types 2 and 3 are dominated by neurological disease, which may also lead to secondary lung complications. Treatment is with enzyme therapy (which, however, will not reverse neurological disease) or bone marrow transplantation.

Mucopolysaccharidoses At least nine forms are known, characterised by abnormal tissue deposition of glycosaminoglycans (GAGs) as a result of mutations in lysosomal enzyme genes. Respiratory issues include upper airway obstruction leading to sleep disordered breathing (especially in Hurler syndrome) and restrictive lung disease. This is multifactorial, is especially seen in Hunter and Hurler syndromes, and includes deposition of GAGs in the lung and skeletal deformity, indirectly *via* hepatosplenomegaly. The child may have recurrent respiratory infections. Indirect pulmonary effects may also arise from the effects of cardiomyopathy. Finally, instability of the odontoid process, which may cause fatal cord compression, should be remembered, especially in type IV (Morquio's syndrome).

Niemann–Pick disease There are at least six forms, all of which may show pulmonary infiltrates, but especially type B (the visceral form). The first presentation may be with interstitial lung disease. Other direct pulmonary manifestations include recurrent infection and haemoptysis. There may be extensive bronchial casts. There is a restrictive pattern of lung disease, and progressive respiratory failure. Liver and neurological involvement may also impact lung disease.

Lung manifestations of miscellaneous disorders

Familial dysautonomia (Riley–Day syndrome), an autosomal recessive disorder, is mainly found in Ashkenazi Jews, and is characterised by progressive autonomic dysfunction and crises. The most common respiratory manifestations include aspiration leading to recurrent pneumonia

Table 4. Systemic vasculitides that may affect the lung

Predominant large vessel vasculitis: Takayasu's arteritis
Predominant medium vessel vasculitis: Kawasaki disease, childhood polyarteritis nodosa, cutaneous polyarteritis
Predominantly small vessel arteritis
Granulomatous: granulomatosis with polyangiitis (Wegener's), Churg–Strauss syndrome
Nongranulomatous: Henoch–Schönlein purpura, microscopic polyangiitis, Goodpasture's syndrome
Others: Behçet's disease, associated with connective tissue disease

and bronchiectasis, and nocturnal hypoventilation. Respiratory disease is the major cause of morbidity.

Lymphangiomatosis is rare and characterised by abnormal proliferation of lymphatics affecting the lung, mediastinum, liver, soft tissue, bones and spleen. 80% of cases have lung involvement, manifested by chylous effusions, interlobular septal thickening and thickened pleura. Bony infiltration and rib fractures can worsen respiratory status. Typically, fractures fail to heal. Prognosis is poor, and death usual from extensive pulmonary and systemic disease. Successful treatment with interferon-α2b has been reported.

Yellow nail syndrome (YNS) This condition is characterised by nail dystrophy, and combinations of (nonpitting) lymphoedema and bronchiectasis, sometimes with chronic sinusitis, recurrent pneumonia or a high-protein pleural effusion. Lung cysts have been described in YNS. The underlying cause is thought to be structural or functional lymphatic dysfunction. Presentation is mainly, but not exclusively, in adult life. The diagnosis is clinical. Autosomal dominant cases have been reported, although most are sporadic. There is no specific treatment for YNS, although anecdotally, some improvement with vitamin E therapy has been reported. Management of bronchiectasis is as for the idiopathic condition. Recurrent troublesome pleural effusions may mandate pleurodesis or thoracic duct ligation. There is a tendency for improvement over time, although overall survival is decreased. Although a number of rare associations with YNS have been described (including immunodeficiency, malignancy, connective tissue disease and endocrinopathy), these are probably spurious in many cases.

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Lung transplantation and management of post-lung transplant patients

Paul Robinson and Paul Aurora

- Lung transplantation is now a well-established treatment for children with end-stage lung disease, with >120 paediatric lung transplantations now performed worldwide each year, across 40–50 centres (Benden *et al.*, 2012).
- The majority of centres (>80%) perform fewer than five transplantations a year, with only two or three centres performing >10 procedures each year .
- Infant lung transplantation has been established at centres in North America but this remains a small proportion of total paediatric transplantations (only eight performed in 2010).
- Procedures performed have changed: bilateral single sequential lung transplantation now is preferred to heart–lung transplantation, with the latter reserved mainly for cases with significant left heart dysfunction (*e.g.* idiopathic pulmonary arterial hypertension (IPAH) and congenital heart disease).
- Single-lung transplantation is rarely performed in the paediatric age range, mainly reflecting its contraindication in suppurative lung disease, such as CF.

Indications for lung transplantation

The most common indication for lung transplantation in the paediatric age range is CF, although the indications are age dependent (table 1). CF is the most common indication from school age, whereas in younger children, other pathologies such as IPAH, congenital heart disease, idiopathic pulmonary fibrosis and surfactant protein dysfunction are the indications.

Key points

- Short- and long-term outcomes have improved but still lag behind other solid-organ transplant groups. Chronic graft rejection remains a significant barrier to further improvements in survival.
- Donor organ shortage remains a critical issue. Given this limited resource, optimal timing of transplantation is both essential and challenging, especially in conditions where survival can be difficult to predict.
- A lifelong regimen of triple immunosuppression is used, consisting of a CNI, a cell cycle inhibitor (or antimetabolite) and a corticosteroid. Important drug interactions exist with CNIs which the physician must be aware of.
- Post-transplantation management focuses on ongoing rehabilitation, careful surveillance, and treatment of acute and chronic complications, including infection and graft rejection.

Selection for lung transplantation

Current international guidelines for referral and selection of lung transplant recipients (Orens *et al.*, 2006) are based upon limited paediatric data and the decision to list a child for lung transplant is often based on a multidisciplinary team consensus within the individual centre. Potential survival and

Table 1. Common indications for lung transplantation by age group

Indication	Cases %
Infancy (age <1 year)	
Surfactant protein B deficiency	18
Congenital heart disease	15
IPAH	13
Preschool (age 1–5 years)	
IPAH	23
Idiopathic pulmonary fibrosis	18
Bronchiolitis obliterans	8
Early school age (6–11 years)	
CF	54
IPAH	10
Bronchiolitis obliterans	7
Adolescence (12–17 years)	
CF	72
IPAH	7
Bronchiolitis obliterans	4

Data from Benden *et al.* (2012).

quality of life (QoL) benefits are offset against an individual's risk of perioperative mortality and both short- and long-term complications of transplantation. Early referral is preferable, as late referral potentially affects not only the ability of the family to make a carefully considered decision about whether they want a transplant, but also because poor clinical status may adversely affect suitability for listing. Lung transplantation is indicated in children where lung function parameters and QoL are declining despite maximal medical therapy (Aurora, 2004). Broad criteria for listing are as follows.

- Predicted life expectancy, without transplantation, of ⩽2 years.
- Poor QoL, which is likely to be improved by transplantation. Assessment of QoL is taken ideally from the child's perspective, and details their ability to complete daily routine activities, participate in school and social activities, and the time spent in hospital.
- No specific contraindications (table 2). Relative contraindications are assessed on a case-by-case basis.
- An acceptable psychological profile.
- Fully informed commitment by the child and family. This includes good social support to aid rehabilitation following transplantation surgery and a commitment to the procedure involved, the required lifestyle adjustments and strict adherence to the medication regimen.

Life expectancy criteria also account for the probable waiting period for a suitable organ to become available and may vary depending on the centre. Existing survival prediction models for CF are only estimations and have limitations: changing CF survival rates over time, lack of paediatric-specific validation and lack of validation in children being assessed for transplantation. The referral criterion of FEV_1 <30% predicted is widely quoted but important exceptions, where referral should be considered at higher FEV_1 due to an increased risk of accelerated future decline, exist:

- females;
- very young patients;
- subjects declining quickly;
- subjects with a history of massive haemoptysis, pneumothorax or increasing acute exacerbation frequency.

Donor allocation

- Standard donor criteria exist but have been criticised for being too restrictive. Only 20–30% of lungs offered for use in organ transplantation are usable.
- "Marginal donors" are considered but only used with informed consent from the recipient and family.
- Organs procured from brain-dead donors, the use of non-heart beating donors (used in other solid-organ transplant groups successfully) and *ex vivo* lung perfusion attempt to address this imbalance, with encouraging results (Cypel *et al.*, 2012).

Table 2. Specific contraindications to lung transplantation in children

Absolute	Relative
Active malignancy Active TB Major psychiatric illness Hepatic, renal and left ventricular failure[#] Irreversible and significant respiratory muscle dysfunction	Pan-resistant bacterial infection Nontuberculous mycobacterial infection Other organ failure HIV infection Nonadherence to treatment Invasive ventilation Long-term high-dose steroid therapy Hepatitis B or C *Burkholderia cenocepacia* (genomovar III) Severe scoliosis or thoracic rib cage deformity Severe tracheomegaly and/or tracheomalacia Severe transpleural systemic to bronchial artery collateral arteries

Contraindications vary between transplant centres and the referring physician should always check with their own centre. [#]: multiorgan transplantation (*e.g.* lung–liver, heart–lung or lung–kidney) may be considered in this situation.

- Living-related lobar lung transplantation has decreased in recent years, in part due to the potential 300% mortality risk.
- The lung allocation score (LAS) allocates organs to recipients based on calculated survival benefit but is not appropriate for use in children due to a lack of paediatric data. Paediatric allocation is based upon donor–recipient blood group compatibility, size matching and the current clinical conditions of individual waiting list patients at that centre.

Management following referral

Changes in clinical status during the pre-transplant period may affect suitability, necessitating regular review. Optimisation of current management during the pre-transplantation period is an essential component of managing future transplantation risk. This includes:

- maintaining good nutrition and bone density;
- optimising anti-infective and anti-inflammatory therapies;
- screening for and treatment of associated respiratory failure with NIV.

