The mind is not a vessel to be filled but a fire to be kindled.

Plutarch

Why an ERS Handbook of Respiratory Medicine? Education is one of the pillars of the European Respiratory Society (ERS) and the fundamental aim of the ERS School is to provide excellence in education in the field of respiratory medicine. Five years ago, the School started a very ambitious project, to Harmonise Education in Respiratory Medicine for European Specialists (HERMES). A preliminary survey among 29 European countries showed considerable variation in post-graduate training. Based on these findings, the School developed a range of consensus documents: a core syllabus describing the competencies required, a curriculum of recommendations indicating how competencies should be taught and learned, an accreditation methodology for training centres, and a voluntary European examination to assess whether specialists have acquired the knowledge-based component of competence. Moreover, during the past few years, a vast array of educational material, such as lectures, articles published in two of the society’s publications – Breathe and the European Respiratory Monograph – web lectures and courses, have been produced and made available on the School website (the ERS School maintains the biggest online resource in respiratory medicine, which functions both as an e-library and as an interactive education).

The School committee has now decided that the time is right to deliver the first edition of the ERS Handbook of Respiratory Medicine. We hope it will inform our trainees and provide an easily accessible, comprehensive update for medical, nursing and paramedical colleagues at all levels across the specialty. The ERS Handbook consists of concise state-of-the art summaries which will be updated regularly in electronic and hard copy versions. Hard copy users will have access to electronic updates and further CME questions. Our contributors are all clinical experts in the field. We are particularly indebted to the ERS School Committee, Managing Editor Matt Broadhead who curated the contents of the handbook, Tania Séverin who oversaw the project, and all the contributors.

Paolo Palange, Anita Simonds
CHIEF EDITORS
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GENETICS

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Genetics addresses the composition, function and transmission of inherited entities (genes). Generally, the term “gene” is understood as a unit coding for a single RNA that gives rise to a single and specific protein. However, due to alternative splicing, one gene may code for different proteins and in addition there are also genes coding for catalytic RNA (tRNA, rRNA) or regulatory (micro)RNAs (miRNA).

The genotype is the specific composition of genes of an individual; it influences the phenotype of an individual. However, in contrast to the genotype, which is simply inherited, a phenotype is shaped by epigenetic phenomena, environment, climate, nutrition and other external factors.

It is, in some respect, worthwhile to stress that genes code for proteins, and not for “diseases”. Every genetic disease is based on an altered or missing protein. Because we are all equipped with a double set of chromosomes, in the vast majority of cases, a dysfunctional gene is corrected by its counterpart gene with normal function. A deficiency occurs only when the respective gene is dysfunctional on both chromosomes, or the gene product is either missing or does not exert its task.

Diseases caused by the alteration of a single gene that pulmonologists are most frequently faced with are cystic fibrosis (CF) and α1-protease inhibitor (πI) deficiency (formerly α1-antitrypsin (AT) deficiency; see below). In other diseases, such a clear-cut relationship between a gene and a disease is not evident, although facts such as geographical distribution or familial clusters indicate a genetic background to the disease. This is the case in asthma, sarcoidosis, pulmonary fibrosis and primary pulmonary hypertension. Table 1 shows mutated genes involved in respiratory disorders.

There are also a number of gene variations that are regarded as neutral variation of the human gene pool. These variations are not harmful per se but, together with distinct external stimuli, they foster the development of certain diseases. Glutamine at position 69 in the human leukocyte antigen (HLA)-DPB1 gene is not considered as an illness; however, when in contact with beryllium dust, carriers of Glu69+ HLA-DPB1 are at an increased risk of developing chronic beryllium disease (CBD). Up to 97% of CBD patients are Glu69+ HLA-DPB1 positive. Another example is the lack of functional receptors for interferon-γ or interleukin-12. In this case, individuals grow up normally and reach

Key points

- A few respiratory diseases, such as CF and α1-πI deficiency, are single-gene conditions.
- A large range of respiratory diseases, including asthma, sarcoidosis and primary pulmonary hypertension, have a genetic background.
- Non-harmful gene variants can nonetheless confer susceptibility to conditions such as chronic beryllium disease.
- The role of epigenetic regulatory mechanisms in respiratory disease is likely to be very significant.
adolescence; however, after BCG vaccination or when they encounter environmental mycobacteria (e.g. *Mycobacterium fortuitum*, *Mycobacterium chelonae*), these patients develop severe and sometimes fatal diseases.

**Epigenetics and regulatory genes**

In addition to these classical forms of genetics, coded in the sequence of the four bases A/T and C/G, additional mechanisms of genetic regulation – epigenetics and regulatory genes – have been discovered in recent years.

The term epigenetics describes a wide field of DNA and histone modifications that contribute to the regulation of gene transcription. One of these modifications is the methylation of the nucleobase cytosine. Cytosine is methylated only in CG islands; single cytosines are not methylated. Cytosine methylation inhibits binding of RNA polymerases to the gene, which is subsequently not translated. Cytosine methylation is important in promoter silencing and inactivation of the X chromosome.

Histone modifications are an additional form of epigenetic regulation. Histones are protein spheres that bind DNA; there are four different histones, and two of each histone together with the bound DNA make up a nucleosome, the core of a chromosome. Histones can be modified, mainly by acetylation, methylation and various other mechanisms. Generally, acetylation of histones opens the nucleosome structure and the gene becomes accessible for transcription. In contrast, histone methylation leads to the accumulation of other proteins leading to a compacted nucleosome, which inhibits gene transcription.

miRNAs are short, highly conserved, noncoding RNAs binding to 5' untranslated regions (5'UTR) of messenger RNAs. Incomplete binding leads to silencing, and complete binding to degradation of the RNA. In fact, miRNAs are powerful regulators. Activation of transcription factors such as nuclear factor-kB leads to transcription of a variety of immune mediator genes. Simultaneous activation of miRNAs suppresses certain mediators giving rise to a specific pattern of mediator activation. This area of research is at an early stage, and novel aspects of gene regulation might be expected.

**Genetics in CF**

As mentioned above, CF is caused by the dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which codes for a chloride channel. However, although in all CF patients the CFTR is dysfunctional, there are >1,500 different mutations known to affect CFTR and lead to a dysfunctional chloride channel. CF is inherited

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HLA: human leukocyte antigen; SNP: single nucleotide polymorphism.
in an autosomally recessive fashion: the disease becomes manifest only when the CFTR genes on both chromosomes are mutated, although not necessarily by the same mutation. The most common defect is the deletion of a phenylalanine at position 508 (ΔF508), which is responsible for up to 70% of all CF cases. Interestingly, there is a marked difference in the frequency of this disease in different populations. With a frequency of 1:2,000, CF is most common in Caucasians (being highest in Scotland and the Faroe Islands). Populations of African descent have a risk of 1:15,000; populations of Asian descent have the lowest risk (1:30,000). CFTR mutations can be grouped into classes based on their functional consequences on the CFTR within the cell: CFTR is either not synthesised, inadequately processed, not regulated, shows abnormal conductance, discloses partially defective production, or shows accelerated degradation.

**Genetics in PiS**

The Pi α1-AT belongs to a family of serine PiS (serpins) and blocks serine proteases such as neutrophil elastase, cathepsin G and proteinase 3, all released by neutrophils. Because more than one proteinase is blocked by this inhibitor, it is more precisely named α1-PI. The lack of α1-PI leads to an incomplete or absent containment of proteinases resulting in severe organ damage (emphysema), mostly in the lung. In the USA, α1-PI deficiency causes 7.6% of lung transplantations.

There are several known mutations in the α1-PI gene, such as base substitutions, in-frame deletions, frame shift mutations and exon deletions. >90% of the cases are caused by single amino acid exchange at position 342 (glycine to lysine), which is called Z mutation. The Z mutation results in a structural alteration, which inhibits post-translational modifications and secretion. Patients bearing the Z allele disclose <15% of the normal α1-PI level in serum, which, additionally, seems to be nonfunctional.

The gene frequency of the Z allele is rather common in Europe, with up to 4% of the population being heterozygotic. However, the frequency declines to <1% in southern Europe. The lowest frequency is found in African-Americans (0.4%).

**Genetics in interstitial lung diseases**

There is some indication that interstitial lung diseases such as sarcoidosis, CBD, or idiopathic pulmonary fibrosis (IPF) are based on a specific genetic background. In sarcoidosis and IPF, familial clusters are seen. In Europe, sarcoidosis frequency increases from South to North. This might also be a matter of climate, as the same distribution is seen in Japan. However, the Ainu, a minority distinct from the Japanese population in northern Japan, exhibit a markedly lower frequency. The Swedish population encounters the highest prevalence in Europe (55–64 per 100,000); in contrast, the Finnish population live at the same latitude but the prevalence is just half that of the Swedish (28 per 100,000). These differences point to a strong genetic background in the pathogenesis of sarcoidosis.

The contribution of an inherited predisposition to the aetiology of sarcoidosis is indicated by an increased risk of sarcoidosis in close relatives of patients. The percentage of patients with a positive family history ranges from 2.7% in Spain to 17% in African-Americans. Analysis of familial sarcoidosis suggests that multiple small or moderate genetic effects cause a predisposition for sarcoidosis.

Genes of interest have been HLA class II antigens. Although some of these linkages are largely dependent on the population investigated, several associations do seem to be preserved, e.g. HLA-DRB1*03 associates with spontaneous resolution and mild disease, as demonstrated in Swedish, Polish, Croatian and Czech populations.

Using genome-wide association scans, two additional candidate genes were identified, the butyrophilin-like 2 gene (BTN2L2) and Annexin A11 (ANXA11) gene. The BTN2L2 disease-associated splice site (rs 276530)
introduces a premature stop resulting in truncated nonfunctional protein. Because BTNL2 is necessary for the down-regulation of T-cell activation, the dysfunctional gene product contributes to the exaggerated T-cell activation in sarcoidosis.

Annexin A1 exerts complex and essential functions in several biological pathways, including apoptosis and proliferation.

There is a large body of studies analysing the association of cytokine genes with sarcoidosis. With exception of the association of Löfgren’s syndrome and a variant of the tumour necrosis factor (TNF) gene related to higher cytokine production (TNFA2), these studies did not reveal conclusive results.

Angiotensin-converting enzyme (ACE) is often used in the diagnosis and clinical monitoring of sarcoidosis. However, serum levels of ACE (sACE) are highly variable, which impairs the clinical use of ACE. The variability of sACE is based on a deletion/insertion in intron 16 of the ACE gene. The homozygote deletion variant is associated with higher sACE, whereas homozygote insertion is associated with lower levels. Heterozygotes exhibit intermediate values. Therefore, in populations of Caucasian origin, the knowledge of the zygosity of the deletion/insertion variants allows the application of genotype-corrected reference values of sACE, which leads to an improvement of the clinical application of this marker. However, this is not applicable in populations of African origin: the ACE gene in these populations is much more polymorphic and sACE levels are not linked with the deletion/insertion polymorphism.

Familial pulmonary fibrosis is linked with two mutations in the surfactant protein C (SPC) gene. The first mutation causes a change from guanine to adenine at the starting point of exon 4, resulting in a splice deletion of exon 4 and subsequently a final protein lacking 37 amino acids. This shortened protein is misfolded and accumulates in a perinuclear pattern in the cells. The misfolded SPC protein aggregates with the normal SPC, which subsequently leads to a lack of mature SPC in the alveolar lumen. This phenomenon provides an explanation for the dominant autosomal heredity of this mutation.

The second mutation causes a change from thymidine to adenine in exon 5 that results in the substitution of glutamine (position +188) by leucine. This variant of SPC cannot be processed and accumulates as pro-SPC in the cell. The pathological pattern of fibrosis is in both forms consistent with nonspecific interstitial pneumonitis in younger patients and usual interstitial pneumonia in the elderly.

CBD is largely linked with Glu69+ HLA-DPB1, as 97% of CBD patients bear this HLA variant. However, the frequency of Glu69+ HLA-DPB1 is also increased in beryllium-sensitised healthy individuals. Interestingly, Glu69+ HLA-DPB1 homozygosity was higher in CBD patients compared with beryllium-sensitised individuals. Therefore, Glu69+ HLA-DPB1 is a risk marker of beryllium sensitisation and homozygote Glu69+ HLA-DPB1 increases the risk for the progression from beryllium sensitisation to CBD; however, there is a large variation in the time course for this conversion. This, together with the fact that Glu69+ HLA-DPB1 heterozygotes also develop CBD, implies that additional genes may add to the predisposition to CBD.

Genetics in asthma

There is a plethora of work related to the genetics of asthma. The idea of a genetic basis for asthma is supported by the fact that there are familial clusters of asthma and differences of asthma frequency in different populations (with the highest being >20% of the population of the South Atlantic island Tristan da Cunha). However, no single gene is responsible for the development or the clinical course of asthma; instead, several genes are regarded as risk genes for developing asthma. The gene products of these genes are involved in T-cell activation, cytokine release and balance, epithelial function and repair or smooth muscle contractility.

As methods in association studies improve rapidly, new candidate genes will be added to this list in future.
Nevertheless, although there are predisposing genes in asthma, the influence of lifestyle on the development of asthma is also evident. There is a clear increase in asthma incidences in developing countries. Therefore, asthma might be an elucidating example for the complex genotype/phenotype relationship.