The use of more invasive ''bridging'' measures to transplantation, such as ventilation and extracorporeal membrane oxygenation, is controversial and not universally adopted. Despite demonstrated feasibility in paediatric patients (Schmidt *et al.*, 2012), post-transplantation outcomes remain inferior. The projected timeframe of bridging until suitable donor organ availability is an unknown factor.

The early post-transplant period is characterised by establishment of effective immunosuppression (started immediately prior to surgery), minimisation of infection risk, rehabilitation, and protection of both the newly implanted donor organ and other important organ systems.

A lifelong regimen of triple immunosuppression is used, consisting of the following.

- A calcineurin inhibitor (CNI), most commonly Tacrolimus. CNIs act by binding to calcineurin in the cytoplasm and interfere with the transcription of important cytokine genes, thereby inhibiting T-cell stimulation. Tacrolimus is favoured over cyclosporin in paediatric centres due to its more favourable side-effect profile, aiding compliance (less hirsuitism and gingivism, but a greater incidence of diabetes).

- A cell cycle inhibitor (or antimetabolite), most commonly mycophenolate mofetil. Cell cycle inhibitors inhibit the proliferation of T- and B-cells by interrupting DNA, RNA and purine synthesis.
- Corticosteroids: initially high-dose methylprednisolone, subsequently weaned to oral prednisolone.

Many centres further augment this with ''induction therapy'' at the time of transplantation, namely a monoclonal antibody such as basiliximab or daclizumab, which bind irreversibly to T-cell interleukin (IL)-2 receptors. Increasing levels of immunosuppression must be balanced against increased risk of severe infection or later malignancy (*e.g.* Epstein–Barr virus (EBV)-driven post-transplant lymphoproliferative disease (PTLD)).

Anti-infective prophylaxis starts with attempts to minimise bacterial load prior to transplantation, and extends through stringent surgical aseptic techniques and, in some cases, thoracic cavity washout with weak antibiotic solutions prior to organ implantation. Other aspects after lung transplantation include the following.

- Intravenous antibiotics based on the sensitivities of organisms present before transplantation, especially in CF, are given until the patient is mobilising and able to clear secretions. Nebulised antibiotics are often continued for a prolonged period if the recipient lungs are chronically infected with *Pseudomonas aeruginosa* before transplantation, as it is assumed that the sinuses will remain chronically infected.
- Antifungal prophylaxis in children with CF and others in whom pre-transplantation fungal colonisation is suspected: oral nystatin during the first 6–12 months; and either oral itraconazole or voriconazole, or nebulised amphotericin for $\geqslant$6 months.
- Antiviral prophylaxis in patients at increased risk: prophylactic valganciclovir in those at high risk for cytomegalovirus (CMV) disease reactivation (transplant from a CMV-positive donor to a CMV-negative recipient) or medium risk (donor and recipient both CMV positive); and valaciclovir in those at increased risk of herpes simplex virus (HSV) re-activation.
- Prophylaxis against *Pneumocystis jirovecii*: co-trimoxazole.

Ventilation is weaned as rapidly as can be tolerated, with extubation often occurring within the first 24 hours. Inotropic support may be brief, particularly if transplantation occurs on cardiopulmonary bypass. A relative hypovolaemia strategy protects the lung from ischaemia–reperfusion injury and pulmonary oedema.

Primary graft failure:

- occurs in ~10% and resembles the clinical appearance of acute respiratory distress syndrome (ARDS);
- is a risk with marginal donors and longer graft ischaemia times (>6 h);
- is managed supportively.

In CF subjects, regular aperients (*e.g.* lactulose, *N*-acetylcysteine and magrocol) and early introduction of enteral feeds are used to prevent distal ileal obstruction syndrome (DIOS), which may occur in 10%. Physical mobilisation following chest drain removal aids respiratory secretion clearance in conjunction with regular chest physiotherapy. The typical in-patient stay in uncomplicated cases is 64 weeks.

Ongoing management

Management focuses on ongoing rehabilitation, and surveillance for and treatment of acute complications, including infection and graft rejection, and education regarding transplant-orientated medication and follow-up regimens.

- Careful surveillance and monitoring of both immunosuppression (using tacrolimus trough levels) and graft function (using daily home spirometry) aims to maintain adequate immunosuppression and protect the graft from both immune and nonimmune insults to prevent rejection (both cellular and antibody-mediated).

- Bronchoscopy and transbronchial biopsy is performed in almost all transplant recipients, across centres, at defined surveillance points during the first year following transplantation and additionally as clinically indicated, based on respiratory symptom monitoring and daily home spirometry readings, with drops of >10% triggering urgent clinical review.
- CNIs operate within a narrow therapeutic window, which gradually shifts to lower targeted trough levels during the first year before plateauing at a suitable level dictated by the relative balance of episodes of rejection, infection and CNI side-effects.
- Minimising the risk of infection and other unwanted side-effects of immunosuppressive therapy (in particular renal dysfunction).
- Specific drug-related side-effects and medication interactions must be monitored for and considered (tables 3 and 4).
- Adopting a strict routine of drug timing, administration and compliance is a key element to better outcomes.

Graft rejection The clinical picture of early acute rejection is nonspecific and may be difficult to distinguish from infection. As a result, periods of coughing, malaise, low-grade pyrexia or a minor drop in lung function should be thoroughly evaluated (De Vito Dabbs *et al.*, 2004).

- Chest radiography may be normal and does not distinguish the two pathologies.
- Urgent flexible bronchoscopy, bronchoalveolar lavage and transbronchial biopsy are indicated.

The presence and severity of rejection in biopsy specimens is classified on the presence of perivascular and interstitial mononuclear cell infiltrates in alveolar tissue (from grade A0, for no acute rejection, to grade A4, for severe rejection), with an additional classification for associated airway inflammation (from B0, for no airway

Table 3. Common side-effects of maintenance immunosuppression

Drug	Side-effect
Tacrolimus	Nephrotoxicity Tremor Paraesthesia/hypersensitivity Hypertension Hypercholesterolaemia Neurotoxicity Diabetes mellitus Alopecia
MMF	Bone marrow suppression Nausea, dyspepsia, diarrhoea, constipation Hyperglycaemia Hypercholesterolaemia
Prednisolone	Cushing's syndrome Dyspepsia Peptic ulceration Osteoporosis Proximal myopathy Increased appetite Neuropsychiatric effects Glaucoma, papilloedema, cataracts Skin atrophy, striae, bruising, acne

MMF: mycophenolate mofetil.

Table 4. Agents interacting with CNIs

CYP3A inhibitors (increase CNI levels)	CYP3A inducers (decrease CNI levels)
Antibiotics	**Antibiotics**
Erythromycin	Rifampicin
Clarithromycin	Clindamycin
Chloramphenicol	Ethambutol
Ciprofloxacin (rare)	**Antifungals**
Antifungals	Caspofungin
Itraconazole	**Antiepileptics**
Fluconazole	Phenytoin
Voriconazole	Phenobarbitone
Imidazoles (*e.g.* ketoconazole)	Carbamazepine
Triazoles (*e.g.* posaconazole)	**Others**
Cardiovascular drugs	Cigarette smoking
Amiodarone	St John's wort
Calcium channel blockers (*e.g.* verapamil, diltiazem, felodipine)	
Nifedipine (rare)	
Gastrointestinal	
Cimetidine	
Omeprazole (rare)	
Other	
Grapefruit juice	
Antiretrovirals (*e.g.* atazanavir, nelfinavir and ritonavir)	
Danazol	

This is not intended to be an exhaustive list. CYP: cytochrome P450.

inflammation, to B4, for severe airway inflammation).

- The clinical relevance of A1 rejection is unclear, although frequent A1 episodes have been linked to a greater risk of chronic graft rejection in adults (Benden *et al.*, 2010; Hopkins *et al.*, 2004). At present, A1 is not usually treated.
- More severe episodes (A2–A4) are managed with a 3-day course of high-dose methylprednisolone (typically 10 $mg \cdot kg^{-1} \cdot day^{-1}$), though some centres will occasionally treat A2 rejection with oral corticosteroids.
- Steroid-resistant rejection is exceptionally rare, although true cases may require second-line therapy such as polyclonal anti-lymphocyte antibodies (anti-thymocyte globulin).
- The clinical relevance of airway inflammation and optimal method of treatment remains unclear.
- Patients with positive bacterial or fungal cultures should be treated.
- Many centres use specific therapies like ribavirin for proven cases of lower respiratory tract infection (LRTI) with respiratory syncytial virus (RSV) and paramyxoviruses (*e.g.* parainfluenza and human metapneumovirus).
- The role of viral infections in acute and chronic refection remains more controversial (Vu *et al.*, 2011; Liu *et al.*, 2009), and is particularly relevant in children given the increased frequency, particularly in the infant–preschool age range. Day-care is discouraged, compliance with active immunisation is critical and prophylactic palivizumab may be considered in infants.

The histological diagnosis of chronic rejection (or bronchiolitis obliterans) is challenging due to the patchy distribution of disease; therefore, a clinical diagnosis based on the pattern of lung function seen following transplantation has been developed, termed "bronchiolitis obliterans syndrome" (BOS) (table 5) (Estenne *et al.*, 2002).

Table 5. Grading of BOS

Grade	Definition
BOS 0	FEV_1 >90% of baseline and $FEF_{25–75\%}$ >75% of baseline
BOS 0-p	FEV_1 81–90% of baseline and/or $FEF_{25–75\%}$ ⩽75% of baseline
BOS 1	FEV_1 66–80% of baseline
BOS 2	FEV_1 51–65% of baseline
BOS 3	FEV_1 ⩽50% of baseline

Baseline lung function is defined as the average of the two highest values achieved after transplantation, recorded ⩾3 weeks apart. $FEF_{25–75\%}$: forced expiratory flow at 25–75% of FVC. Reproduced and modified from Estenne *et al.* (2002) with permission from the publisher.