Genetics in cancer

Mutations and epigenetic modifications are passed to the offspring as far as the germ cells are concerned. However, there are also mutations outside the germline — so-called somatic mutations. As these mutations accumulate over years, a growing organism resembles a genetic mosaic rather than a unique clone of the germ cell it is derived from.

Most of these somatic mutations are silent and either do not cause any defect or are corrected by its respective counterpart. However, there is a variety of somatic mutations that finally cause tumour genesis. An example of such a somatic mutation involved in cancer is a mutation in the MYC gene, leading to the overexpression of c-myc. c-myc is a regulatory protein inducing histone acetylation (see above). Overexpression of c-myc leads to histone hyperacetylation and subsequently to the transcription of a variety of genes. Overexpression of c-myc is an important factor in the pathogenesis genesis of small cell lung cancer (SCLC). However, no single event, like the mutation of c-myc, is responsible for tumour genesis. In general, tumours like SCLC or nonsmall cell lung cancer present with a large variety of genetic alterations, like DNA methylation, alternative splicing, or histone modifications, which all might be involved in oncogenesis.

As genetic tools become more common, the analysis of the individual pathways involved in the individual cancer pathogenesis might help to develop individual targets for therapy.

Conclusion

Genetic aspects have to be considered in all areas of pulmonary medicine. As physicians are faced with phenotypes, the underlying degree of genetic influence is not always obvious. The knowledge of the genotype causing a respective phenotype might be a promising tool to predict outcome or therapeutic options, and would enable individual genotype/phenotype-based therapies.

References

Understanding of lung disease on the cellular and molecular level is crucial to develop new approaches for the diagnosis, treatment and prevention of lung disease. Although our knowledge on the molecular level is steadily increasing, we still have a limited understanding of the molecular events underlying the diseases, which is reflected by the fact that very few therapies target specific defects.

The field of molecular biology focuses on the interactions between various systems of a cell and between cells, and particularly includes:

- gene structure, expression, replication, and recombination
- structure, function, chemistry, and in vivo modification and processing of proteins and nucleic acids
- cellular and developmental biology
- genetics, structure and growth cycles of viruses, bacteria, and bacteriophages.

This article focuses on selective (signal) molecules and structures, all of which are altered in various lung diseases and are important topics in the field of molecular biological research.

**The extracellular matrix**

Components of the extracellular matrix (ECM) surround and support the cell and cell-cell interaction. In the lung, the ECM around the conducting airways, alveolar cells and the vascular system has a major impact on lung architecture and function, in particular gas exchange. All lung cell types interact and signal through the ECM via adhesive molecules, surface receptors or growth factors.

The lung fibroblast is the main producer of pulmonary ECM, which consists of collagens, elastins and proteoglycans. The interstitium of the lung parenchyma contains mostly collagen type I and III, which are mainly responsible for tensile strength.

The pulmonary ECM is subjected to a continuous turnover of >10% of the total ECM per day. Thus, a dynamic equilibrium between synthesis and degradation of the pulmonary ECM maintains the physiological balance. This balance is tightly controlled by three regulatory mechanisms: 1) de novo synthesis and deposition of ECM components such as collagens, mainly by interstitial fibroblasts; 2) proteolytic degradation of existing ECM by matrix metalloproteinases (MMPs), a family of zinc enzymes; and 3) inhibition of MMP activity by specific endogenous antiproteases, the tissue inhibitors of metalloproteinases (TIMPs).

**Key points**

Major features of lung diseases are:

- altered deposition of extracellular matrix
- impaired surfactant metabolism
- distorted endogenous defence mechanisms
Excessive or inappropriate expression of MMPs is related to the pathogenesis of tissue destructive processes in many of lung diseases, such as MMP-12 in emphysema, or MMP-7 in lung fibrosis.

**The surfactant system**

The maintenance of normal lung function throughout the life of an organism is ensured largely by alveolar epithelial cells, which form a tight functional barrier essential for gas exchange. The alveolar epithelium is composed of alveolar type I (ATI) and type II (ATII) cells. ATII and ATI cells produce and secrete components of the extracellular matrix and growth factors thereof, which facilitates restoration of the interstitium and, subsequently, functional alveolar structure. ATII cells are cuboidal secretory cells mainly responsible for surfactant secretion.

Pulmonary surfactant is a complex mixture of phospholipids and proteins, with surfactant proteins (SP)-A, -B and -C constituting 10% of surfactant. Its main role is to reduce surface tension in the alveoli following the onset of breathing, thereby leading to lung expansion. Mechanical stretching of the lung forces the secretion of lamellar bodies, the intracellular storage granules of surfactant, which form tubular myelin. The surfactant film stabilises the alveolar–air interface with a low surface tension and prevents lung collapse. Following secretion, both surfactant proteins and lipids are recycled by the respiratory epithelium.

Surfactant abnormalities have been described in many infant and adult lung diseases, such as respiratory distress syndrome, bronchiolitis, chronic obstructive pulmonary disease (COPD) or interstitial lung disease.

**Defence and clearance mechanisms**

From the above-mentioned proteins, surfactant proteins SP-A and SP-D are primarily involved in the innate host defence of the lung. In addition, antimicrobial peptides (AMPs), such as defensins, cathelicidins or lactoferrin, are present in the airways to prevent infection. Moreover, cellular defence mechanisms include macrophage- and neutrophil-mediated release of cytokines, such as interleukins 1 and 8, tumor necrosis factor (TNF)-α, or granulocyte macrophage colonystimulating factor (GM-CSF).

Pulmonary alveolar proteinosis is caused by disruption of GM-CSF signalling. Loss of GM-CSF signalling in macrophages results in an impaired ability to catabolise surfactant proteins. Abnormal surfactant accumulation leads to respiratory insufficiency.

Mucociliary clearance represents the primary physiological defense mechanism. The ciliated airway cells clear the mucus, which is produced by secretory cells, by forcing the mucus toward the larynx for elimination. An impaired mucociliary clearance is the main feature of cystic fibrosis.

**Transforming growth factor-β**

The transforming growth factor (TGF)-β superfamily is critically involved in embryonic development, organogenesis and tissue homeostasis. TGF-β superfamily members act as multifunctional regulators of cell growth and differentiation. The TGF-β superfamily comprises more than 40 members, including TGF-βs themselves. Three TGF-β isoforms have been characterised so far: TGF-β1, TGF-β2 and TGF-β3. TGF-β1 is the most important isoform in the cardiopulmonary system, as it is ubiquitously expressed and secreted by several cell types, such as endothelial, epithelial and smooth muscle cells, as well as fibroblasts and most cells of the immune system. TGF-β is secreted in covalent association with the latent TGF-β binding protein (LTBP), thus providing a reservoir in the ECM. For active signalling, TGF-β needs to dissociate from the complex by a mechanism that involves proteases, such as plasmin or matrix metalloproteinases, as well as interaction with integrins. Active TGF-β ligands bind to the type II TGF-β receptor, which binds to the type I TGF-β receptors. Subsequent transphosphorylation of the type I receptor results in recruitment of specific intracellular signals mediators, called Smad proteins. Smad2 and Smad3 have been shown to be phosphorylated by the type I receptor,
followed by complex formation with Smad4 and, finally, nuclear translocation and regulation of gene transcription (fig. 1). The receptor-regulated Smad2 or Smad3, in combination with the co-Smad Smad4, positively regulate TGF-β-induced effects, while the inhibitory Smads (Smad6 and Smad7) negatively regulate TGF-β signalling.

Increased TGF-β signalling is the key pathophysiological mechanism that leads to fibrotic lung disease, which is characterised by an increase in activated (myo)fibroblasts and excessive deposition of ECM.

There is emerging interest in the role of TGF-β in the pathogenesis of COPD, particularly

Figure 1. Transforming growth factor-β signalling.
since genetic studies have demonstrated an association of gene polymorphisms of the TGF-β superfamily with COPD. In addition, increased expression of TGF-β1 in COPD has been reported, suggesting an impact of TGF-β signallng in the development and progression of COPD.

**Nuclear factor-κB**

Nuclear factor (NF)-κB is a ubiquitous transcription factor present in all cell types. In its resting stage, this factor resides in the cytoplasm as a heterotrimer consisting of p50, p65 and the inhibitory protein IκBα. Upon activation, the IκBα protein undergoes phosphorylation, ubiquitination and degradation. p50 and p65 are then released to be translocated to the nucleus, where they bind specific DNA sequences present in the promoters of various genes and initiate transcription. IκBα kinase or IKK is responsible for the initial phosphorylation. Several kinases have been shown to activate IKK, such as AKT, mitogen-activated protein/extracellular signal-regulated kinase kinase 1 (MEKK1), and protein kinase C. In the nucleus, NF-κB induces a range of gene expression, in particular of mediators of inflammation, cell proliferation, metastasis and angiogenesis.

Many noxious substances related to lung disease, such as cigarette smoke, radiation, chemotherapeutic agents, or cytokines and growth factors, activate NF-κB, and increased NF-κB signalling has been associated with COPD or asthma.

**References**

The thoracic structures include the vital organs for respiration and circulation. This anatomical section will focus on the pleura, lungs, mediastinum and the diaphragm. The anatomy of the heart is not discussed.

**Pleura**

The lungs are covered by a fine membrane known as the pleura. The parietal pleura is the outer layer and the visceral pleura is adherent to the lungs. The two are in continuity with each other and there is a very fine space between the two, the pleural cavity. The parietal pleura is described according to the surface that it is adjacent to: costo-vertebral, diaphragmatic, cervical and mediastinal. There are also pleural recesses where the two different pleural surfaces are situated next to each other without any intervening lung in normal respiration. The costo-diaphragmatic recesses are a thin area between the costal and diaphragmatic pleura. The costo-mediastinal recess is between the costal and mediastinal pleura and is found behind the sternum and costal cartilages.

The pleura is supplied by its regional blood vessels. Hence, the cervical pleura is supplied by branches of the subclavian artery, the costo-vertebral pleura by the intercostal arteries, and the diaphragmatic pleura from the vascular plexus from the surface of the diaphragm. The venous drainage occurs into the corresponding veins, which then drain into the vena cava. The lymphatic drainage is into the corresponding lymph nodes, e.g. the intercostal lymphatics drain into the posterior lymph nodes and then into the thoracic duct.

The visceral pleura is supplied by the bronchial vessels and the lymphatics drain into the intercostal and peri-bronchial lymphatics. The parietal pleura is supplied by the regional nerves and contains the pain fibres. The costal and peripheral aspects of the diaphragmatic pleura are supplied by the corresponding intercostal nerves, whereas the diaphragmatic and mediastinal pleura are supplied by the phrenic nerves.

**Lungs**

The apex of the lung extends into the thoracic inlet and on the anterior aspect lies above the first costal cartilage. On the posterior aspect, the apex of the lung is level with the neck of the first rib. At its highest position it is ~2.5 cm above the clavicle. The base of the lung is a concave structure and lies over the diaphragm. The main surface of the lung is the costal surface, which is smooth and shaped according to the chest wall. The

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**Key points**

- The anatomy of the thorax can be divided broadly into the pleura, lungs, mediastinum, diaphragm and heart.
- The lungs can be further sub-divided into lobes, segments, trachea and bronchi and hila.
- The mediastinal space contains structures including the thymus gland, thoracic lymph nodes, thoracic duct, vagus nerve and autonomic nerve plexus.
medial surface of the lung is shaped posteriorly according to the vertebral column and medially by the heart. The lungs are also indented by the numerous vascular structures, such as the aorta, that are in contact with them.

The right lung consists of upper, middle and lower lobes. The left lung is composed of an upper and lower lobe. In the right lung there are two fissures. The oblique fissure separates the lower lobe from the upper and the middle lobe. The smaller horizontal fissure separates the upper and middle lobes. In the left lung, the oblique fissure separates the upper lobe from the lower lobe.

**Bronchopulmonary segments**

The main bronchi divide into lobar bronchi that in turn divide into segmental bronchi. Each divides into a structurally and functionally independent unit of tissue. The right lung consists of 10 bronchopulmonary segments, three in the upper lobe, two in the middle lobe and five in the lower lobe.

The left lung comprises nine segments, five in the upper lobe, including two within the lingula, and four in the lower lobes. There is no true medial segment in the left lower lobe as this area is occupied by the heart.

Each bronchus continues to subdivide into smaller narrower airways until they finally form terminal bronchioles and then respiratory bronchioles, which are devoid of cartilage. These in turn lead to several alveolar ducts, which in turn end in several alveoli. The collective structure is termed an acinus. The secondary pulmonary lobule is the smallest part of the peripheral lung bounded by connective tissue and usually consists of six bronchi forming a hexagonal pattern with a central artery, lymphatic and peripheral veins.