- BOS is defined by an irreversible fall in lung function when other causes have been excluded, such as infection.
- Important potential contributing factors include gastro-oesophageal reflux disease (GORD) or airway infection (*e.g.* RSV or *Pseudomonas*), and should be treated aggressively to reverse this dysfunction.
- GORD is common in transplant recipients (Benden *et al.*, 2005), and emerging data in adults appear to support early surveillance and fundoplication, although equivalent paediatric data are lacking.
- Low-dose macrolide therapy appears to be beneficial in those with neutrophilic inflammation.
- In general, advanced BOS is poorly responsive to therapy and interventions aim to stabilise and prevent ongoing lung function decline. Other BOS therapeutic options include leukotriene receptor antagonists, augmentation of immunosuppression, total body lymphoid irradiation or photopheresis.
- Retransplantation is offered in some centres but the risks are often increased due to previous thoracotomy, making explantation more challenging, and the increased prevalence of other complications such as renal dysfunction.

Graft monitoring by spirometry is challenging in the preschool age range due to the cooperation and coordination required. Modification of reported indices may be required (*e.g.* $FEV_{0.75}$ rather than FEV_1). The use of age-appropriate reference equations is essential, and longitudinal spirometry and CT data suggest the lungs continue to grow with age (Cohen *et al.*, 1999).

Complications A variety of noninfectious complications may be encountered subsequent to lung transplantation (table 6).

Early surgical complications, beyond the immediate post-transplantation period, include:

- bronchial anastomosis stenosis, managed with balloon dilatation with or without laser treatment (repeated as necessary);
- damage to the phrenic nerve affecting diaphragmatic function;
- damage to the vagus nerve causing delayed gastric emptying.

Common later complications include the following.

- Hypertension, ~70% at 5 years; typically managed with calcium channel blockers such as amlodipine.
- BOS, ~50% at 5 years.
- Diabetes mellitus, approximately one-third at 5 years; corticosteroids and CNIs are major risk factors.
- CNI-induced nephropathy, approximately one-third at 5 years; due to the prevalence of renal dysfunction in survivors, exposure to other agents associated with potential renal toxicity are minimised or avoided (*e.g.* nonsteroidal anti-inflammatory drugs (NSAIDs), amphotericin and aminoglycosides).

Table 6. Common noninfectious complications after lung transplantation

Time	Complication
Early	Anastomotic dehiscence or stenosis Pulmonary vein or artery stenosis Nerve damage (phrenic or vagal nerve injury, loss of cough reflex, swallowing difficulty)
Intermediate and late	Malignancy (*e.g.* lymphoproliferative disease) Nephrotoxicity Hypertension Hyperlipidaemia Osteopenia and osteoporosis Avascular necrosis of the femoral head Growth failure Diabetes mellitus Hyperuricaemia/gout Viral papillomatosis Cytopaenias (anaemia, leukopaenia, thrombocytopaenia) Thromboembolism GORD

- Increased malignancy risk due to ongoing immunosuppression, with PTLD (typically EBV-driven B-cell expansion) and skin cancers being the most relevant to the paediatric population; advice about sunlight exposure is important.
- CF children continue to be at risk of nonrespiratory complications of their underlying disease (*e.g.* DIOS, malabsorption and bone disease).

Long-term outcomes

Median survival after lung transplantation is now ~5 years, and is identical in children and adults. Better survival of recipients aged 1–11 years is seen compared with those aged 12–17 years (Benden *et al.*, 2012). The onset of puberty and adolescence brings with it several challenges, including risk-taking behaviour and noncompliance, with adverse effects on post-transplantation outcomes. While there is little evidence of how best to manage this, most centres encourage adolescents to take increasing responsibility for their own care, maintain adherence to therapy, and develop long-term goals and ambitions.

Conclusion

Lung transplantation is now an established, accepted treatment option for children with end-stage lung disease at many centres around the world. Long-term outcomes are steadily improving for paediatric patients but have yet to reach those achieved by other solid-organ transplants. There are many similarities in management between adult and paediatric subjects but several differences unique to the paediatric age range exist. Future work to improve the availability and allocation of suitable organs will hopefully see this therapeutic option offered to a greater proportion of children who are eligible.

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Rehabilitation programmes and nutritional management

Andreas Jung

Key points

Rehabilitation programmes in children and adolescents with chronic respiratory disorders:

- aim at preventing worsening of the disease, improving self-management and restoring quality of life in order to enable full participation in daily life, including school, and social and physical activities,
- consist of standardised multidisciplinary interventions,
- include diagnostic procedures, specific medical care and nursing, nutritional and psychological counselling and educational interventions,
- address a broad spectrum of chronic respiratory conditions and can contribute efficiently to a general improvement in morbidity and mortality, in the context of a complex disease management.
- Advanced lung disease results in increased energy expenditure, an augmented level of inflammation and diminished appetite, contributing to a loss of body weight and requiring specific nutritional management, including counselling, installation of a daily nutrition plan, high-protein calorie supplementation and substitution of vitamins and micronutrients.

Targets of rehabilitation programmes in childhood and adolescence

Pulmonary rehabilitation is defined as "an evidence-based multidisciplinary and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Integrated into the individualised treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimise functional status, increase participation, and reduce health care costs through stabilising or reversing systemic manifestations of the disease" (Nici *et al.*, 2006). Rehabilitation programmes in children and adolescents target preventive measures, which aim to stop the disease worsening, improve self-management and restore quality of life. It is anticipated that the child, or the adolescent, will be able to fully participate in daily life, such as school, social activities and sports, in the same ways as their healthy peers. Today, rehabilitation programmes have been developed in many countries in inpatient and outpatient settings. Inpatient programmes are often more standardised than outpatient programmes, as the latter are often tailored to meet local needs. In addition, inpatient programmes provide the possibility of individual, daily monitoring of patients over several weeks in specific institutions in order to optimise therapeutic interventions and complete diagnostic procedures that are beyond the possibilities of an outpatient setting. Independent of the rehabilitation setting, objectives of current rehabilitation programmes include a number of specific considerations, as shown

in table 1. Rehabilitation centres and sponsors of healthcare systems have defined criteria for the eligibility of an individual intending to participate in a rehabilitation programme (table 2). If the criteria of the rehabilitation institution, the patient and their family are met, the most important preconditions for successful pulmonary rehabilitation are given.

Elements of paediatric rehabilitation programmes for respiratory diseases

Pulmonary rehabilitation programmes consist of standardised, multidisciplinary interventions performed by a range of highly qualified health professionals. Depending on the disease spectrum and the severity addressed by rehabilitation centres, potentially essential components include a wide range of actions, such as diagnostic procedures, specific medical care, educational interventions and a multidisciplinary team approach (table 3). Standardised care may also include consultation of specific medical professionals in case of multi-organ or psychiatric symptoms and diseases. In inpatient programmes, children and adolescents often participate in educational preschool or school activities for the duration of the hospitalisation period. Some rehabilitation centres offer a family-oriented intervention and treat parents and other family members together with their children.

Table 1. Goals of pulmonary rehabilitation programmes in children and adolescents

Maintenance and restoration of social and professional activities
Improvement of health condition
Preventive measures of disease worsening or progression
Amendment of disease perception and management
Improvement of compliance
Restoration of quality of life
Change of lifestyle

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A multidisciplinary team closely follows each patient or family during the whole interventional period. This approach facilitates an individual treatment in the context of an often group-based rehabilitation programme. As patients can be monitored intensively over a longer period of time, individual symptoms and risk factors, as well as psychological aspects, can be evaluated continuously and, as a result, specific diagnostic procedures can be applied. In the same way, treatment modifications can be carried out and the subsequent course of the disease can be observed over time.

Patient education: a core element of rehabilitation programmes

Educational programmes are important components of contemporary rehabilitation programmes, featuring theoretical instructions accompanied by practical exercises. Knowledge is disseminated to promote disease understanding, and recognition of individual risk-factors and coping strategies. Practical training is provided to improve medication application skills and techniques. Written action plans foster the adherence to the individual treatment strategy. As a result, compliance, self-management and outcome of the disease are often significantly increased.

Educational programmes for children and adolescents have been developed for various diseases in many countries. In the respiratory field, the most wide-spread and best standardised protocols exist for asthma. Asthma education programmes have often been developed independently of pulmonary rehabilitation programmes and are often performed in an outpatient setting. Inpatient rehabilitation programmes have integrated sections or whole protocols of national or regional asthma education programmes, resulting in standardised en bloc interventions.

Disease-specific rehabilitation programmes

A vast spectrum of chronic respiratory conditions are addressed by paediatric rehabilitation programmes, including asthma, CF, bronchopulmonary dysplasia,

Table 2. General criteria for children and adolescents to participate in rehabilitation programmes

Ability for rehabilitation is fulfilled: willingness to actively participate in the programme, capacity to fulfil rehabilitation aims and ability to integrate into groups
Improvement of prognosis can be achieved: improvement of health and restoration of professional and/or social activity
Measures of outpatient care are exhausted but not sufficient to adequately ameliorate health or suspend health impairment
Secondary health damage is imminent or has already occurred
Psychosomatic or psychosocial problems are difficult to address in an outpatient setting (demarcation from the social environment)
Interventions to promote coping and to adhere to treatment are necessary

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primary ciliary dyskinesia, neuromuscular disorders, interstitial lung diseases, cardiovascular diseases and pre- and post-lung transplantation. A recent joint statement of the American Thoracic Society and the European Respiratory Society on pulmonary rehabilitation highlights the huge progress that has been made in evidence-based support for pulmonary rehabilitation in the management of patients with chronic respiratory disease, focusing on adults with COPD. Similarly, there is a growing body of evidence that rehabilitation programmes for chronic respiratory diseases in the paediatric population are efficient in terms of health improvement. Most published studies investigated protocols and outcome in patients with asthma and CF, as these disorders constitute the majority of indications for pulmonary rehabilitation in the first two decades of life. In future, structured interventions before and after lung transplantation will become more and more important in light of a growing number of patients on the transplantation waiting list, as well as a rapidly increasing number of transplanted individuals.