**Trachea and bronchi**

The trachea (fig. 1) is 100 mm long and made up of anterolateral cartilage rings with a fibro-muscular posterior wall. The trachea divides at the level of the fourth vertebral body (level with the aortic arch) into the right and left bronchi. The right main bronchus is ~25 mm long and divides into the right upper lobe at the level of the fifth thoracic vertebra. It then continues as the bronchus intermedius, which is ~20 mm in length. The right main bronchus is wider, shorter and more vertical than the left main bronchus and hence foreign bodies tend to lodge more frequently into the right main bronchus. The bronchus intermedius then branches into the middle and lower lobes. The right middle lobe is formed on the anterior aspect of the bronchus intermedius. The right lower lobe bronchus gives off a branch to the superior segment and continues to descend posterolaterally giving off branches to the medial, anterior, lateral and posterior segments of the lower lobe.

The left main bronchus is longer, measuring ~40 mm in length, and enters the hilum of the left lung at approximately the level of the sixth thoracic vertebra. It divides into the left upper lobe and left lower lobe bronchus; the left upper lobe bronchus in turn gives off the superior division and supplies the apical posterior and anterior branches of the left
upper lobe and the inferior division, which supplies the superior segment of the lingula and inferior segment of the lingula. The left lower lobe descends posterolaterally and first gives off a posteriorly located branch to the apical segment of the lower lobe and then gives branches to antero-medial, lateral and posterior basal bronchi.

The trachea is supplied superiorly by branches of the inferior thyroid arteries and more inferiorly by branches of the bronchial arteries. The venous drainage tends to be towards the inferior thyroid venous plexus and the lymphatic drainage to the para-tracheal and peritracheal lymph nodes. The bronchi and the airways are supplied by the bronchial arteries, which originate from the systemic circulation and arise either directly from the descending thoracic aorta or indirectly via the intercostal arteries. The venous drainage of the airways is more complicated and consists of deep bronchial veins that communicate with pulmonary veins that drain back into the left atrium. There are also superficial bronchial veins that drain into the azygos or the intercostal veins. The innervation of the endobronchial tree is via the anterior and posterior pulmonary plexus, which include branches from the vagus, recurrent laryngeal and sympathetic nerves.

Hila

The pulmonary hila join the medial aspect of the lung to the heart and the trachea. In each hilum there are a number of structures either entering or leaving the structure. They include the main bronchi, pulmonary artery, superior pulmonary vein, inferior pulmonary vein, bronchial artery, bronchial vein, pulmonary autonomic neural plexus, lymphatics and loose connective tissue.

Pulmonary vasculature and lymphatic drainage

The pulmonary artery carries deoxygenated blood to the alveoli and the oxygenated blood then returns via the pulmonary veins to the left atrium. The pulmonary arteries lie anterior to the carina and the corresponding main bronchi. The artery then enters the lung via the hilum. On the right side the upper lobe branch of the pulmonary arteries is anterior and lateral to the right upper lobe whereas the inferior branch of the pulmonary artery passes laterally and posterior to the lower lobe bronchus. On the left side, both upper and lower lobe pulmonary artery branches are lateral and posterior to the corresponding airways. The descending branch of the left pulmonary artery passes behind the left upper lobe and travels laterally and inferior to the left lower lobe bronchi.

There are two pulmonary veins on each side (superior and inferior pulmonary veins) that pass anterior and inferior to the pulmonary artery and bronchi. The lymphatic vessels drain into the hilar and subsequently into the tracheo-bronchial lymph nodes.

Mediastinum

The mediastinum is the space between the two lungs. The superior extent of the mediastinum is the thoracic inlet and the inferior extent the diaphragm. The anterior border is the sternum and the posterior border is the vertebral column. It is divided into the superior, anterior, middle and posterior mediastinum. The mediastinum contains numerous structures, such as the thymus gland, thoracic lymph nodes, thoracic duct, vagus nerve and the autonomic nerve plexus.

The thymus gland lies in the superior and anterior mediastinum. The lower border is down to the fourth costal cartilage. Its blood supply is derived from a branch of the internal thoracic artery and the inferior thyroid artery. The thymic veins drain into the left brachial cephalic vein and internal thoracic veins. The lymphatic drainage is into the tracheobronchial lymph nodes.

The mediastinum lymph nodes have special significance in the staging of lung cancer. They are found in the pretracheal, paratracheal, subcarinal and paraoesophageal positions. They are classified according to the International Association for the Study of Lung Cancer (IASLC) lymph node...
map into lymph node stations, e.g. station 4 is the right paratracheal lymph node. The thoracic duct starts at the lower level of the 12th thoracic vertebra and enters the mediastinum through the aortic opening of the diaphragm. It runs in the posterior aspect of the mediastinum just right of the mid line between the aorta and the azygos vein. In the superior mediastinum, it ascends onto the left side adjacent to the oesophagus. It finally terminates into one of the subclavian veins or the internal jugular vein.

The vagus nerve on the right side is found lateral to the trachea and posterior medial to the right brachial cephalic vein and superior vena cava. It then passes behind the right main bronchus and continues to the posterior aspect of the right atrium. Here it divides into braches, which form the pulmonary autonomic plexus. The left vagus nerve is found between the left common carotid and subclavian artery and behind the left brachiocephalic vein. It crosses the aortic arch and passes behind the left hilum. Here it divides and forms the pulmonary plexus. The autonomic nervous plexus in the mediastinum is formed from the vagus nerve, thoracic sympathetic chain and the autonomic plexus (cardiac, oesophageal and pulmonary plexus).

The right phrenic nerve descends lateral to the superior vena cava anterior to the pulmonary hilar and then along the pericardium (over the right atrium) before reaching the diaphragm. The left phrenic nerve runs antero-medial to the vagus nerve above the aortic arch and then anterior to the left hilum. It then runs along the pericardium (covering the left ventricle) before supplying the diaphragm.

**Diaphragm**

This is a musculo-fibrous sheet that separates the thorax and abdomen. The diaphragm has an important role in the mechanism of breathing and coughing. It is a convex upper surface and is circumferentially attached to the lower aspect of the thorax with muscle fibres that converge to a central tendon. The diaphragm has three openings within it through which pass the inferior vena cava (at the level of eighth thoracic vertebra, T8), the oesophagus (T10) and the aorta (T12). Its blood supply is from the lower five intercostal arteries, the subcostal artery and phrenic arteries. The venous drainage is from the phrenic nerves, which drain into the inferior vena cava. The diaphragm is supplied by the phrenic nerve, which primarily originates from C4, C5 and C6 cervical nerve root (the course of which is described above).

**Development**

The development of the respiratory system occurs at ~26 days of gestation with proliferation of a diverticulum that originates from the foregut. The larynogotracheal tube and main bronchi are formed first. Over the next 10 weeks, the lower conducting airways develop and finally the acinar structures develop. The alveoli and interstitial tissue is then formed. Alveolar development occurs from 28 weeks gestation and continues during early childhood.

**References**

The appropriateness of the ventilatory \((V'\text{E})\) response to a challenge such as hypoxia or altered metabolic rate depends not on the level of \(V'\text{E}\) achieved but whether the pulmonary gas-exchange and acid-base requirements are achieved: i.e. regulating arterial CO\(_2\) tension \((P_{a,\text{CO}_2})\), pH (pHa) and O\(_2\) tension \((P_{a,\text{O}_2})\) within the relatively narrow range that provides optimal functioning. This regulation involves a cascade of mechanisms: airflow and volume generation, pulmonary O\(_2\) uptake \((V'\text{O}_2)\) and CO\(_2\) output \((V'\text{CO}_2)\), and \(V'\text{E}\) control with its associated respiratory perceptions. Each of these mechanisms can be adversely affected in pulmonary disease, with impaired respiratory-mechanical and gas-exchange function increasing the \(V'\text{E}\) demands of a particular task and, in turn, the costs of meeting these demands in terms of respiratory-muscle work, perfusion and O\(_2\) consumption.

### Ventilatory requirements

Alveolar, and hence arterial, CO\(_2\) and O\(_2\) tension \((P_{A,\text{CO}_2}, P_{A,\text{O}_2}, P_{a,\text{CO}_2}\text{ and } P_{a,\text{O}_2})\) can only be regulated if alveolar ventilation \((V'\text{A})\) increases in an appropriate proportion to \(V'\text{CO}_2\) and \(V'\text{O}_2\), respectively. With respect to CO\(_2\) exchange (Fick's principle):

\[
V'\text{A} = 863 \cdot V'\text{CO}_2/P_{A,\text{CO}_2} \tag{1}
\]

where 863 is the constant that corrects for the different conditions of reporting gas volumes (i.e. standard temperature and pressure, dry, body temperature and pressure, saturated) and the transformation of fractional concentration to partial pressure.

Similarly, for O\(_2\):

\[
V'\text{A} = 863 \cdot V'\text{O}_2/[P_{I*,\text{O}_2} - P_{A,\text{O}_2}] \tag{2}
\]

where \(P_{I,\text{O}_2}\) is the inspired \(P_{\text{O}_2}\), and * is a relatively small correction factor \((= F_{A,N_2}/ F_{I,N_2}\), where \(F_{A,N_2}\) and \(F_{I,N_2}\) are the alveolar and inspired nitrogen fractions, respectively) that takes account of inspired ventilation normally being slightly greater than expired ventilation. This is a consequence of the body’s metabolic processes releasing less CO\(_2\) relative to the O\(_2\) used for a normal western diet, for which the respiratory quotient \((RQ = \text{metabolic CO}\_2 \text{ production}/\text{metabolic O}\_2 \text{ consumption})\) is normally ~0.85.

As \(V'\text{A}\) is common to equations 1 and 2, then:

\[
[863 \cdot V'\text{CO}_2]/P_{A,\text{CO}_2} \leftrightarrow V'\text{A} \rightarrow [863 \cdot V'\text{O}_2]/[P_{I*,\text{O}_2} - P_{A,\text{O}_2}] \tag{3}
\]

Thus, if \(V'\text{CO}_2\) and \(V'\text{O}_2\) are equal (i.e. respiratory exchange ratio \((\text{RER}) = 1\)), both \(P_{A,\text{CO}_2}\) and \(P_{A,\text{O}_2}\) can be regulated. However,
both cannot be regulated if \( V'CO_2 \) and \( V'O_2 \) differ, as is the case when: 1) RQ changes as a result of dietary- or activity-related alterations in the metabolic substrate utilisation profile or 2) there are transient variations in body gas stores (particularly the CO2 stores) that occur as metabolic rate changes. Under such conditions \( V'A \) changes in closer proportion to \( V'CO_2 \) than to \( V'O_2 \), with \( P_{A,CO_2} \) consequently being the more closely regulated variable and \( P_{A,O_2} \) consequently being allowed to change. However, as these \( P_0 \) changes are normally within the range in which the \( O_2 \) dissociation curve is relatively flat, arterial \( O_2 \) content (\( Ca,O_2 \)) will not be affected to any great extent. The regulatory outcome becomes more complex if, for example, significant arterial hypoxaemia develops when \( V'A \) increases out of proportion to \( V'CO_2 \) (hyperventilation) in order to constrain the fall in \( P_{A,O_2} \) or with metabolic acid–base disturbances that evoke respiratory compensatory responses to ameliorate the \( pHa \) change.

However, it is the total \( V'E \) rather than \( V'A \) that is controlled to effect these regulatory functions. Account can be taken of the influence of the physiological dead space volume (\( VD \)) by substituting \( V'E\cdot(1-VD/Vt) \), where \( Vt \) is the tidal volume, for \( V'A \) in equation 1 (where \( VD/Vt \) is the physiological dead space fraction of the breath), and \( P_{A,CO_2} \) being assumed equal to \( P_{A,O_2} \), i.e.

\[
V'E = [863\cdot V'CO_2]/[P_{A,CO_2}\cdot(1-VD/Vt)]
\]

Thus, the \( V'E \) requirement is determined by \( P_{A,CO_2}, V'CO_2, \) and \( VD/Vt \). Furthermore, the influence of metabolic acid–base disturbances can be accommodated by substituting for \( P_{A,CO_2} \) from equation 4 into the Henderson–Hasselbalch equation, i.e.

\[
pHa = \text{pK}' + \log([HCO_3^-]/\alpha\cdot P_{A,CO_2})
\]

where \( \alpha \) is the \( CO_2 \) solubility coefficient which relates \( P_{A,CO_2} \) to \( CO_2 \) content. This yields:

\[
pHa = \text{pK}' + \log([HCO_3^-]/25.6\cdot[V'CO_2]/[V'O_2\cdot(1-VD/Vt)]
\]

\[
\downarrow \quad \downarrow \quad \downarrow
\]

set-point control efficiency

**Respiratory mechanics**

A particular \( V'E \) requirement can, in theory, be accomplished with an infinite combination of \( Vt \) and breathing frequency (\( fR \)). The \( Vt\cdot fR \) combination, in turn, will influence the inspiratory-muscle pressure (\( PMUS \)) needed to effect inspiration:

\[
PMUS = E\cdot V + R\cdot V' + I\cdot V''
\]

where \( V, V' \) and \( V'' \) are volume, air (and pulmonary tissue) flow and acceleration, respectively, and \( E, R \) and \( I \) are the pulmonary elastance, resistance and inertance, respectively. Normally, the inerterelated term does not make a significant contribution, i.e. although the acceleration of the air can be large, its mass is small, and while the mass of the thorax is relatively large, its acceleration is small (c.f. conditions such as obesity where the mass of the thorax can be abnormally increased). Thus, \( PMUS \) typically has a static, or volume-related, component (i.e. with no associated air flow) and a resistive, or flow-related, component.