Asthma In the USA, asthma camps often focus on health education and interaction with peers. Despite the fact that asthma camps cannot replace specific rehabilitation programmes, there is evidence that these interventions can:

- improve the parent's and child's knowledge of asthma,
- increase a child's locus of control,
- improve self-efficacy and attitude to disease,
- improve asthma-related behaviour and pulmonary function measures,
- improve metered-dose inhaler technique.

Furthermore, asthma camps decrease anxiety, symptoms, exacerbations, school absences, emergency department visits and hospitalisations. Although asthma camps also exist in Europe, standardised inpatient asthma rehabilitation programmes in specialised hospitals are predominant. Nevertheless, the literature on protocols and outcome of the intervention is relatively limited. Studies found significant improvements in pulmonary function and bronchial inflammation, as well as a decrease in days absent from school and in visits to a physician, supporting the importance of multidisciplinary rehabilitation programmes for disease management and compliance modification. Long-term effects following an inpatient intervention in terms of better lung function parameters, less asthma-related school absence, and improved asthma management and quality of life compared to an outpatient reference group have been documented.

Several studies have implicated lifestyle changes, specifically decreased physical activity, as a contributor to the increase in asthma prevalence and severity. Moreover, the capacity for asthmatic subjects to

Table 3. Essential components of a comprehensive paediatric pulmonary rehabilitation programme

Respiratory diagnostics including body plethysmography
Comprehensive allergy testing including provocation tests
Routine laboratory including blood gas analysis
(Chest) radiograph
Disease-specific nursing
Separation of patients according to microbiological profile
Monitoring of vital parameters and possibility of oxygen application
Physiotherapy
Physical exercise training and sports therapy
Occupational therapy
Nutritional intervention and advice by a dietician
Psychological counselling and family support
Standardised specific education in disease understanding and management
Advice in matters of financial, educational and occupational aspects

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exercise safely and to significantly improve their cardiovascular fitness and quality of life has been demonstrated. From this perspective it seems logical to subject asthmatic patients to exercise training to increase fitness and strength. Indeed, many rehabilitation centres focus on exercise interventions with remarkable success on quality of life and exercise capacity, leading to the assumption that exercise training should be part of all asthma rehabilitation programmes.

Cystic fibrosis During the past decades the fear of cross-infection, especially for *Pseudomonas aeruginosa*, has determined the evolution of rehabilitation programmes for CF patients. To date, rigorous hygiene standards addressing disinfection and segregation (spatial and temporal) are a widely accepted prerequisite to qualify centres for inpatient CF rehabilitation programmes. Still, in the view of potential cross-infections, close contact between the CF centres and the rehabilitation clinics is advisable to foster mutual trust, minimise risk for the patient and optimise intervention outcome. To achieve this goal, structured interventions need to take into account all aspects of CF multi-organ disease and, therefore, exceed the general requirements of pulmonary rehabilitation programmes. Physiotherapists, sports therapists, psychologists, dieticians, diabetologists, gastroenterologists, pulmonologists and other healthcare specialists need to work closely together in a multidisciplinary setting. If this aspect is properly addressed, rehabilitation programmes are likely to significantly ameliorate the short- and long-term quality of life of affected individuals and improve symptom score, pulmonary function, grade of inflammation and weight. Exercise and endurance training results in significant improvements in exercise tolerance, aerobic fitness, peak work capacity, strength, coordination and ventilation parameters. Moreover, clinical experience demonstrates a remarkable improvement in treatment adherence after rehabilitation as a result of educational activities, possibly leading to longer periods of mild symptoms and prolonging the time between intravenous antibiotic cycles, thus demonstrating the importance of such programmes in CF care.

Pre- and post-lung transplantation Published data on protocols and outcome of rehabilitation programmes for patients with

chronic lung diseases pre- and post-lung transplantation are largely lacking. However, with the increasing number of paediatric and adult transplanted patients, specific rehabilitation programmes will have to be established. The majority of the transplanted paediatric population consists of patients with CF, followed by pulmonary fibrosis. Rehabilitation programmes for severely affected individuals clearly exceed the general requirements for pulmonary rehabilitation. Next to medical experience and know-how, specific psychological and educational conditions have to be provided by the rehabilitation centre. Access to acute interventions and intensive care units should be available, as well as an emergency laboratory and advanced respiratory diagnostics, such as bronchoscopy.

Major objectives for programmes pre-transplantation are the stabilisation of general and pulmonary health in conjunction with psychological priming with respect to the intervention. The effect of rehabilitation for adults awaiting lung transplantation has been demonstrated by a significant increase in physical efficiency and endurance.

Rehabilitation programmes following lung transplantation have to consider various complex aspects, from education in adherence to treatment to early recognition of organ rejection and, at the same time, promoting physical fitness to prepare the individual for re-entry into the social community, including school or workplace. Next to inpatient interventions, protocols for outpatient rehabilitation programmes have been established, with reported success in terms of patient satisfaction. Nevertheless, both inpatient and outpatient interventions need to be scientifically evaluated and better standardised in future to meet the complexity of the requirements of paediatric transplant rehabilitation programmes and to improve their outcome.

Nutritional management In many chronic respiratory disorders, nutritional interventions are mandatory to improve respiratory function and ameliorate disease symptoms and outcome, although available literature in this field focuses on the pancreatic insufficient type of CF. However, advanced lung disease in many other conditions can lead to an enhanced calorie need and, subsequently, to a decreased BMI. This process is often a result of increased energy expenditure due to respiratory work, as well as of a general augmented level of inflammation and/or regular use of systemic corticosteroids. Diminished appetite and a consequently decreased energy intake might contribute to a loss of body weight. If weight gain cannot be achieved by regular nutrition, coordinated actions need to be implemented to improve the patient's condition. These potentially include intensive counselling by a dietician, installation of a daily nutrition plan, prescription of high-protein calorie supplementation or substitution of vitamins and micronutrients. In case of progressive weight loss or failure to regain weight over a longer period of time, insertion of a percutaneous, gastrointestinal tube and subsequent additional feeding might become indispensable. The specific nutritional management of CF patients with pancreatic insufficiency leading to malnutrition, which includes regular counselling by a nutritionist, oral substitution of pancreatic enzymes and fat-soluble vitamins, and high-protein calorie supplementation, is discussed elsewhere in this *Handbook*.

When respiratory disease leads to general inactivity, uncontrolled weight gain and obesity can result. Prevention of becoming overweight is, therefore, an important element of the management of chronic respiratory disorders such as asthma. As well as encouraging patients to exercise regularly and supporting their sportive ambitions, it is crucial to provide individuals and their families with specific education on the prevention of and behaviour in emergency situations. This includes knowledge about individual risk factors, awareness of the available rescue medication and an action plan, which the patient needs to follow in the case of severe respiratory symptoms. The goal is to foster

trust of the patient and the families in their self-management skills and in the implemented treatment strategies in order to overcome the fear of respiratory symptoms in situations of increased physical activity. At the same time, nutritional education should be implemented to support the efforts of physical activity, especially when excess weight is already an issue and weight reduction is desired. This might include shopping and cooking guidance, education in nutritional components and meal plans, and even in offering temporary household support, where available.

In situations where increased physical activity is not or is hardly possible, such as neuromuscular disorders, optimisation of the nutritional management by the families is of general importance, especially because many parents tend to allow their sick or disabled children any desired foods that are high in carbohydrates as comfort. Empathic nutritional guidance, *e.g.* by a dietician, can often strengthen awareness of the families of a more reasonable food composition, and must include regular and thorough diet education and advice.

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Prevention of indoor and outdoor pollution

Giuliana Ferrante, Velia Malizia, Roberta Antona and Stefania La Grutta

Asthma is a multifactorial disease affected by biological, environmental and social factors. Consequently, reducing asthma morbidity requires management that addresses the several contributing factors and not only the clinical aspects. It is well known that environmental triggers, such as in- and outdoor allergens and irritants, can elicit and exacerbate acute attacks in asthmatic children. Many studies have demonstrated the effectiveness of environmental trigger reduction in lowering the burden of the disease at the individual level (table 1).

Today, children spend most of the day in indoor environments. The most common indoor allergens and irritants are dust mites, pets, mould and environmental tobacco smoke (ETS) (Crocker *et al.*, 2011).

Dust mites

House dust mite (HDM) is considered one of the most common indoor allergens and the main trigger for allergic asthma. Dust mites are prevalent in rural and in tropical areas compared to urban centres and areas with a temperate climate. Temperatures ranging between 15°C and 30°C and relative humidity of 60–80% represent the ideal parameters for their development and survival. The home represents an optimal environment for dust mites as it is a source of food with good microclimate conditions (Brunetto *et al.*, 2009). Easy measures are suggested to reduce the risk of mite exposure (allergen-impermeable pillow and mattress covers; washing bedding in hot water; removing carpet, upholstered furniture and stuffed toys; and reducing humidity levels to <60%), but evidence of a reduction in asthma morbidity is controversial, mainly due to the inhomogeneity of the studies (sample size, multiple sensitisation and exposures) (Rao *et al.*, 2011).

Key points

- Environmental triggers, such as in- and outdoor allergens and irritants, can elicit and exacerbate acute attacks in asthmatic children.
- Children are particularly susceptible to air pollution because of their higher ventilation rate, with an increased risk of medication use and hospitalisation.
- Interventions must be addressed to multiple triggers through multiple intervention components.
- Simple measures (mattress covers, HEPA filters, air filtration, home repairs, and limiting levels of exertion in outdoor activities when pollutant concentrations are elevated) may protect children's respiratory health, reducing asthma symptom-days, school days missed and healthcare utilisation.

Pets

Cat and dog dander are well-known asthma triggers in sensitised individuals. In particular, Fel d 1, the major cat allergen, is widespread in homes as well as in public places (schools). There is conflicting evidence whether pet elimination prevents childhood asthma development. The current standard of care, including pet removal in patients with a proven allergy, is reported to reduce the need for medication, even if the efficacy of this recommendation is still unclear (Rao *et al.*, 2011).

Table 1. Essential measures to reduce the exposure to main in- and outdoor allergens and pollutants

Allergen/pollutant	Measures to reduce exposure	Comments
HDM	Allergen-impermeable pillow and mattress covers Washing bedding in hot water Removing carpet, upholstered furniture and stuffed toys Reducing humidity levels to <60%	Evidence is controversial
Fel d 1	Pet removal in patients with a proven allergy	Cat owners may diffuse cat allergen through their clothes, making it ubiquitous
Mould	Removing mould from surfaces Discarding mould-contaminated materials Addressing the source of moisture responsible for mould growth	Reduction in emergency department visits and hospitalisation after home renovations
ETS	Counselling to encourage parents to quit smoking Use of HEPA air cleaners	Ineffectiveness of most of the intervention studies in lowering ETS exposure in children
Outdoor pollutants (PM, NO_x, VOCs, ozone)	Limiting level of exertion in outdoor activities when pollutants concentrations are elevated Breathing through the nose, at rest or at low level of exertion Exercising early in the morning, when air pollution levels are lower	Decreasing levels of PM_{10} were associated with reduced prevalence of respiratory symptoms in children
Indoor pollutants (PM, NO_x, VOCs)	HEPA filters Air filtration/ventilation Home repair	Interventions to address multiple triggers through multiple interventions are suggested

Mould

Early exposure to mould or damp is strongly related to asthma in children and adolescents. Mould remediation includes removing mould from surfaces, discarding mould-contaminated materials and addressing the source of moisture responsible for mould growth (Crocker *et al.*, 2011). A study reported an important reduction in emergency department visits and hospitalisation after home renovations such as leak repair, removal of water-damaged materials and improvements of damp basements (Rao *et al.*, 2011).

ETS and exposure to air pollutants

Interventions to reduce ETS exposure focus on counselling to encourage parental smoking cessation and use of high-efficiency particulate air (HEPA) air cleaners to lower airborne particles in the air (Crocker *et al.*, 2011). The education of children with asthma, including avoidance of asthma triggers, showed an association between ETS exposure reduction and fewer episodes of poorer asthma control, respiratory-related emergency department visits and hospitalisations (Gerald, 2009). A recent Cochrane review showed the ineffectiveness of most of the intervention studies in lowering ETS exposure in children (Priest *et al.*, 2008). Finally, ETS should be an integral part of the standard environmental assessment, education and evaluation components in home-based environmental interventions (Crocker *et al.*, 2011).

Children are more susceptible to air pollution because of their higher relative ventilation, with an increased risk of medication use and hospitalisation (Laumbach, 2010). Exposure to outdoor air pollution has been associated with respiratory outcomes in children. Asthmatic people are considered to be especially vulnerable because outdoor pollutants, such as particulate matter, nitrogen oxides (NO_x), volatile organic compounds (VOCs) and ozone, can trigger exacerbations. Recently, it has been demonstrated that decreasing levels of particulate matter $<10\,\mu m$ in diameter (PM_{10}) were associated with reduced prevalence of respiratory symptoms in children. Simple recommendations to reduce exposure and prevent health effects might be to: avoid heavy traffic areas, if possible; spend less time outdoors and limit level of exertion in outdoor activities when pollutants concentrations are elevated; breathe through the nose at rest or at low levels of exertion to reduce the amount of pollutants reaching the lung; and exercise early in the morning, when air pollution levels are lower (Laumbach, 2010).

Interventions aimed at limiting exposure to indoor pollutants may be more easily applicable, less costly and more effective in reducing respiratory health outcomes. Recent studies suggest that interventions that address a single trigger may not be as effective as those that address multiple triggers through multiple intervention components (Crocker *et al.*, 2011). Since single preventive measures are seldom effective, comprehensive strategies combining the most appropriate measures are recommended. In fact, a large number of environmental variables can affect the patterns of exposure as well as sensitisation, development of symptoms and exacerbations. Even if attempting to control every possible kind of exposure may be difficult, simple measures (mattress covers, HEPA filters, air filtration and home repairs) may protect children's respiratory health, reducing asthma symptom-days, school days missed and healthcare utilisation.

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Respiratory physiotherapy

Beatrice Oberwaldner

Paediatric respiratory physiotherapy has some origins in the attempt to clear tenacious secretions from the airways of children with CF by simple mechanical means. From this starting point, it has developed into a broad spectrum of techniques and a wide field of therapeutic approaches to various disease entities and patients. It should, therefore, be understood as a rapidly developing area of knowledge- and skill-based competencies with considerable potential for further growth. Most of these competencies have been developed at the bedside by trial and error, but more recently there has been interest in establishing a scientific basis for paediatric respiratory physiotherapy and to understand how these mechanical interventions work.

Key points

- Paediatric respiratory physiotherapy has developed into a wide field, encompassing airway clearance, rehabilitation, aerosol treatment, tracheostomy management and long-term home ventilation programmes.
- Paediatric respiratory physiotherapy is a special therapeutic approach to respiratory disorders in newborns, infants, children and adolescents. As such it needs a profound understanding of the structure and the function of the growing respiratory tract and the necessary competencies required for working with paediatric patients.
- An individualised approach to the treatment of a specific patient is preferable to any kind of rigid therapeutic routine.
- Airway clearance employs basic mechanisms like expiratory airflow, forced expiration and gas–liquid pumping. It might, therefore, be considered as a therapeutic application of respiratory physiology.

Aims and general principles

Aims vary with the patients treated and pathophysiology encountered. However, there are a few general principles that constitute the basis of every therapeutic approach. A detailed knowledge of the structure and function of the immature and growing respiratory tract of the premature, newborn, infant, toddler, schoolchild and adolescent are fundamental. Based on a careful analysis of prevailing pathophysiology, as derived from history, clinical investigation, imaging, lung function testing and other relevant investigations, a therapeutic goal and a treatment plan should be defined for any individual patient. An individualised approach to the patient is preferable to any kind of routine that uses standardised techniques for the management of certain disease entities. Depending on the vulnerability of the patient, avoiding unwanted side-effects is a predominant principle when planning treatment. In situations where cooperation of the patient is required, an age-dependent psychological approach is a prerequisite. Furthermore, involving parents and caregivers in the therapeutic management is essential for young patients, but also helps to provide a supportive environment for older ones.

Airway clearance therapy

Aims Airway clearance therapy (ACT) aims at preventing, treating or alleviating the mechanical (atelectasis, local hyperinflation, ventilation/perfusion imbalance and increased work of breathing) and biochemical (increased proteolytic stress on the airway walls, local proliferation of infectious agents and mechanisms) consequences of intrabronchial retention of secretions. Sometimes ACT also has diagnostic aims, such as the need for bacteriological analysis of mucus from the lower airways.

Techniques One can distinguish between therapist-applied and self-applied techniques.

Therapist-applied techniques: Chest-clapping, vibration and compression, all in combination with assisted coughing, are traditional therapeutic approaches that are still valid for uncooperative patients such as newborns and infants, as well as the unconscious. Suction techniques for patients with and without an artificial airway remove secretions that have been mobilised and transported by the former interventions. Lung volume management (manual hyperinflation/bagging and CPAP) is a complementary approach for patients unable to inspire sufficiently to bring air behind the obstructing secretions. Positioning effects redistribution of ventilation; by locally changing lung distension and ventilator excursions, it may serve as a means to target gas–liquid pumping and opening airways. For patients who require ACT in the long term, parents and other caregivers are trained in these techniques by the therapist.

Some techniques, originally developed for self-application, can also be used by therapists, such as assisted autogenic drainage and positive expiratory pressure (PEP) techniques, for infants and severely ill and weak patients.

Self-applied techniques: These are taught to cooperating patients who require ACT regularly over several months and years. Several techniques have been developed, *e.g.* the active cycle of breathing techniques, autogenic drainage, PEP therapy, oscillating PEP, hi-PEP and various combinations of these. They are of special interest for patients with bronchiectasis-effected airway wall instability, where a subtle balance between sustained expiratory airflow and moderate airway compression is found on one side and the avoidance of compression-effected airway closure on the other.

Mechanisms The physiology of cough, which mobilises and transports secretions, serves as a model for all these techniques. Expiratory airflow transports material towards the airway opening; its effectiveness depends on airflow velocity, bronchial calibre and viscoelasticity of secretions. The physiology of a forced expiration combines expiratory airflow with the upstream migration of bronchial choke-points, thereby catching material in a stenosis through which it is blown downstream. In the airway periphery, where airflow is almost negligible, gas–liquid pumping takes over for mobilising secretions. This incompletely understood mechanism is based on breathing-effected lung volume changes, mixing secretions and air. All these key mechanisms, in combination with posture-effected redistribution of ventilation, are modified and combined in different ways in the various techniques mentioned above.

Physical exercise and sports often contain some of these key mechanisms; in particular, exercise-induced hyperventilation may effect significant gas–liquid pumping. Consequently, physical activity must be seen as a complementary means for ACT and thus should constitute an important element in the long-term management of patients with bronchiectasis.

Patients and disease entities Patients with bronchiectasis (CF, primary ciliary dyskinesia and localised bronchiectasis) require ACT in the long term. In any kind of atelectasis that is caused by airway occlusion (after removal of a foreign body or mucoid impaction), therapeutic ACT is indicated. Due to an immature respiratory tract with a very special physiology, the term newborn, and especially the preterm newborn, is particularly prone to airway

obstruction by mucus impaction and other respiratory complications. This highly vulnerable patient group requires specialised therapeutic approaches in order to achieve the desired therapeutic effects with a minimum of risk. Paediatric patients undergoing thoracic surgery are also prone to airway occlusion and therefore often need ACT post-operatively. The special group of children with neuromuscular disorders suffer from an unstable chest in combination with small breathing excursions and a weak cough and, therefore, require long-term support from paediatric respiratory physiotherapy.