The static component of \( PMUS \) equals the increment in transpulmonary pressure (\( PTP \)) required to effect the required degree of lung distension under static conditions, i.e.

\[
PTP = P_{ALV} - P_{IP} = V/C
\]

where \( P_{ALV} \) and \( P_{IP} \) are the alveolar and intrapleural pressures, respectively; and \( C \) is lung compliance. \( C \) is determined by the elastic properties of the lung parenchyma and also by the surface-active forces operating at the alveolar air–liquid interface; the latter being offset by the influence of surfactant.

The static \( V-PTP \) relationship (fig. 1, line 2) shows \( C \) to be largely independent of \( V \) over the tidal range; however, \( C \) decreases progressively as total lung capacity (TLC) is approached. A decreased compliance (e.g. restrictive lung disease) requires a greater than normal increase in \( PTP \) to effect a given lung inflation (fig. 1, line 1), while a reduced compliance (e.g. emphysema) requires a smaller \( PTP \) increment (fig. 1, line 3). Also, as forced residual capacity (FRC) and the
associated $P_{IP}$ are determined by the magnitude of the opposing chest wall and lung recoil forces, FRC is smaller and $P_{IP}$ more subatmospheric under conditions of increased recoil (fig. 1, line 1) than when recoil is reduced (fig. 1, line 3).

The resistive or flow-related component of $P_{MUS}$ is the increment in "driving" pressure required to effect air flow, i.e. the difference between $P_{ALV}$ and pressure at the airway opening (atmospheric pressure, $P_{ATM}$):

$$P_{ALV} - P_{ATM} = \Delta P = k_1 \cdot v^2 + k_2 \cdot v^2$$

The major site of this resistance lies in the segmental bronchi and larger-sized small bronchi; because of their very large number, the bronchioles, which individually constitute sites of high resistance because of their very small radius, collectively contribute relatively little to the overall resistance (only $\sim 10$–$20\%$ of the airway resistance being related to airways $<2$ mm in diameter). The term $k_1 \cdot v^2$ reflects the "laminar" component of airflow, with $k_1 = 8\eta / \pi r^4$ where $l$ is airway length, $r$ is airway radius and $\eta$ is gas viscosity. The term $k_2 \cdot v^2$ reflects the "turbulent" component, which imposes a greater demand on pressure generation because of the $v^2$ term. Turbulent flow develops when the "Reynolds" number (Re) exceeds a value of $\sim 2,000$. As $Re = v \cdot 2r \cdot \rho / \eta$, where $v$ is the linear velocity and $\rho$ is gas density, it is readily apparent that turbulent flow predominates when $v$ is high, or at branch points, or across constricted regions. Hence, reducing $\rho$, e.g. by breathing high concentrations of helium instead of nitrogen ("heliox"), makes turbulence less likely.

The thoracic expansion that occurs during inspiration causes $P_{ALV}$ to become negative (i.e. below $P_{ATM}$) and flow to occur, until the end of inspiration when $P_{ALV}$ again equals $P_{ATM}$ (fig. 2a). Thus, the pressure requirements for inspiratory flow and volume generation are reflected in $P_{IP}$: under static conditions, volume changes are simply related to changes in $P_{IP}$ through the static lung compliance relationship (as $P_{ALV}$ is zero) while, during a normal inspiration, the additional muscular force needed to overcome $R$ causes a greater negativity of $P_{IP}$ at any given lung volume. The difference between the $P_{IP}$ change needed to provide $v'$ and that required to distend the lung statically is represented by the blue area in figure 2a, and is consequently greatest when $v'$ is greatest.

The respiratory-muscle work ($W$) performed in producing the inspiration can thus be calculated as: $\Delta V \cdot \Delta P_{IP}$ (fig. 2b), i.e. the sum of the elastic work required to overcome the static lung recoil forces (red area) and the resistive work (blue area). When breathing is stimulated (e.g. in exercise), the greater $P_{ALV}$ required to generate the increased $v'$ amplifies the dynamic component of the $V$–$P$ relationship (fig. 2a, right) and therefore increases $W$. A similar effect is seen in patients with an abnormally increased $R$, in whom a greater $P_{ALV}$ is required to achieve a particular $v'$. Expressing $W$ relative to time yields the power output ($W'$) of the inspiratory muscles which, when related to their $O_2$ consumption ($Q'_O_2$), allows considerations of overall respiratory muscle efficiency. It is only at very high levels of $V'$ (e.g. at peak exercise in highly fit endurance athletes) or when
respiratory impedance is abnormally high (as in pulmonary disease) that $W$, $W'$ and $Q'_{O_2}$ are anything other than insignificant in magnitude; this can lead to respiratory muscle fatigue.

When $V'E$ is low, expiration can be achieved entirely through the recoil pressure ($P_{REC}$) generated in the elastic structures of the lungs during the previous inspiration, i.e. providing the necessary driving pressure by increasing $P_{ALV}$ (fig. 2a, left):

$$P_{TP} = P_{REC} = P_{ALV} - P_{IP} = R \cdot V' \quad (10)$$

Flow at any point in expiration is thus determined by the interplay between static lung recoil, $P_{IP}$ and resistance:

$$V' = P_{REC} + P_{IP}/R \quad (11)$$

Furthermore, the equality for $P_{REC}$ deriving from equations 8 and 9 yields:

$$\frac{V}{C} = R \cdot V'$$

which can be rearranged as:

$$\frac{V'}{V} = \frac{1}{R \cdot C} \quad (12)$$

The term $R \cdot C$ is the “mechanical time constant” (τ) of the respiratory system, and has the unit of time, i.e. (cmH$_2$O·L$^{-1}$·s$^{-1}$)·(L·cmH$_2$O$^{-1}$) = s. Thus, if $R$ or $C$ (or, of course, both) are large, then $\tau$ will be low for a given lung volume. Complete passive emptying (i.e. down to FRC) for a spontaneous expiration requires expiratory duration to be sufficiently long (i.e. effectively four time constants for an exponential process). Considering a normal $\tau$ of $\sim$0.4 s ($R$ and $C$ being $\sim$2 cmH$_2$O·L$^{-1}$·s and 0.2 L·cmH$_2$O$^{-1}$, the driving pressure $P_{IP}$ is relatively low and expiration is completely passive, requiring no active muscle effort:

$$P_{IP} < P_{ALV}$$

When $P_{IP} > P_{ALV}$, the alveoli are deflated below FRC, requiring active muscle effort to inflate the lung.

**Figure 2.** a) Tidal volume ($V_t$), intrapleural pressure ($P_{IP}$) and flow ($V'$) changes for normal resting and exercising breaths. The dashed line on the $P_{IP}$ curve represents pressure needed to produce lung inflation statically. The shaded area is the extra $P_{IP}$ required to generate flow. The stippled area represents static inspiratory work of breathing; the shaded area is the dynamic component. I: inspiration; E: expiration.
respectively), this minimum period is \( \sim 1.6 \) s and translates to a total breath duration (\( t_{\text{tot}} \)) of \( \sim 3 \) s, assuming an “inspiratory duty cycle” (\( t_{\text{I}} / t_{\text{tot}} \), where \( t_{\text{I}} \) is inspiratory duration) of \( \sim 0.4 \). Thus, if \( f_R \) exceeds \( \sim 20 \) min\(^{-1} \), complete emptying requires expiratory flow to be augmented by expiratory muscle action; without this, end-expiratory lung volume will be greater than FRC. Such “dynamic hyperinflation” is a hallmark of the exercising chronic obstructive pulmonary disease (COPD) patient (fig. 3, right), where disease-related increases in \( R \) and/or \( C \) can lower this limiting \( f_R \) quite considerably.

That the maximal volitionally generated expiratory \( \nu' \) is greater at high lung volumes than when lung volume is low (fig. 3) is, of course, implicit in equation 11. That is, \( R \) and \( P_{\text{REC}} \) are each volume-dependent: at high volumes, \( R \) is relatively low reflecting a modest degree of airway distension (whose effect is amplified through the \( R^2 \) term) while \( P_{\text{REC}} \) is relatively high. Indeed, for a given \( \tau \), \( \nu' \) decreases as a linear function of \( V \) (equation 12), accounting for the descending limb of the maximal expiratory flow–volume curve normally being so linear (fig. 3, left).

In COPD, however, the lower maximal \( \nu' \) at TLC, despite the higher absolute lung volume (fig. 1, line 3), is indicative of an increased \( R \) and, for emphysema, decreased \( P_{\text{REC}} \) (fig. 3, right), and thus \( \nu' \) at a particular lung volume is lower than normal. In contrast, for restrictive lung disease, while maximal \( \nu' \) at TLC is low owing to poor dispensability (fig. 1, line 1), \( \nu' \) at a particular lung volume can be even slightly higher than normal owing to an increased \( P_{\text{REC}} \). Furthermore, when there is regional nonuniformity of \( \tau \), as in COPD, for example, this can contribute to the typically “scooped” maximal expiratory \( \nu' \) profile (fig. 3, right).

The effects of \( P_{\text{IP}} \) on expiratory \( \nu' \) are not quite as straightforward, however, as those of \( R \) and \( P_{\text{REC}} \) (equation 12). \( P_{\text{IP}} \) is an index of the effort transmitted from the respiratory muscles to the lungs via the chest wall. During expiration, \( P_{\text{IP}} \) can become positive as a function of the applied expiratory effort, i.e. the chest wall volume decreases faster than the lungs’ intrinsic recoil. This results in a compressive force being applied to the intrapleural space. As \( P_{\text{ALV}} = P_{\text{IP}} + P_{\text{REC}} \) (equation 10), \( P_{\text{ALV}} \) will be more positive than \( P_{\text{IP}} \) by an amount equal to \( P_{\text{REC}} \). Airway pressure (\( P_{\text{AW}} \)) declines from the alveolar value down to zero at the mouth as a result of frictional losses along the airways. At the point at which \( P_{\text{AW}} = P_{\text{IP}} \) (i.e. the transmural pressure across the airway is zero) (fig. 4), an “equal pressure point” (EPP) results.

In normal subjects, the EPP occurs in the large airways (lower trachea or mainstem bronchi), which, despite the tendency to become compressed, are prevented from collapsing by their cartilaginous support. Thus, the EPP becomes the limiting point for expiratory flow generation, dictating the maximum expiratory flow (\( \nu'_{\text{max}} \)):

\[
\nu'_{\text{max}} = \frac{P_{\text{REC}}}{R_{\text{us}}} \tag{13}
\]

where \( R_{\text{us}} \) is the resistance of the “upstream segment” of the airways (between the alveolus and the EPP) (fig. 4). This explains why progressively greater expiratory efforts, although leading to a progressively more positive \( P_{\text{IP}} \), do not lead to a progressively greater \( \nu' \); greater expiratory effort simply compresses the airways more, raising downstream resistance in proportion to the

Figure 3. Inspiratory (downwards) and expiratory (upwards) flow–volume curves at rest, maximal exercise and with maximal volitional effort for a) a normal subject and b) a patient with chronic obstructive pulmonary disease. Reproduced from Kus (1989), with permission from the publisher.
increased effort. \( V' \) therefore becomes maximised at a constant value (at that lung volume), independent of effort.

With loss of lung recoil and/or increases in small airways resistance, however, the EPP migrates upstream. If it encroaches into the small unsupported airways, airways collapse occurs – with, consequently, profound effects on \( V'_{\text{max}} \) (equation 13).

**Pulmonary gas exchange**

The effectiveness of pulmonary O\(_2\) exchange is conventionally judged by the magnitude of the alveolar-arterial O\(_2\) tension difference (\( P_{A\text{-}O_2} \)) where \( P_{A\text{-}O_2} \) is considered the \( P_{A\text{-}O_2} \) of the "ideal lung", which hypothetically exchanges gases ideally. \( P_{A\text{-}O_2} \) thus circumvents the difficulty of providing a single representative value for \( P_{A\text{-}O_2} \) when there are regional variations in gas-exchange efficiency, and can be derived as follows (i.e. by re-arranging and amalgamating equations 1 and 2):

\[
V'CO_2/V'O_2 = \text{RER} = \frac{[V'A-\{P_{A,O_2}-F_{A,N_2}/F_{I,N_2}\}PA_{I,O_2}]}{[V'A-P_{A,CO_2}]].
\]

\[
P_{A,O_2} = P_{I,O_2} - P_{a,CO_2}/R (14)
\]

Impairments of pulmonary gas exchange typically result in arterial hypoxaemia and, in some instances, arterial hypercapnia. Six mechanisms can be identified as independent causes of arterial hypoxaemia: three of these affect \( P_{A,O_2} \) (ambient hypoxia as occurs on ascent to altitude, reduced \( RQ \) and alveolar hypoventilation) and three affect \( P_{A\text{-}a,O_2} \) (diffusion limitation, increased right-to-left shunt and ventilation-perfusion (\( Q' \)) maldistribution (\( V'\text{A}/Q' \)).