Rehabilitation

Aims Rehabilitation aims at preventing and alleviating disease-inflicted disabilities that interfere with the age-specific activities of childhood and adolescence. Paediatric respiratory physiotherapists, by their expertise in working with children of all ages, may design, organise and conduct rehabilitation programmes.

Techniques, mechanisms and patients
Endurance training has been proven to be a valuable component of rehabilitation for patients with chronic respiratory disorders. Strength training may prevent disease-inflicted abnormalities of posture, thoracic mobility, breathing excursions and body image. Breathing exercises and respiratory muscle training may be desirable additions in special cases.

It is of note that the effective application of these principles in paediatric patients requires an age-specific approach, which considers the special characteristics of children such as shorter attention span and enjoyment of games/playing, as well as a general tendency towards increased mobility. Programmes designed for adults may work in adolescents but are rarely suitable for younger children. In these, fun group activities and competitions are more important than strict adherence to formal training plans.

The effective mechanisms for the rehabilitation of paediatric patients with chronic respiratory disorders are complex. Improved aerobic fitness and exercise capacity, and a gain in muscle strength and motor skills, as well as more effective ACT are important components. Clearly the medical management of these patients must be optimised in order to provide a solid basis for any rehabilitation effort.

Rehabilitation is an option for all paediatric patients with chronic respiratory disorders, malformations or severe respiratory complications and side-effects from other disorders and/or treatments.

Aerosol therapy

Aims Aerosol therapy is a targeted approach to the inner surface of the respiratory tract and thereby offers itself as a means to deliver medication topically. In contrast to this simple and convincing principle, the technical details of aerosol therapy are complex and complicated. Paediatric respiratory physiotherapists, by their competence in working with the breathing patterns of their patients, may serve as teachers and trainers, thereby providing the necessary quality assurance. The aim is to provide optimised aerosol therapy to the individual patient.

Techniques, mechanisms and patients
Depending on the disorder, disease situation, prevailing pathophysiology, age and psychosocial profile of the child, nebulisers and metered-dose inhalers with or without spacers, as well as powder inhalers may be the ideal choice. Interfaces (masks and mouthpieces) are dependent on age and cooperation. The required breathing manoeuvres have to be demonstrated, taught and optimised. Patients with an artificial airway require specific approaches.

The paediatric asthma spectrum is a wide field for aerosol therapy, but, beyond that, all other respiratory disorders may also require aerosol medication either intermittently or in the long term.

Management of the technology-dependent child

Aims The long-term management of children with a tracheostomy and those on home ventilation calls for a highly specialised,

multidisciplinary approach and the paediatric respiratory physiotherapist may be an important member of this team. Aims range from maintenance of upper airway patency to the mechanical substitution of inefficient breathing movements, and in all those cases successful management is characterised by achieving these aims while avoiding tracheostomy- and ventilation-related complications, as well as respiratory inefficiency.

Techniques, mechanisms and patients The respiratory physiotherapist may have a crucial role in selecting the appropriate tracheal cannula, choosing the optimal home ventilator and interface, training patients and parents and monitoring the entire long-term management.

The patient spectrum is wide, ranging from children with severe upper airway stenosis and infants with bronchopulmonary dysplasia, to children with central hypoventilation syndrome and those with severe and progressive neuromuscular disease. Furthermore, home ventilation is a means to bridge the time-span to lung transplantation for patients with end-stage lung disease. All these disease situations require a highly individualised approach where, again, careful analysis of the prevailing pathophysiology is a prerequisite for successful management.

Other aspects

Occasionally there are other disease situations and problems where the expertise of the paediatric respiratory physiotherapist may be of significant benefit for patient and disease management. For patients undergoing any kind of surgery, the therapist may provide valuable help in pre-surgical respiratory optimisation, early extubation and post-operative respiratory care and return to baseline function. In paediatric intensive care the therapist may assist in the weaning process from mechanical ventilation. Therapists can help in adapting the home environment for long-term ventilation and they may also offer home visits in special cases. Group events, like training classes and rehabilitation camps, may be planned, organised and conducted by the paediatric respiratory physiotherapist, while always considering infection control issues and guidelines. Last but not least, by their familiarity with chronically diseased patients, therapists may grow into the role of a trusted confidant of the patient and their family in various psychosocial situations.

Evidence

There is a certain discrepancy between a paucity of studies and the wide clinical application of paediatric respiratory physiotherapy. Some studies document beneficial effects of ACT techniques in chronic respiratory disorders. Such studies, however, are difficult to conduct since outcomes are multifactorial and patients, as well as disease situations, vary considerably. Studies comparing different ACTs are, at least in part, contradictory. Such comparisons are based on the potential misconception that one ACT is superior to another; maybe, however, there is no ''best technique'' that is equally effective in all patients. An individualised approach employing key components of several techniques, skilfully tailored to the prevailing disease situation, may be superior to any rigid application of therapeutic protocols. Another interesting analytic approach is the attempt to more profoundly understand the basic physiologic mechanisms behind various ACTs. This means asking the question ''how'' paediatric respiratory physiotherapy works. Today, leading experts consider airway clearance in paediatric respiratory physiotherapy as a therapeutic application of respiratory physiology.

Organisational aspects

The role of the paediatric respiratory physiotherapist in the caregiving team varies widely across Europe and worldwide depending on local traditions, formal training, specialisation and professional expertise, as well as the legal and administrative background and framework. Authorities responsible for hospital structure and function must provide appropriate professional positions of respiratory physiotherapists in caregiving teams, thus ensuring maximum effectiveness within a multidisciplinary care. General training in

physiotherapy, however, rarely suffices to provide enough competencies to manage patients with chronic, complex and severe respiratory disorders. Lack of sufficient expertise carries the risk of side-effects and complications. It follows that specialised training is required and should be available across Europe and internationally. At present this is not the case and different countries have different concepts and traditions (or lack thereof) in their paediatric respiratory physiotherapy training. Scientific medical societies like the European Respiratory Society are called upon to provide trans-European harmonisation and standardisation of training and standards.

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Fitness-to-fly testing

Mary J. Sharp and Graham L. Hall

Aircraft cabins are pressurised to 1500–2400 m, resulting in an oxygen tension (P_{O_2}) of 15 kPa (112 mmHg), which is equivalent to an ambient oxygen level of 15–17%. At sea level the alveolar oxygen tension (P_{AO_2}) is ~98 mmHg while at the maximum cruising altitude the P_{AO_2} drops to 55 mmHg, which corresponds to an oxygen saturation of 90%. In healthy passengers >6 months of age, S_{pO_2} declines to 89–94% during flight without changes in clinical status, whereas 35% of healthy ex-preterm infants flying near term exhibit significant desaturation (S_{pO_2} <85%). Figure 1 shows the S_{pO_2} for a term and pre-term infant during air travel. In infants between birth and 6 months of age little is known about oxygen saturation levels during flight.

Key points

- Infants and children with chronic lung disease are at risk of developing hypoxia and respiratory symptoms during air travel.
- The hypoxia challenge test is the currently recommended tool for the identification of at-risk indviduals.
- The hypoxia challenge test does not predict the incidence of in-flight hypoxia in infants born preterm and travelling by air at near term.
- The accuracy of the hypoxia challenge test in infants and young children has not been assessed.
- Further research into the prediction of in-flight hypoxia is required in infants and young children.

The normal physiological compensation to this hypoxia is an increase in V'_E, mostly by increasing tidal volume, and a moderate tachycardia. A patient with pulmonary disease may not be able to increase V'_E enough to compensate for the fall in P_{AO_2} and their P_{AO_2} may end up on the steep part of the oxygen dissociation curve resulting in low oxygen saturation. Physiological factors such as lower respiratory system compliance, more horizontal rib placement, higher airways resistance and fewer alveoli in infants and young children mean they are more at risk than adults of developing hypoxaemia in aircraft. In addition, infants are at risk of even greater hypoxaemia due to fetal haemoglobin, increased pulmonary vascular reactivity and biphasic hypoxic ventilation response.

The aim of this chapter is to highlight the key points for paediatricians and neonatologists considering the safety of air travel in newborns and young infants. Readers seeking more detailed information relating to the broader changes that occur during air travel and the most appropriate approach in older children are directed to the recent guidelines from the British Thoracic Society (BTS) on identifying which patients with lung disease are at risk during air travel.

Methods of pre-flight testing for infants and children

The hypoxia challenge test was first reported by Gong *et al*., (1984) and subsequently validated in a variety of adult populations with chronic respiratory disease. The primary aim of the hypoxia challenge test is to identify patients prior to flight who are at

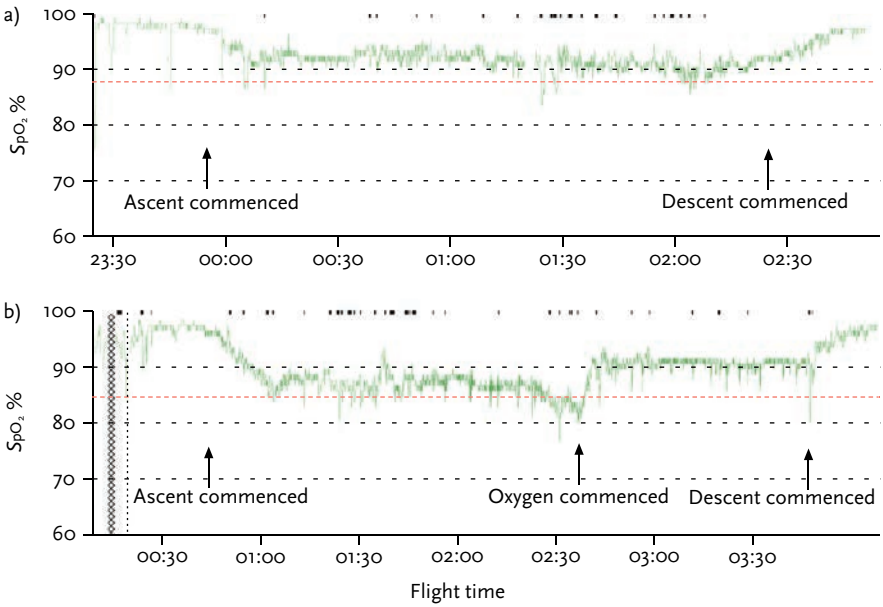

Figure 1. Recording of in-flight SpO_2 in a) a 7 month-old term born infant and b) a 9.6 month-old preterm infant (corrected post-natal age 27 weeks). The red dotted line indicates a SpO_2 of 85%. The term infant maintained their SpO_2 above 90% for the majority of the flight. The SpO_2 of the preterm infant decreased to 85–90% once cruising altitude was reached and remained stable for approximately half of the flight before decreasing to <85%. Supplemental oxygen was commenced at this time for the remainder of the flight. Reproduced from Withers (2011) with permission from the publisher.

risk of significant in-flight respiratory symptoms. During the hypoxia challenge test the infant or young child sits on a carers lap in a body plethysmograph and 100% nitrogen is introduced to reduce the inspiratory oxygen fraction (FIO_2) to 14–15%. Alternatively, the infant can have a face mask placed over their nose and mouth through which high flow 14% oxygen is administered. The typical duration of the test is 20 min. Oxygen saturations are monitored throughout but, unlike in adults, arterial gas samples are not routinely collected and ECGs are not monitored. Nasal cannulas are worn so that if SpO_2 decreases supplemental oxygen can be commenced and titrated to an appropriate level.

Whilst the hypoxia challenge test is a valuable tool there are a number of unanswered questions, including how reliable is the test in infants and children? A preliminary study reported the hypoxia challenge test was able to predict in-flight hypoxia in children aged 11–16 years with CF; however, in a larger study of children with CF the hypoxia challenge test predicted in-flight hypoxia in only two out of 10 cases. One study has reported that the hypoxia challenge test is not accurate in ex-preterm infants flying near term. These studies imply there may be a developmental trajectory for the hypoxia challenge test. In addition, there have been no studies between the body box and face mask technique to compare whether they give similar results. The cut-off for normal and abnormal hypoxia challenge test results is also unclear. The BTS guidelines recommend that infants <1 year of age with a hypoxia challenge test result of <85% should fly with supplemental oxygen but in children >1 year of age the cut-off is 90%. There are no studies supporting the choice of 85% or 90% in children >1 year of age. One study compared hypoxia challenge test cut-off

levels of 85% and 90% and found that the 90% cut-off in children <2 years of age did not discriminate between healthy children and those with a history of neonatal chronic lung disease whereas the 85% cut-off did. However, this study did not report whether the hypoxia challenge test results predicted in-flight oxygen saturation levels.

The European Lung Foundation (www.european-lung-foundation.org) has developed a database that provides information facilitating the organisation of air travel and supplemental oxygen for respiratory patients and healthcare providers. The most relevant guidelines are from the BTS and these are briefly summarised below. Readers are directed to the guidelines for detailed information.

- Healthy term infants should delay air travel for 7 days after the expected term date.
- Preterm infants that have not yet reached their expected date of delivery should fly with supplemental oxygen available, should respiratory symptoms develop.
- Infants and children receiving supplemental oxygen at the time of air travel should have their oxygen flow doubled.
- Young infants (<1 year of age) with a neonatal lung disease should be referred to a paediatric respiratory physician and a hypoxia challenge test performed. Supplemental oxygen should be available if the hypoxia challenge test results in a S_{PO_2} <85% or if S_{PO_2} is 85–90% and there is physician doubt.
- Infants and children with recent long-term oxygen therapy (in the past 6 months) should have a hypoxia challenge test.
- Children with chronic lung disease (such as CF) with a FEV_1 <50% predicted should have a hypoxia challenge test and in-flight oxygen should be used if the hypoxia challenge test result is <90%.

In summary, infants and children with chronic lung disease are at risk of the development of respiratory symptoms and signs, including hypoxia when undertaking air travel. In older children the risk appears to be restricted to those individuals with severe airway obstruction. In infants the primary risk group is those born preterm or with chronic lung disease requiring supplemental oxygen. While the hypoxia challenge test is the currently recommended tool for the identification of at-risk indviduals it does not predict the incidence of in-flight hypoxia in infants born preterm and travelling by air near term and its accuracy in older infants and young children has not been established.

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Sports medicine

Giancarlo Tancredi, Giovanna De Castro and Anna Maria Zicari

Definition

Sports medicine concerns scientific and medical aspects of physical activity, physical fitness, and sports performance. The World Health Organization defines *physical activity* as any bodily movement produced by skeletal muscles that requires energy expenditure and *physical fitness* as the ability to perform muscular work satisfactorily.

Key points

- A physically active lifestyle including sports and supervised conditioning programmes provides physiological improvements in muscle function, cardiopulmonary efficiency, immune system function, obesity prevention and self-esteem.
- Cardiopulmonary exercise testing provides a global assessment of the integrative exercise responses involving the pulmonary, cardiovascular, and skeletal muscle systems.
- $\dot{V}O_2max$ reflects the maximal ability of the body to take in, transport and utilise oxygen and it is the best single measure of aerobic fitness.
- Exercise prescriptions to improve cardiopulmonary fitness in patients with chronic health diseases are based on the initial level of fitness and include the modalities of physical activity as well as the frequency, intensity and duration of the training.

When considering sports activity, it is possible to differentiate between "competitive" and "non-competitive" or leisure-time sports. According to a scientific statement of the American Heart Association (2005), a competitive athlete is defined as one who participates in an organised team or individual sport that requires systematic training and regular competition against others and that places a high premium on athletic excellence and achievement.

Pre-competition medical assessment and screening is an important part of preventive measures to detect compromising health conditions in competitive athletes. The physical examination should include, but not be limited to, cardiovascular, pulmonary, and musculoskeletal assessment.

Since 1982, Italian law has mandated that every participant engaged in competitive sports must undergo a clinical evaluation to obtain eligibility. Furthermore, a medical history, physical examination, and any required additional assessments are recommended for all subjects who practice physical activity.

Benefits of sports programmes

Participation in sports programmes provides an opportunity for children to increase their physical activity and develop physical and social skills.

In particular, the American Academy of Pediatrics recommends that organised sports programmes for pre-adolescents should complement, not replace, the regular physical activity that is a part of free play,

child-organised games, recreational sports, and physical education programmes at school.

Inactivity is a risk factor for many chronic diseases such as hypertension, diabetes, obesity, depression, cancer and cardiovascular disease. Conversely, a physically active lifestyle helps to maintain body weight, and leads to favourable health habits, such as not smoking and a healthy diet.

The numerous benefits of regular physical activity include physiological improvements in skeletal muscle function, cardiopulmonary efficiency, immune system function, obesity prevention, self-esteem and psychological and social conditions. In particular, physical activity may induce beneficial immune system changes with a reduction in pro-inflammatory cytokines of allergic inflammation.

Risks of physical activity

The most significant, but extremely rare, risk associated with exercise in youth is a sudden death event. Among children and adolescents, cardiovascular causes of death include hypertrophic cardiomyopathy, myocarditis, anomalous coronary artery anatomy, Marfan syndrome and commotio cordis. Exercise-induced arrhythmias – with or without pre-existing anomalies of cardiac electrical excitation and repolarisation – may also lead to death.

Becker *et al.* (2004) reported that sudden fatal asthma can occur in competitive and recreational athletes during sporting activities. These subjects were usually white male subjects in the age range of 10–20 years, and many of them had mild asthma. The possible causes of this type of fatal asthma attack include sudden severe asphyxia as well as a reduced chemosensitivity to hypoxia and blunted perception of dyspnoea by the patient. In this study, only three subjects were reported to be using long-term control medications. It is essential to ensure that an athlete with asthma is receiving proper care and therapy.

Sports injuries are other common problems associated with physical activity; they include musculoskeletal injuries, which can occur from excessive amounts of activity or sudden beginning of an activity for which the body is not conditioned. These include muscle tears, acute damage to joints and ligaments, fractures, and overuse injuries. However, many injuries associated with physical activity may be prevented by gradually increasing the level of activity and avoiding excessive amounts of activity.

Doping in sports is a big social problem. Adolescents employ a wide variety of drugs hoping to improve their athletic performance and to look better. Studies report that 3–12% of male adolescents admit they have used an anabolic-androgenic steroid.

''Female athlete triad'' is a syndrome characterised by the presence of disordered eating, amenorrhoea, and osteopenia or osteoporosis. The prevalence of this syndrome is unknown but it will probably continue to grow because of the increased number of girls participating in sports such as cross-country running, gymnastics, and figure skating.

Adolescents engaged in contact sports after having infectious mononucleosis are at potential risk of splenic rupture secondary to abdominal trauma. It is safe to allow these athletes to return to contact sports after a period ranging from 3–6 months.

Physical activity in children with chronic pulmonary diseases

Asthma The prevalence of bronchial asthma in children is about 10%, and 40–90% of these patients have exercise induced asthma (EIA), a manifestation that is frequently undiagnosed. EIA is defined as a condition in which physical activity triggers acute airway narrowing in people with heightened airway reactivity. The exact mechanisms of how exercise may trigger an asthmatic attack in susceptible people are still a matter of research. It is likely that cytokine release and parasympathetic nerve reflexes triggered by water and heat loss from the respiratory epithelium associated with the exercise-induced increase in ventilation play a key role.