**Reduced RQ**

Recalling that \( V'E \) normally operates to regulate \( P_{a,CO_2} \), by responding in a proportional fashion to \( V'E \) when the RQ of the dietary substrate is reduced (i.e. by ingestion of a high-fat diet), the associated reduction in metabolic CO\(_2\) production will require less ventilation to maintain a stable \( P_{a,CO_2} \) (equation 3). This leads to hypoventilation relative to \( O_2 \), i.e. \( V'E \) is normal relative to \( V'CO_2 \) but low relative to \( V'O_2 \). Thus, \( P_{A,O_2} \) and \( P_{A,O_2} \) will fall.

**Alveolar hypoventilation**

Alveolar hypoventilation can occur in diseases or with drugs that affect the medullary respiratory-integrating centres or respiratory neuromuscular function and therefore reduce the level of respiratory motor output. It may also be seen in severe COPD, consequent to the abnormally increased small-airways resistance and high resistive work of breathing. Arterial hypoxaemia and hypercapnia result (equations 2 and 1, respectively), with the fall of \( P_{A,O_2} \), being related to the rise of \( P_{a,CO_2} \) by \( R \) (equation 14). Thus, when \( R=1 \), the increase in \( P_{a,CO_2} \) and the fall in \( P_{A,O_2} \), which result from a reduction in \( V'A \), are numerically equal, as notionally are the corresponding changes in \( P_{a,CO_2} \) and \( P_{A,O_2} \). However, as \( R \) is normally ~0.8 at rest, for each 10 mmHg decrease in \( P_{A,O_2} \), that results from a fall of \( V'A \), \( P_{a,CO_2} \) will increase by ~8 mmHg. It should be noted...
that the hypoxaemia can be offset by administration of supplementary O\textsubscript{2}.

**Diffusion impairment**  Fick’s law indicates that impairments in the pulmonary diffusive flux of O\textsubscript{2} (or CO\textsubscript{2}) can result from 1) a reduction in the “driving pressure” (for O\textsubscript{2}, \(\Delta P_{O_2}\)); 2) a reduction in the available surface area for diffusion (A); and/or 3) an increased path length for diffusion (l):

\[
V'_{O_2} = A/l \cdot d \cdot \Delta P_{O_2} \quad (15)
\]

where \(d\) is the diffusion coefficient for O\textsubscript{2} which is inversely proportional to gas molecular weight (MW) in the gas phase (\(d = 1/MW\)), while directly proportional also to gas solubility (s) in the blood phase (\(d = s/\sqrt{MW}\)). Hence, as O\textsubscript{2} is lighter than CO\textsubscript{2}, it diffuses 18% more rapidly in the gas phase for the same partial pressure gradient. In the blood phase, however, CO\textsubscript{2} is 20 times more diffusible than O\textsubscript{2}, owing to its greater solubility.

During inspiration, O\textsubscript{2} is transported down the tracheobronchial tree by convective or bulk flow. At the level of the alveolar ducts, owing to the large overall cross-sectional area of the airways and the resulting reduction in the linear velocity of the inspired gas, movement to the alveolar–capillary membrane relies on diffusion. Diffusion through the alveolar gas space does not normally limit gas transfer into pulmonary capillary blood. Thus, as the average alveolar diameter is normally only \(\sim 100 \, \mu\text{m}\), diffusion equilibrium (i.e., \(\Delta P_{O_2} = 0\)) throughout the alveolus is attained rapidly: this is normally 80% complete within \(\sim 0.002\) s, which is several orders of magnitude less than the time for which the pulmonary capillary blood is exposed to the alveolar gas-exchange surface (i.e., the pulmonary–capillary transit time (\(t_{TR}\)), which is \(\sim 0.8\) s at rest). In conditions such as emphysema, air sac enlargement increases intra-alveolar diffusion distances, predisposing to less efficient O\textsubscript{2} and CO\textsubscript{2} exchange.

More commonly, however, diffusion limitation reflects exchange impairments between alveolar gas and pulmonary capillary blood. The rate of diffusive uptake of O\textsubscript{2} into blood is given by:

\[
V'_{O_2} = A/l \cdot d \cdot \Delta P_{O_2} \quad (15)
\]

where A is the alveolar surface area in contact with perfused pulmonary capillaries; l is the diffusion pathlength which extends from the alveolar surface fluid lining to the erythrocyte interior to include the alveolar epithelium, interstitial space, capillary endothelial cells, plasma, the erythrocyte cell membrane and, for a reactive gas species such as O\textsubscript{2}, its chemical combination with haemoglobin (Hb); and \(P_{cO_2}\) is the mean pulmonary capillary \(P_{O_2}\). It is conventional to combine A, l and d into a single term, the pulmonary diffusing capacity of the lung for O\textsubscript{2} (\(D_L, O_2\)) or transfer factor:

\[
V'_{O_2} = D_L, O_2 \cdot \Delta P_{O_2} \quad (15)
\]

\(D_L, O_2\) can be usefully subdivided into its functional components, i.e., the “membrane” component (\(D_M, O_2\)) and that due to chemical combination:

\[
1/ D_L, O_2 = 1/ D_M, O_2 + 1/ \theta \cdot V_c \quad (17)
\]

where \(\theta\) is the reaction rate coefficient for chemical combination of O\textsubscript{2} with haemoglobin (Hb), and \(V_c\) is the pulmonary capillary blood volume. Because of technical limitations associated with estimating \(P_{cO_2}\), it is conventional to determine diffusing capacity of the lung and membrane in terms of carbon monoxide (\(D_L, CO\), \(D_M, CO\)) as the high affinity of Hb for CO ensures that the pulmonary capillary CO tension (\(P_{CO}\)) is effectively zero (see Chapter 3, Gas transfer).

The initial driving pressure across the alveolar–capillary membrane (i.e., at the entrance to the capillary bed) is given by the difference between \(P_{A, O_2}\) (normally \(\sim 100\) mmHg) and the mixed venous \(P_{O_2}\) (\(P_{vO_2}\), normally \(\sim 40\) mmHg at rest, although the latter decreases as in exercise). The rate at which O\textsubscript{2} is taken up into the blood decreases from this point as blood traverses the capillary, reflecting the increasing \(P_{cO_2}\) (and consequent decrease in \(P_{A, O_2}\)) which in turn reduces the instantaneous \(\Delta P_{O_2}\). Diffusion
equilibrium is normally reached within 0.25–0.3 s (i.e. well before the blood reaches the end of the capillary), such that pulmonary end-capillary $P_{O_2}$ ($P'_{O_2}$) $=$ $P_{A,O_2}$. This large safety margin becomes compromised, however, when $TR$ is shortened to a degree that there is insufficient time for the attainment of diffusion equilibrium, i.e. $P'_{O_2}$ $<$ $P_{A,O_2}$. As $TR$ $=$ $V/Q'$ (where $Q'$ is pulmonary blood flow), an increase in $Q'$ (e.g. high-intensity exercise) predisposes to lack of diffusion equilibrium resulting in arterial hypoxaemia. However, the decrease in $TR$ with increases in $Q'$ is less than expected because $Q_c$ actually increases with $Q'$, consequent to distension of already-perfused capillaries and recruitment of previously unperfused capillaries; this serves to protect against diffusion disequilibrium.

A lowered $P_{A,O_2}$, as occurs with ascent to high altitude, or when a subject breathes an hypoxic inspirate or with hypoventilation, will slow the $P_{C,O_2}$ rise time. This is because the initial driving pressure ($P_{A,O_2}$ $-$ $P_{C,O_2}$) is smaller, as the operating slope of the $O_2$ dissociation curve ($\beta$) is steeper, with the arterio-venous $O_2$ content difference expressing a smaller arterio-venous $P_{O_2}$ difference.

A useful expression relating to the interplay of factors which dictate whether or not diffusion equilibrium will actually be attained (i.e. whether $P'_{O_2}$ $=$ $P_{A,O_2}$) is:

$$(P_{A,O_2} - P_{C,O_2}) = (P_{A,O_2} - P_{C,O_2}) \cdot e^{DLO_2/2Q' - \beta}$$

(18)

The term $DLO_2/Q' \cdot \beta$ has been termed the “equilibrium coefficient” by Piper and Scheid (1980) and the “diffusive-perfuse conductance” ratio by West and Wagner (1998). Thus, diffusion equilibrium is less likely to be attained if $DLO_2$ is low, and $Q'$ and $\beta$ are high. For example, an increased path length (e.g. alveolar proteinosis, pulmonary oedema) and/or a reduced surface area for exchange (e.g. pulmonary embolism, restrictive lung disease) slow the diffusive flux of $O_2$ because of their effects on $DLO_2$. With very high levels of $Q'$ (e.g. highly fit endurance athletes exercising at or close to maximum) or very high linear velocities (e.g. pulmonary embolism, where there are fewer participating capillaries), the reduction in $TR$ can lead to a widening of the $PA-aO_2$ and arterial hypoxaemia. Supplemental $O_2$ can, through its effects on $PA-aO_2$ and therefore driving pressure, speed the increase of $P_{T,O_2}$ and thus ameliorate the degree of gas-exchange impairment.

Even though severe degrees of arterial hypoxaemia can result from diffusion impairment, $CO_2$ retention is rarely a problem. This is because any increase in $P_{A,CO_2}$ that might occur tends to be corrected by ventilatory control mechanisms, which are considered to be exquisitely sensitive to $CO_2$ (i.e. central and carotid body chemoreflexes); in contrast, hypoxic ventilatory stimulation only becomes appreciable when $P_{A,O_2}$ falls below $\sim$ 60 mmHg (see Chapter 3, Control of ventilation). Hence, moderate diffusion impairment is accompanied by a decreased $P_{A,O_2}$, a widened $PA-aO_2$ and a relatively normal $P_{A,CO_2}$; more severe impairment which leads to hypoxic ventilatory stimulation will evidence more marked arterial hypoxaemia, greater widening of $PA-aO_2$ and a low $P_{A,CO_2}$.

**Right-to-left shunt** A right-to-left shunt (Q’s) occurs when venous blood by-passes the pulmonary capillary circulation, thus providing a degree of venous admixture with blood from the exchanging alveolar units. It normally reflects venous drainage from the larger airways (which enters the pulmonary veins) and from coronary venous blood (which enters the left ventricles via the thebesian veins). This represents only a small percentage of the cardiac output (Q’) and therefore amounts to a reduction in $PA,O_2$ of only a few mmHg below $P_{C,O_2}$. However, Q’ $/Q'$ can be markedly increased in patients with congenital heart disease (e.g. atrial or ventricular septal defects; pulmonary arteriovenous fistulae), leading to significant arterial hypoxaemia and widening of the $PA-aO_2$.

The Q’ $/Q'$ relationship derives from the recognition that the rate of $O_2$ delivery into the systemic arterial circulation can be viewed as being made up of a homogeneous “ideal”
pulmonary capillary component and a “pure” shunt component. Reverting again to the Fick
principle, but now for the “blood” side, and using the simple equality \( Q’ = Q’c + Q’s \):

\[ Q’ \cdot C_{a,O2} = Q’c \cdot C_{c,O2} + Q’s \cdot C_{s,O2} \]

which rearranges to yield:

\[ Q’s/Q’ = (C_c \cdot O_2 - C_{a,O2})/(C_c \cdot O_2 - C_{s,O2}) \] (19)

where \( C_{s,O2} \) and \( C_c \cdot O_2 \) are mixed-venous and pulmonary end-capillary \( O_2 \) content, respectively. \( C_{a,O2} \) and \( C_{s,O2} \) can be measured directly from blood samples, while \( C_c \cdot O_2 \) is derived through the standard \( O_2 \) dissociation curve, assuming \( P_c \cdot O_2 = P_{a, O2} \) (equation 14). It should be noted that this equation also assumes that all the shunted blood is of mixed-venous composition, which may not necessarily be the case for bronchial venous blood. This estimate of \( Q’s/Q’ \) thus provides an overestimate of the true shunt, as it incorporates a fraction of the perfusion draining from units having poorly functional capillaries (with low \( V’/A’Q’ \) values), i.e. creating a “shunt-like” effect.

A right-to-left shunt must therefore result in arterial hypoxaemia, i.e. even a small contribution from nonarterialised blood will depress the resulting \( C_{a,O2} \), owing to the influence of the nonlinear \( O_2 \) dissociation curve. The severity of the hypoxaemia will depend both on \( Q’s/Q’ \) and \( C_{s,O2} \), being more marked when the former is larger and the latter is lower. A hallmark feature of a pure right-to-left shunt is that the response of \( P_{a,O2} \) to administration of 100% \( O_2 \) is appreciably less than expected. This is because the shunt flow cannot “see” the elevated \( P_{a, O2} \) in the exchanging alveoli, and also that further increases in \( P_{a,O2} \) will have little effect on the \( C_{c,O2} \), because the blood is already essentially fully saturated; it is only the dissolved component of the \( O_2 \) content that can be increased, and this will be relatively small because of the low solubility of \( O_2 \) in plasma.