The diagnosis of EIA is suggested by the symptoms of cough, wheezing, chest tightness or dyspnoea during or shortly after exercise, and demonstrated by a decrease of 12–15% in forced expiratory volume in 1 s (FEV_1). EIA is usually studied with ergometers such as the treadmill and cycle ergometer, or free running. These tests are complex, expensive or require a large space. The current authors have found that the step test is a quick, economical, reproducible and portable alternative procedure for identifying EIA in out-patients and epidemiological studies.

Moreover, it is necessary to underline that exercise testing is less sensitive but more specific than pharmacological challenges (histamine, methacholine) in detecting EIA.

In a systematic review of 16 studies and 516 subjects, Crosbie (2012) evaluated the effect of physical training in children with asthma. This review confirms that there is an increase in aerobic capacity as measured by $V'O_2max$ ($mL \cdot kg^{-1} \cdot min^{-1}$) in asthmatic children with physical training, with a response similar to healthy controls. However, physical training does not improve pulmonary function in asthmatic children.

Finally, it is important to underline that asthmatic children can be active and participate in any sports they choose when their asthma is well controlled.

Exercise-induced anaphylaxis Exercise-induced anaphylaxis (EIAn) is a rare but potentially life-threatening clinical syndrome characterised by anaphylaxis concomitant with exercise. EIAn may occur independently of food allergen ingestion or may require the combined ingestion of sensitising food before exercise to trigger symptoms. Clinical features and management do not differ significantly from other types of anaphylaxis. Therapy includes epinephrine, antihistamines, and systemic corticosteroids.

Cystic fibrosis is the most common hereditary disease in white populations. It is caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene.

There is good evidence suggesting that children with mild-to-moderate CF can benefit in terms of pulmonary function from either an aerobic or resistance training programme. Moreover, team sports are important for the social integration of any child with a chronic disease.

Specific sports such as scuba diving and sports at high altitude should be discouraged for children with CF with significant air trapping. In both types of activity, unfavourable situations can happen in which oxygen becomes limited and severe desaturation can occur over longer time-periods.

Pulmonary barotrauma is relevant in scuba diving. The lung injury is caused by overdistention of alveoli and rupture of alveolar walls as a consequence of expanding gases during ascent.

Other problems that may occur include pneumothorax with weight training, rupture of spleen and oesophageal varices in patients with portal hypertension performing contact sports, and dehydration and electrolyte losses during prolonged exercise in the heat.

Most patients with congenital lung diseases (*e.g.* pulmonary hypoplasia) and other conditions such as bronchopulmonary dysplasia are relatively sedentary. It is important to motivate these children to increase their fitness level through participation in regular physical activity. In these subjects it is necessary to perform an evaluation including an accurate clinical and functional assessment before starting a sport to minimise any potential risk.

Clinical exercise testing

Cardiopulmonary exercise testing provides a global assessment of the integrative exercise responses involving the pulmonary, cardiovascular, and skeletal muscle systems. The primary cardiovascular parameters routinely measured during exercise testing are the electrocardiogram, heart rate, blood pressure, cardiac output, stroke volume and systemic vascular resistance. All these parameters are

measurable using standard noninvasive techniques. Cardiopulmonary exercise testing is essential because pulmonary and cardiac function assessed at rest cannot reliably predict exercise performance or functional capacity, and overall health status will correlate more closely with exercise tolerance than with measurements taken at rest. Exercise testing has been proven to be useful for differentiating between cardiovascular and pulmonary causes of exercise intolerance and identifying disorders of pulmonary gas exchange, certain muscle diseases and psychological disorders.

$V'O_2max$ reflects the maximal ability of the body to take in, transport and utilise oxygen. It is widely recognized as the gold standard indicator of aerobic fitness and may be determined using standardised testing on a treadmill or a cycle ergometer.

$V'O_2max$ is correctly defined by the Fick equation:

$$V'O_2max = Q \times (CaO_2 - CvO_2)$$

when these values are obtained during an exertion at a maximal effort, and where Q is the cardiac output, CaO_2 is the arterial oxygen content and CvO_2 is the venous oxygen content. $V'O_2$ can be measured noninvasively and directly by the product of ventilation and the difference of oxygen concentration of inhaled and exhaled air that has been utilised by the working muscles. $V'O_2max$ can be influenced by age, sex, exercise habits, body size, heredity, and cardiovascular clinical status.

Measurement of oxygen saturation on exercise, using a pulse oximeter, at rest and on exertion, is a noninvasive method allowing the monitoring of arterial oxygen saturation (SaO_2). The assessment of SaO_2 is an important indication in patients with chronic lung disease since neither the presence nor the severity of desaturation during exercise can be predicted readily from resting SaO_2.

METs or metabolic equivalent is a physiological measure expressing the amount of oxygen consumed at rest (approximately 3.5 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$), and serves as a unit to estimate the amount of oxygen used by the body during physical activity. Activity that burns 3–6 METs is considered moderate-intensity physical activity.

It is established that well-directed aerobic training programmes result in a significant improvement in $V'O_2max$. Classically, $V'O_2max$ will increase by about 15–20%, although there may be a large inter-subject variation owing to genetic factors.

We have measured $V'O_2max$ during a cardiopulmonary exercise test in children with different pathologies, girls with Turner syndrome and children after a renal transplant. In these patients $V'O_2max$ provides valuable information on health status and effects of exercise training programs.

Prescription of physical activity

Exercise prescription has received a growing interest in general clinical practice and specifically in the care of people with chronic health conditions. The objective of each prescription would be to recommend a particular quantity of physical activity to an individual in a way that results in specific therapeutic goals such as health benefits or improved cardiorespiratory fitness.

The principles that rule exercise prescription are based on exercise mode, frequency, intensity and duration. The recommended mode of aerobic exercise in chronic respiratory disease is walking or any type of aerobic exercise that uses large muscles; the optimal frequency is 3–5 days per week; and the intensity of exercise is at 50–85% of maximum oxygen uptake or at limits as tolerated by the patient. Duration of exercise should be 20–60 min of continuous aerobic activity.

In patients with significant cardiac or pulmonary disease, interval training can be a valid alternative. Interval training is a type of physical training that consists of high intensity work alternated with periods of rest or low activity.

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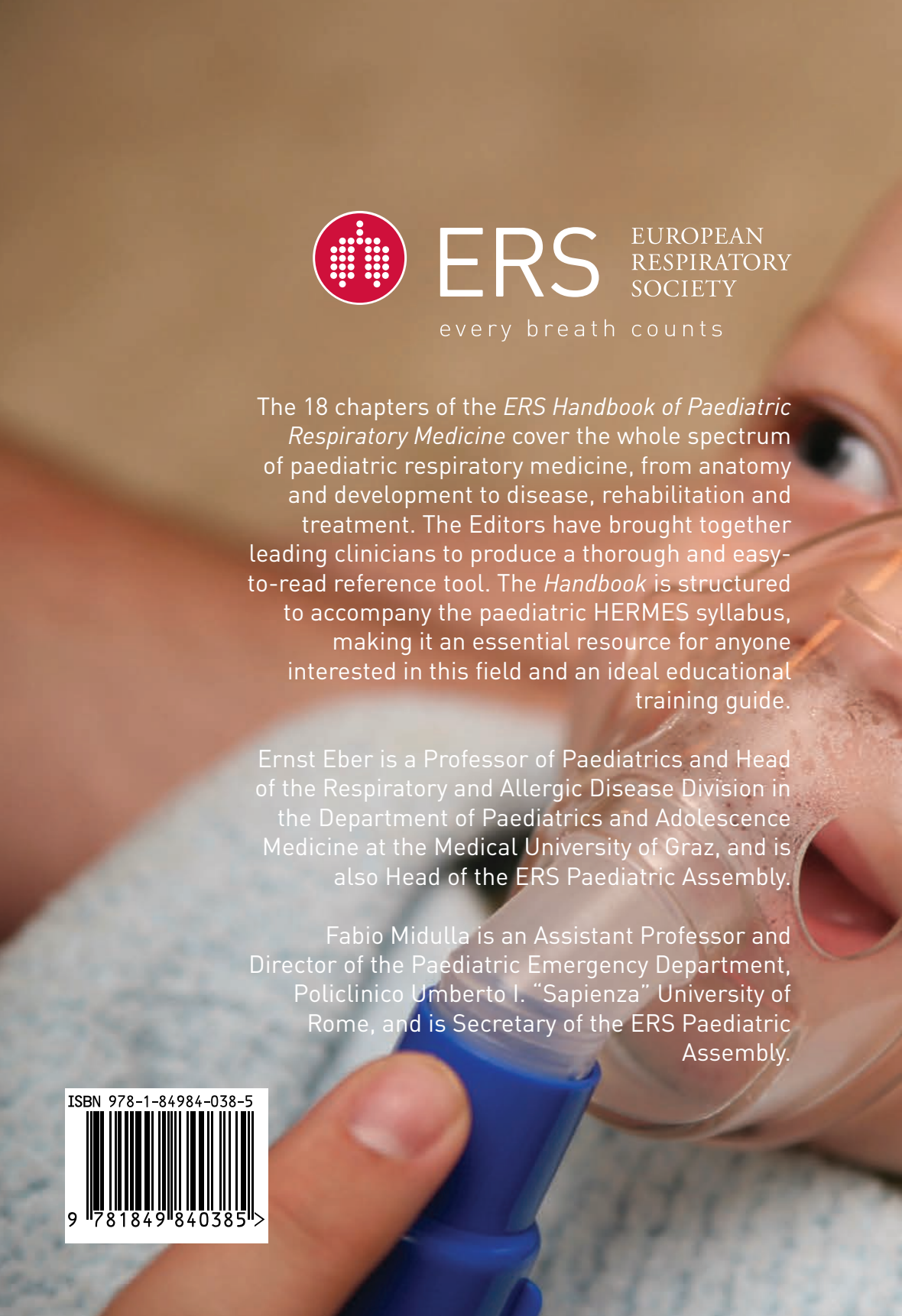

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