A right-to-left shunt also has the potential to cause \( CO_2 \) retention, but this is rarely observed owing to the normally small venous-to-arterial \( CO_2 \) tension \( (P_{CO_2}) \) difference (~6 mmHg at rest; c.f. ~60 mmHg for \( O_2 \)) and also (see above) the mechanisms of ventilatory control can normally restore an increased \( P_{a, CO_2} \) back to normal. Again, however, should \( P_{a, CO_2} \) fall sufficiently to cause hypoxic stimulation of the carotid chemoreceptors, then \( P_{a, CO_2} \) will fall (see Chapter 3, Control of ventilation); but, without this, \( P_{a, CO_2} \) will rise. Thus, a moderate right-to-left shunt leads to a reduced \( P_{a,O2} \), a widened \( P_{a-3,O2} \), but a relatively normal \( P_{a, CO_2} \). Severe right-to-left shunts cause a markedly reduced \( P_{a,O2} \) and a markedly widened \( P_{a-3,O2} \), with the possibility of a lowered \( P_{a, CO_2} \).

\( V’/A’Q’ \) maldistribution Although overall \( V’/A’ \) may be approximately equal to overall \( Q’ \) in the lung, there may nonetheless be regions with high, normal and low \( V’/A’Q’ \) ratios. This has important implications for regional alveolar gas and pulmonary end-capillary blood composition, and therefore for overall arterial blood-gas status. That is, gas and blood from low \( V’/A’Q’ \) regions will reflect hypoventilation (i.e. low \( P_D \), high \( P_{CO_2} \)) and, in the extreme, alveolar shunt (\( V’/A’Q’ = 0 \)) (see above); gas and blood from normal \( V’/A’Q’ \) regions will have a normal \( P_D \), and \( P_{CO_2} \); and gas and blood from high \( V’/A’Q’ \) regions will reflect hyperventilation (i.e. high \( P_D \), low \( P_{CO_2} \)) with alveolar dead space in the extreme (\( V’/A’Q’ = \infty \)).

An analogous formulation to that for estimation of \( Q’s/Q’ \) can be applied to the estimation of \( V_D/V_T \) (recalling that \( V_D \) reflects the sum of the anatomical and alveolar dead spaces). That is, the assumption is made that the volume of \( CO_2 \) cleared in exhalation originates solely from a homogeneous exchanging alveolar compartment (Bohr technique):

\[ V_D \cdot F_E,CO_2 = V_A \cdot F_A,CO_2 \]

where \( F_E,CO_2 \) is the mixed expired \( CO_2 \) fraction and \( V_A \) is the volume of exchanging alveoli. Rearranging and substitution yields:

\[ V_D/V_T = (P_{a, CO_2} \cdot F_E,CO_2)/(P_{a, CO_2}) \] (20)
(The shift from $P_{A,CO_2}$ to $P_{a,CO_2}$ is attributable to Enghoff.)

Even in the normal lung, there is evidence of mild $V_A/Q$ maldistribution. Owing to the influence of gravity, $Q$ is distributed preferentially to the dependent regions of the lung (i.e., towards the base in the upright posture). A similar, gravitationally induced effect is also seen for $V_A$, though it is less striking. Thus, the alveoli in the dependent regions of the lung adopt a smaller volume, with a greater hydrostatic pressure in the alveolar interstitium. They are therefore constrained to operate over the steeper, lower portion of the lung compliance curve, in contrast to the larger apical units. Thus, the smaller basal units undergo a greater volume increase for a given increase of $P_{TP}$ during inspiration, and are therefore better ventilated than are the apical units. Taking these effects together, the apical units have a relatively high $V_A/Q'$ while the basal units have a lower $V_A/Q'$. Naturally, the degree of $V_A/Q'$ maldistribution is considerably more marked in many pulmonary disease states (e.g., COPD, diffuse interstitial fibrosis, pulmonary vascular occlusive disease), and its topographical location is not predictable.

In the presence of $V_A/Q'$ maldistribution, the overall (or mean) $P_{A,O_2}$ and $P_{A,CO_2}$ will result from an averaging of the respective gas concentrations from each individual gas "stream", in proportion to the local $V_A$. Likewise, the overall (or mean) $P_{a,O_2}$ and $P_{a,CO_2}$ will result from a flow-weighted averaging of the respective gas contents from each individual blood "stream". However, it is important to recognise in this regard that account has also to be taken of the shape of the $O_2$ and $CO_2$ dissociation curves in order to derive these $P_{a,O_2}$ and $P_{a,CO_2}$ values (fig. 5).

Owing to the sigmoid shape of the $O_2$ dissociation curve, low $V_A/Q'$ regions lead to low $P_{O_2}$ and low $O_2$ content in pulmonary end-capillary blood; in contrast, while high $V_A/Q'$ regions lead to a high $P_{C',O_2}$, $C_c'O_2$ is only slightly increased above normal value because the $O_2$ dissociation curve is relatively flat in this range (fig. 5). Mixing blood from low $V_A/Q'$ regions with blood from high $V_A/Q'$ regions will therefore result in an average $P_{A,O_2}$ that is "weighted" towards low $V_A/Q'$ blood values (fig. 5). The $P_{A,O_2}$ will also depend on the volumes of blood from each "region" contributing to the mixed arterial blood. Thus, the high $V_A/Q'$
regions (even if Hb is completely saturated) are unable to "compensate" for the low $V'\text{A} \text{Q}'$ regions, as their perfusion is usually less. Consequently, even though the overall $V'\text{A} \text{Q}'$ may be normal, $V'\text{A} \text{Q}'$ maldistribution results in arterial hypoxaemia, with mean $P_{A,O2}$ being lower than the actual mean $P_{A,O2}$ or its "ideal" representation; i.e. $P_{A-a,O2}$ is widened.

In contrast, the $CO_2$ dissociation curve is essentially linear in the physiological range (fig. 5). This therefore allows the hyperventilatory effects of the high $V'\text{A} \text{Q}'$ regions to better counterbalance the hypoventilatory effects of the low $V'\text{A} \text{Q}'$ regions on the resulting mean $P_{A,CO2}$ (fig. 5). It should be noted, however, that the high $V'\text{A} \text{Q}'$ regions exert a proportionally greater influence on mean $P_{A,CO2}$ than do the low $V'\text{A} \text{Q}'$ regions. Hence, $P_{A,CO2} < P_{a,CO2}$.

The pattern of arterial blood and alveolar gas tensions in $V'\text{A} \text{Q}'$ maldistribution is such that with mild or moderate maldistribution, $P_{A,O2}$ is low, $P_{A-a,O2}$ is widened, with $P_{A,CO2}$ being normal or low depending on the degree of ventilatory stimulation consequent to the hypoxaemia. In severe $V'\text{A} \text{Q}'$ impairment associated with severe airways obstruction, hyperventilation can ensue owing to the increased work of breathing, and therefore cause an increased $P_{A,CO2}$. This, of course, reduces $P_{A,O2}$ even more.

References

Each day, 10,000–15,000 L of air is inhaled by the respiratory system. This air contains micro-organisms and pollutant gases and particles. It is conceivable therefore that adequate and efficient immunological and defence mechanisms exist inside the respiratory system to avoid damage to its structure, and to limit the number, extent and severity of upper and lower respiratory tract (URT and LRT) infections.

The first line of defence against pathogens is represented by the epithelial barrier of the airways. Additional protection comes from polypeptide mediators of the innate, non-antibody-mediated host defence and by professional phagocytes. Once the innate host defence system is activated, also by the cytokine and chemokine pathways, acquired antibody-mediated immune responses and subsequent tissue repair and remodelling following infection are orchestrated by immunocompetent cells and mediators.

Anatomical barriers

The density of microbes is greater in the URT than in the LRT. In fact, it is usually considered that only a small number of bacteria are present in the LRT of healthy individuals. This process of exclusion of bacteria is also due to mechanical barriers and reflex mechanisms. The nose itself can be considered a firstline barrier. Its vibrissae, present on the vestibular region of the nasal cavity, are able to filter the largest particles contained in inhaled air. Nasal mucosa is a type of respiratory mucosa able to trap other smaller particles by means of its mucus layer. Nasal cilia are able to transport the mucus toward the oropharynx to be swallowed. LRT airways represent a system with a physical barrier that is difficult to overcome. Dichotomous branching and angulation of airways favour the impact of inhaled particles on to the bronchial mucosa surface. At points of impact, bronchial-associated lymphoid tissue (BALT) is able to interact with inhaled airborne microbes and particles, and to start clearance processes via phagocytes and immune reactions by immunocompetent cells.

Reflex mechanisms

A number of reflex mechanisms may help the defence of the respiratory tract. They are made possible by the presence of irritant and stretching receptors on the mucosa of the airways of the URT and of the larger LRT. Sneezing is a complex reflex initiated by the irritant receptors in the nose, usually triggered by inhaled particles, followed by itching,
mucus secretion and ultimately leading to a forceful and sudden expiration through the nose, preceded by a deep and fast inspiration, able to eliminate the potentially harmful inhaled particles. In the tracheobronchial tree, the cough reflex plays a similar role in eliminating foreign inhaled particles (see the article on Cough and sputum). Dyspnoea can also be considered, at least under certain circumstances, to be a defence mechanism, as it can result from both hypersecretion of mucus and/or bronchospasm. By reducing the airway calibre, both are able to impair the ability of inhaled harmful particles to reach the LRT.

**Mucociliary clearance and fluid homeostasis**

The constant mechanical clearance of mucus from the airways is considered a primary airway defence mechanism. The airway epithelial surface is able to act through ciliary function and mucus secretion with proper salt/water components in order to maintain the mucociliary clearance with a mucus “escalator” from the lower airways to the top. With a mucus layer at the top containing different types of mucins and a largely aqueous layer at the bottom, the airway secretions are, under normal conditions, able to entrap the vast majority of inhaled foreign particles and microbes on the mucus layer and to transport the mucus up to the larger airways to be swallowed or eliminated by coughing. More recent studies have emphasised the role of a “chemical shield” from inhaled bacteria. This view underlines the importance of the production and secretion into the airway lumen by the airway epithelia of two components: salt-sensitive defensins (see below) and low-salt liquid able to activate defensins.

**Innate defence molecules**

The epithelial lining fluid in the airways and in the lung contains myriad molecules, peptides and proteins exerting innate antimicrobial activities, not only against bacteria and viruses but also, in some cases, against fungi and parasites. As a whole, although these innate antimicrobial molecules have many differences depending on the site and cell types producing them, secretory stimuli, and direct and indirect activities (table 1), they provide an evolutionarily highly conserved and powerful screen against infections in the naive host. They also trigger more specific and targeted immune reactions taking place in the airways and alveolar structures. In addition, the same molecules have a role as immune-modulators, and as antioxidants and antiproteases. Not surprisingly, attempts have been made to use some of these “natural antibiotics” for therapeutic purposes.

**Professional phagocytes**

Microbial pathogens activate pattern recognition cell receptors (e.g. toll-like receptors, scavenger receptors, etc.) on phagocytes, namely macrophages and neutrophils, and also epithelial cells, mast cells, eosinophils and natural killer cells. This is followed by the release of several mediators and factors with effector functions and inflammatory cascades, such as the complementary acute phase reactant proteins, oxidative and nitrosative stress molecules, prostaglandins, interferons, cytokines and chemokines. Macrophages are the resident respiratory phagocytes. Although they are present throughout the airways and interstitium, their major roles are played in the alveolar spaces, as alveolar macrophages (AMs). In normal people, the vast majority of cells recovered through bronchoalveolar lavage (BAL) are AMs. These cells initiate and orchestrate the immune reactions against pathogens and chemicals inhaled by the host (e.g. mineral particles). In a hypothetical model of infection by a bacterial species, a pathogen that has reached the alveolar space, eluding URT and LRT first-line defences, represents a risk for the host as its replication and associated alveolar inflammation may damage respiratory structures. This invader microorganism will ultimately be enmeshed with the epithelial lining fluid and thus be coated with opsonins. The latter can be either nonimmune (see previous paragraph) or
immune, i.e. specific immunoglobulins (Ig) originated by previous immunisation of the host against the pathogen. Opsonins facilitate AM phagocytosis and subsequent bacterial clearance by the intracellular killing systems of AMs. The size of the bacterial inoculum, their virulence and resistance and possibly deficits in the local immune mechanisms of the host may alternatively cause the failure, at least in a first round, of host defences. This will cause recruitment of additional phagocytes, as neutrophils, at sites of infection and sustain an immune and inflammatory reaction.

**Acquired immune reactions with Ig, cytokine and chemokine production**

Lymphoid tissue is present in the respiratory tract in different forms: tonsils and adenoids in the URT, lymph nodes in the mediastinum and hila, submucosal aggregates in branching points of the airways (BALT) and immunocompetent cells free on the airways and alveolar surface. BALT is also considered to be part of a lymphoid network common to other types of mucosa. In this model, an immunisation can occur at a distant site (e.g. gastrointestinal mucosa) and, by the recirculation of lymphocytes, protection can also be provided to the respiratory system. Acquired immune reactions also start in the lung, with the interaction between antigens and antigen-presenting cells (APC). In the lung, at least two types of APC exist: macrophages and dendritic cells. Dendritic cells are present in the bronchi, representing roughly 1% of epithelial cells, in the alveolar septa and in the interstitium. Together with a phagocytic function, they share with AMs the ability to process microbial proteins into small peptide fragments that are then transported on the cell surface together with major histocompatibility complex molecules. The complex between the major histocompatibility complex and antigenic epitopes is then presented to T-lymphocytes. Antigen
presentation is made through the T-cell receptor on the T-lymphocyte surface.

The antigen presentation initiates the production of immuno-enhancing cytokines and chemokines. Apart from the interleukins (ILs) and other mediators associated with the T-helper type I or II immune reactions, IL-17 is a pro-inflammatory cytokine mainly produced by T-lymphocytes with an important role in induction of the neutrophil-mediated protective immune response against bacteria or fungal pathogens. IL-17 seems to be an example of the crossroads between different host defence mechanisms, as it regulates cell-mediated immunity and induction of antimicrobial peptides, such as defensins.

The process of specific immune reaction described above also promotes adaptive B-lymphocyte proliferation and specific Ig production. The relative proportions of different Ig classes in the URT and LRT differ, and also differ compared with the blood. In the URT, IgA represents the vast majority of Igs, the latter as a whole being roughly 10% of the total proteins in airway secretions. Airway IgA is predominantly polymeric. Secretory IgA comprises two IgA monomers held together by a joining chain and by another glycoprotein, the secretory component produced by serous and epithelial cells. In contrast with the airways, IgG is predominant in the lung, as detected by BAL, representing roughly 5% of the total protein content in BAL fluid from normal individuals. IgM is present only in trace amounts, due to its large size.

Conclusions

The complex, integrated host defence system described and depicted in table 2 represents a superb model of how the human body is able to efficiently interact with the external environment in order to preserve its structure and function.

Conversely, impairment and/or dysfunction of each of the different and variously acting components of this system represents the pathogenetic basis for the development of many respiratory disorders. As an example, primary ciliary dyskinesia results in recurrent airway infections; cystic fibrosis is associated with dysfunction of mucociliary clearance and fluid homeostasis; while in chronic colonisation and/or infection of the airways and in inflammatory airway disorders, many different mechanisms undergo changes, enhancement or impairment.

To summarise, the respiratory system is exposed to a variety of microbiological, physical and chemical insults through inhaled air. Innate intrinsic and adaptive acquired host and immune defences cooperate in lowering the risk of being damaged for the respiratory structures in an integrated host defence system. In diseased states, one or

<table>
<thead>
<tr>
<th>Intrinsic and innate host defences</th>
<th>Adaptive and acquired immune defences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomical barriers and defence reflexes</td>
<td>S-IgA and other immune opsonins and antigen recognition and presentation</td>
</tr>
<tr>
<td>Mucociliary clearance and fluid homeostasis</td>
<td>Cellular immunity and T- and B-lymphocytes</td>
</tr>
<tr>
<td>Innate defence molecules and nonimmune opsonins</td>
<td>Cytokine/chemokine production and networking</td>
</tr>
<tr>
<td>Professional phagocytes</td>
<td>Chemotactic influx of inflammatory, immunoeffector cells</td>
</tr>
</tbody>
</table>

S-IgA: secretory-IgA.
more of these complex mechanisms can be impaired and/or dysfunctional.

References

CHAPTER 2:

SIGNS AND SYMPTOMS

COUGH AND SPUTUM
A.H. Morice

DYSPNOEA
G. Scano and P. Laveneziana

CHEST PAIN
M. Hind

PHYSICAL EXAMINATION IN RESPIRATORY MEDICINE
M.R. Partridge
Cough is a vital protective mechanism defending the airways from inhalation and aspiration. Patients with a defective cough reflex, such as those with stroke or Parkinson’s disease, have an increase in mortality and morbidity caused by the increased propensity for aspiration. However, in lung disease, cough is often not helpful. Thus, in the commonest form of cough, that due to upper respiratory tract infection, coughing serves no useful purpose from the sufferer’s point of view, but is useful for the virus aiding its transmission to the next victim. In chronic cough, the frequency and severity of coughing bouts may cause serious disruption to the patient’s life. Quality-of-life instruments have indicated that patients with chronic cough may have a similar decrement to that seen with conditions such as cancer and chronic obstructive pulmonary disease. Cough may have significant comorbidity. 50% of the females attending cough clinics are incontinent and cough syncope is thought to be responsible for a number of driving fatalities.

Acute cough

Acute cough due to one of the myriad upper respiratory tract viruses places an enormous demand on the healthcare community. It is the commonest new presentation to primary care, accounting for 50% of consultations. In temperate regions there is a marked seasonal variation with autumn and winter epidemics. Viral transmission requires person-to-person contact, either through airborne droplet infection or the manual passage of secretions. Superimposed on this seasonal pattern are peaks caused by socialisation, e.g. return to school for the autumn term and Christmas family gatherings. Apart from general health measures, such as hand washing and avoidance of contact, there is no specific treatment for upper respiratory tract infection-induced cough. The demonstrable effect of the many cough remedies is likely to be due to a physicochemical (demulcent) effect rather than through a specific pharmacological action of any particular agent.

Chronic cough

Chronic cough is one of the commonest presentations to the respiratory physician. A survey in Yorkshire, UK, indicated that 12% of the normal population complain of a chronic cough and 7% of these thought it interfered with activities of daily living. Many reports from specialist cough clinics point to a particular syndrome in patients with chronic cough. The average patient is middle-aged and female. The cough appears to have no pattern to it but a careful history will often reveal many features in common with other patients’ presentation. It has been traditional to divide this group of patients who have chronic cough without radiographic abnormalities and no obvious other lung disease into a triad of diagnoses, namely asthmatic cough, post-nasal drip syndrome

Key points

- Cough is characterised by irritant receptor hypersensitivity.
- Nonacid reflux into the airways frequently precipitates cough.
- Clinical history followed by therapeutic trials is the management strategy of choice.
and reflux cough (table 1). These subdivisions have recently been called into question. For example, asthmatic cough is unlike classic atopic asthma in that it is of late onset without obvious precipitants and often without evidence of bronchoconstriction. In the form known as eosinophilic bronchitis there is even an absence of bronchial hyperreactivity. Similar caveats apply to the post-nasal drip syndrome and reflux cough, which does not conform to the criteria for heartburn-related gastro-oesophageal reflux disease. Because of the commonality of the clinical history (see table 2), it has been suggested that there is a single unifying diagnosis in chronic cough of the cough hypersensitivity syndrome with the other diagnoses representing different phenotypes of the condition. The risk factors for chronic cough suggest that nonacid reflux may be an important precipitant (see table 3).

Virtually all patients presenting with a chronic cough complain of increased sensitivity to a wide range of environmental stimuli. This hypersensitivity can be objectively demonstrated in the laboratory using cough

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Mean age yrs</th>
<th>Patients n (female n)</th>
<th>Diagnosis (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRWIN 1981</td>
<td>50.3</td>
<td>49 (27)</td>
<td>Asthma syndrome 25</td>
</tr>
<tr>
<td>Poe 1982</td>
<td>-</td>
<td>109 (68)</td>
<td>GOR 10</td>
</tr>
<tr>
<td>Poe 1989</td>
<td>44.8</td>
<td>139 (84)</td>
<td>Rhinitis 29</td>
</tr>
<tr>
<td>IRWIN 1990</td>
<td>51</td>
<td>102 (59)</td>
<td></td>
</tr>
<tr>
<td>Hoffstein 1994</td>
<td>47</td>
<td>228 (139)</td>
<td>Asthma syndrome 25</td>
</tr>
<tr>
<td>O’Connell 1994</td>
<td>49</td>
<td>87 (63)</td>
<td>GOR 24</td>
</tr>
<tr>
<td>Smyrnios 1995</td>
<td>58</td>
<td>71 (32)</td>
<td>Rhinitis 26</td>
</tr>
<tr>
<td>McEVOY 1996</td>
<td>53.1</td>
<td>88 (64)</td>
<td>Asthma syndrome 25</td>
</tr>
<tr>
<td>Marchesani 1998</td>
<td>51</td>
<td>92 (72)</td>
<td>GOR 24</td>
</tr>
<tr>
<td>McGarvey 1998</td>
<td>47.5</td>
<td>43 (29)</td>
<td>Rhinitis 38</td>
</tr>
<tr>
<td>Palombini 1999</td>
<td>57</td>
<td>78 (51)</td>
<td>Asthma syndrome 59</td>
</tr>
<tr>
<td>Brightling 1999</td>
<td>-</td>
<td>91 (-)</td>
<td>GOR 31</td>
</tr>
</tbody>
</table>

The typical patient is a middle-aged female. These diagnoses are now thought to represent phenotypes of the cough hypersensitivity syndrome. GOR: gastro-oesophageal reflux. Studies can be found in Morice et al. (2004).

Table 2. Areas of enquiry in chronic cough

<table>
<thead>
<tr>
<th>Hoarseness or a problem with your voice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearing your throat</td>
</tr>
<tr>
<td>The feeling of something dripping down the back of your nose or throat</td>
</tr>
<tr>
<td>Retching or vomiting when you cough</td>
</tr>
<tr>
<td>Cough on first lying down or bending over</td>
</tr>
<tr>
<td>Chest tightness or wheeze when coughing</td>
</tr>
<tr>
<td>Heartburn, indigestion, stomach acid coming up or do you take medications for this?</td>
</tr>
<tr>
<td>A tickle in your throat, or a lump in your throat</td>
</tr>
<tr>
<td>Cough with eating (during or soon after meals)</td>
</tr>
<tr>
<td>Cough with certain foods</td>
</tr>
<tr>
<td>Cough when you get out of bed in the morning</td>
</tr>
<tr>
<td>Cough brought on by singing or speaking (for example, on the telephone)</td>
</tr>
<tr>
<td>Coughing more when awake rather than asleep</td>
</tr>
<tr>
<td>A strange taste in your mouth</td>
</tr>
</tbody>
</table>

Responses may either lead to further questioning or be scored 0-5 and used as a diagnostic tool to demonstrate the presence of cough hypersensitivity syndrome. A questionnaire version in various languages is available at www.iscc.info
challenge. Thus patients cough with ethanol inhalation, whereas normal subjects do not. There is a wide variation in cough reflex sensitivity in normal subjects, with females being more sensitive than males. Sensitivity is accentuated in cough patients. Inhalation of capsaicin, the pungent extract of peppers, is typically used to demonstrate cough reflex responsiveness (fig. 1). Capsaicin works by stimulating one of a family of nociceptors of the transient receptor potential group (fig. 2). The capsaicin sensitive “hot” receptor (TRPV1) is up-regulated in patients with cough. This is due to pro-inflammatory mediators increasing expression of TRPV1, either on the neurones or in other airway tissues. Rather than directly causing a cough, angiotensin-converting enzyme inhibitors alter cough sensitivity by a TRPV1-dependent mechanism explaining the continued irritation long after drug withdrawal. Another transient receptor potential (TRP) receptor, TRPA1 is highly reactive to a wide range of environmental irritants and causes cough in man. Up-regulation of this receptor provides a mechanism the hypersensitivity in patients to agonist such as acrolein, the pro-tussive ingredient in smoke.

**Management of chronic cough**

All patients presenting with chronic cough should have a chest radiograph. The clinical history should indicate the most likely treatment options. The European Respiratory Society guidelines recommend therapeutic trials based on clinical judgement. Thus, in patients with episodes of wheezing and evidence of eosinophilic inflammation a trial of asthmatic medication may well be beneficial (fig. 3). Where available, exhaled nitric oxide fraction may be a useful screening tool. Bronchoconstriction may not be a major

<table>
<thead>
<tr>
<th>Table 3. Risk factors for chronic cough</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Heartburn</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Regurgitation</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>IBS</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>BMI category</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Overweight</td>
</tr>
<tr>
<td>Obese</td>
</tr>
</tbody>
</table>

Nonacid reflux symptoms in the form of regurgitation are more closely associated with cough than acid reflux. OR: odds ratio; CI: confidence interval; IBS: irritable bowel syndrome.
component of this phenotype of the cough hypersensitivity syndrome and consequently long-acting \( \beta \)-agonists may be less effective than anti-eosinophilic medication such as leukotriene antagonists. Reflux disease may be very problematical since much airway reflux is nonacidic and therefore not amenable to blockade by proton pump inhibitors. Pro-motility agents such as metoclopramide and domperidone may be used. Other motility agents such as erythromycin and magnesium have also been advocated. Finally, operative treatment via Nissan fundoplication can be effective in intractable coughing. An alternative strategy is to use cough suppression in the form of anti-tussive agents such as low-dose morphine. This has been demonstrated to ameliorate cough in a third of patients with otherwise intractable symptoms.

In subjects with chronic cough, production of moderate amounts of sputum does not alter the diagnostic profile. The separation from individuals with excessive sputum production is arbitrary, but is generally regarded as a cup of sputum per day. Above this limit a diagnosis of bronchiectasis becomes increasingly likely. The presence of sputum purulence indicates a greater likelihood, but does not seem to predict the degree of anatomical damage to the airway. Indeed the diagnosis of bronchiectasis, relying as it does on the dilation and destruction of the airways, will not include many patients with functional abnormalities of the bronchi.

In conditions characterised by sputum hypersecretion, there is usually a change in the composition of the mucus. Several mechanisms are responsible for this change. Thus in cystic fibrosis the increase in sodium reabsorption leads to a reduction in the sol phase of airway surface liquid. Airway inflammation, particularly caused by release of enzymes such as myeloperoxidase (which produces the characteristic green colour) and neutral endopeptidase and from polymorphs causes alteration of MUC gene expression through proteinase activated receptors. The death of inflammatory cells and bacteria lead to a soup of DNA which cross-links with filamentous actin-producing gelatinous plugs which increases ventilation/perfusion ratio mismatch with resulting systemic hypoxia.

Figure 1. Capsaicin cough challenge in normal subjects. The effect of capropril increasing cough reflex sensitivity. ■: placebo; ○: capropril.

Figure 2. The thermosensitive transient receptor potential (TRP) channels important in cough reflex sensitivity.

Cough and sputum
The treatment of mucus hyper-secretion may be challenging. In the presence of purulent sputum, every effort should be made to identify the causative organism. Eradication with appropriate high-dose antibiotic therapy may lead to sustained remission. More frequently there is rapid relapse indicating the need for maintenance antibiotics either orally or via the nebulised route. The advantage of this latter strategy is that side-effects may be minimised by using agents with high local potency but poor oral bioavailability such as colomycin or tobramycin. Antioxidant mucolytics are widely prescribed but evidence of efficacy is limited. The largest study of N-acetylcysteine over 3 yrs showed no effect on decline in lung function or exacerbation rate.

**Haemoptysis**

Haemoptysis presents in two clinical scenarios. First, the patient may present with _de novo_ haemoptysis without pre-existing lung disease. Any mucosal lesion may cause haemoptysis of small amounts of blood mixed with sputum. Since a common presentation of this is lung cancer, chest radiography is obligatory in patients when presenting with haemoptysis. Aspergiloma and tuberculosis may similarly cause a blood-stained bronchitis. More peripheral lung pathology, such as lobar pneumonia, gives rise to sputum that is frequently described as ‘rusty’. Haemoptysis of frank blood is a common sign of pulmonary embolism or infarction.

Obviously recurrent haemoptysis initially presents with acute haemoptysis. Typically, bronchiectasis leads to recurrent, sometimes massive and occasionally fatal haemoptysis. The bronchial blood supply arises from the aorta and, in contrast to the pulmonary circulation, is at systemic pressure. In bronchiectasis there is hypertrophy of the bronchial arteries as a consequence of recurrent infection. When the patient presents with life-threatening haemoptysis, percutaneous bronchial artery embolisation is the treatment of choice. Vasculitis is a common and frequently missed cause of recurrent haemoptysis and diffuse alveolar haemorrhage. Whilst the systemic connective tissue diseases, such as systemic lupus erythematosus, may produce small vessel haemoptysis, the commonest cause is microcytic polyangiitis. The perinuclear anti-neutrophil cytoplasmic antibody (pANCA) is positive in ~70% of cases. Finally, haemoptysis may be the result of alveolar haemorrhage. Disease of the vascular or alveolar wall, such as Goodpasture’s syndrome or alveolar haemosiderosis, may present with recurrent haemoptysis. Clearly, disorders of coagulation, such as warfarin therapy or thrombocytopenia, will predispose to haemoptysis.

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• Rogers DF. Physiology of airway mucus secretion and pathophysiology of hypersecretion. Respir Care 2007; 52: 1134–1146.
Dyspnoea is the major reason for referral to pharmacological treatment and respiratory rehabilitation programmes in patients with chronic obstructive pulmonary disease (COPD). Dyspnoea is a subjective experience of breathing difficulty that consists of qualitatively distinct sensations that vary in intensity. This definition underlines the importance of the different qualities (cluster descriptors) covered by the term dyspnoea, the involvement of integration of multiple sources of neural information about breathing and the physiological consequences.

**Aetiology**

Dyspnoea has many pulmonary, cardiac and other causes, which vary by acuity of onset (tables 1 and 2). Different causes of dyspnoea are associated with derangements of a number of functions and apparatus:

- Alveoli
- Ventilatory pump
- Upper and lower airways
- Pulmonary vasculature
- Cardiac pump
- Red blood cells
- Peripheral circulation
- Skeletal muscles

It is important to remember that the most common cause of dyspnoea in patients with chronic pulmonary or cardiac disorders is an exacerbation of their underlying disease.
Table 1. Some common causes of acute (within minutes) and subacute (within hours or days) dyspnoea

<table>
<thead>
<tr>
<th>Suggestive findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute cause</strong></td>
</tr>
<tr>
<td>Pulmonary causes</td>
</tr>
<tr>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Asthma, bronchospasm, or reactive airway disease</td>
</tr>
<tr>
<td>Foreign body inhalation</td>
</tr>
<tr>
<td>Cardiac causes</td>
</tr>
<tr>
<td>Acute myocardial ischaemia or infarction</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Other causes</td>
</tr>
<tr>
<td>Diaphragmatic paralysis</td>
</tr>
<tr>
<td>Anxiety disorder-hyperventilation</td>
</tr>
<tr>
<td><strong>Subacute cause</strong></td>
</tr>
<tr>
<td>Pulmonary causes</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>COPD exacerbation</td>
</tr>
<tr>
<td>Cardiac causes</td>
</tr>
<tr>
<td>Angina or CAD</td>
</tr>
<tr>
<td>Pericardial effusion or tamponade</td>
</tr>
</tbody>
</table>

COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; S3: 3rd heart sound.
Medical history

It is important to ask patients how long they have had dyspnoea and in what situations it occurs. Therefore, clinical history should cover the duration, temporal onset (e.g. abrupt, insidious), and provoking or exacerbating factors (e.g. allergen exposure, cold, exertion, supine position). Severity of dyspnoea can be determined by assessing the activity level required to produce dyspnoea (i.e. dyspnoea at rest is more severe than dyspnoea only with climbing stairs). For this purpose, the Medical Research Council dyspnoea scale can be used (table 3), along with other scales such as the Baseline Dyspnoea Index (BDI). For patients with baseline dyspnoea, the physician should note how much dyspnoea has changed from the patient’s usual state. Dyspnoea can also be evaluated during a physical task, such as cardiopulmonary exercise testing. For this purpose, the 10-point Borg scale can be used (table 3). In the Borg scale, the end-points are anchored such that zero represents “no breathlessness at all” and 10 is “the most severe breathlessness that one had ever experienced or could imagine experiencing”. By pointing to the Borg scale, subjects rate the magnitude of their perceived breathing discomfort during exercise. Most patients with dyspnoea, not just those with heart failure, feel worse when they lie down (orthopnea).

The physician should seek symptoms of possible causes, including chest pain (pulmonary embolism, myocardial ischaemia, pneumonia); dependent oedema, orthopnea and paroxysmal nocturnal dyspnoea (heart failure); fever, chills, cough and sputum production (pneumonia); black, tarry stools or heavy menses (occult bleeding possibly causing anaemia); and weight loss or night sweats (cancer or chronic lung infection). Past medical history should cover disorders known to cause dyspnoea, including asthma, COPD.

<table>
<thead>
<tr>
<th>Pulmonary causes</th>
<th>Suggestive findings</th>
</tr>
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<tr>
<td>Obstructive lung disease</td>
<td>Extensive smoking history, barrel chest and poor air entry and exit.</td>
</tr>
<tr>
<td>Restrictive lung disease</td>
<td>Progressive dyspnoea in patients with known occupational exposure or neurological condition.</td>
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<tr>
<td>Interstitial lung disease</td>
<td>Fine crackles on auscultation.</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>Pleuritic chest pain and lung field that is dull to percussion with diminished breath sounds. Sometimes history of cancer, heart failure, rheumatoid arthritis, systemic lupus erythematosus, or acute pneumonia.</td>
</tr>
<tr>
<td>Cardiac causes</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>Crackles, S3 gallop and signs of central or peripheral volume overload (e.g. elevated neck veins, peripheral oedema). Orthopnea or paroxysmal nocturnal dyspnoea.</td>
</tr>
<tr>
<td>Stable angina or CAD</td>
<td>Substernal chest pressure with or without radiation to the arm or jaw, often provoked by physical exertion, particularly in patients with risk factors for CAD.</td>
</tr>
<tr>
<td>Other causes</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>Dyspnoea on exertion progressing to dyspnoea at rest. Normal lung examination and pulse oximetry measurement. Sometimes systolic heart murmur due to increased flow.</td>
</tr>
<tr>
<td>Physical deconditioning</td>
<td>Dyspnoea only on exertion in patients with sedentary lifestyle.</td>
</tr>
</tbody>
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CAD: coronary artery disease; S3: 3rd heart sound.
and heart disease, as well as risk factors for the different aetiologies:

- smoking history for cancer, COPD and heart disease.
- family history, hypertension and high cholesterol levels for coronary artery disease.
- recent immobilisation or surgery, recent long-distance travel, cancer or risk factors for or signs of occult cancer, prior or family history of clotting, pregnancy, oral contraceptive use, calf pain, leg swelling and known deep venous thrombosis for pulmonary embolism.

Occupational exposures (e.g. gases, smoke and asbestos) should also be investigated.

**Physical examination**

The history and physical examination often suggest a cause and guide further testing.

Physical examination focuses on the cardiovascular and pulmonary systems. A full lung examination is done, particularly including adequacy of air entry and exit, symmetry of breath sounds, and presence of crackles, rhonchi, stridor and wheezes. Wheezing suggests asthma or COPD. Stridor suggests extrathoracic airway obstruction (e.g. foreign body, epiglottitis, vocal cord dysfunction). In-drawing of the lower ribcage towards the end of inspiration (Stock or Hoover’s sign) suggests (but does not prove) the presence of chronic lung hyperinflation from COPD. Paradoxical inspiratory inward motion of the abdomen is seen in bilateral diaphragm paralysis (easier to see when the patients are lying down and/or when they sniff). The presence of contraction of the accessory muscles when the patient is at rest could make the physician think of a more generalised muscle or nerve problem which has affected the diaphragm and the intercostals and parasternal muscles.

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**Table 3. The Medical Research Council (MRC) dyspnoea scale and the Borg scale**

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<thead>
<tr>
<th>MRC Grade</th>
<th>Description</th>
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<tr>
<td>1</td>
<td>Not troubled by breathlessness except with strenuous exercise</td>
</tr>
<tr>
<td>2</td>
<td>Troubled by shortness of breath when hurrying on the level or walking up a slight hill</td>
</tr>
<tr>
<td>3</td>
<td>Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level</td>
</tr>
<tr>
<td>4</td>
<td>Stops for breath after walking ——90 m or after a few minutes on the level</td>
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<tr>
<td>5</td>
<td>Too breathless to leave the house or breathlessness when dressing or undressing</td>
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<table>
<thead>
<tr>
<th>Borg scale</th>
<th>Severity</th>
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<tbody>
<tr>
<td>0</td>
<td>No breathlessness at all</td>
</tr>
<tr>
<td>0.5</td>
<td>Very very slight (just noticeable)</td>
</tr>
<tr>
<td>1</td>
<td>Very slight</td>
</tr>
<tr>
<td>2</td>
<td>Slight breathlessness</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>Somewhat severe</td>
</tr>
<tr>
<td>5</td>
<td>Severe breathlessness</td>
</tr>
<tr>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Very severe breathlessness</td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Very very severe (almost maximum)</td>
</tr>
<tr>
<td>10</td>
<td>Maximum</td>
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Inspiratory squeaks usually mean extrinsic allergic alveolitis, although sometimes they are heard in bronchiectasis. Crackles suggest left heart failure, interstitial lung disease or, if accompanied by signs of consolidation (e.g. egophony, dullness to percussion), pneumonia. The cervical, supraclavicular and inguinal areas should be inspected and palpated for lymphadenopathy. Neck veins should be inspected for distension (suggestive of heart failure, pulmonary embolism or pulmonary hypertension), and the legs and presacral area should be palpated for pitting oedema (suggesting heart failure). Heart sounds should be auscultated with notation of any extra heart sounds, muffled heart sounds, or murmur. It should be remembered, however, that signs and symptoms of life-threatening conditions, such as myocardial ischaemia and pulmonary embolism, can be nonspecific. Furthermore, the severity of symptoms is not always proportional to the severity of the cause (e.g. pulmonary embolism in a fit, healthy person may cause only mild dyspnoea). Thus, a high degree of suspicion for these common conditions is prudent. It is often appropriate to rule out these conditions before attributing dyspnoea to a less serious aetiology. A clinical prediction rule can help estimate the risk for pulmonary embolism. Note that a normal oxygen saturation does not exclude pulmonary embolism. Hyperventilation syndrome is a diagnosis of exclusion. Because hypoxia may cause tachypnoea and agitation, it is unwise to assume every rapidly breathing, anxious young person merely has hyperventilation syndrome.

**Physiology**

To gain more insight into our understanding of dyspnoea, a case can be made for answering the following questions: 1) what is the role of mechanical factors and ventilatory constraints in dyspnoea?; 2) what are the neurophysiological underpinnings of the most selected cluster descriptors that define the qualitative dimension of dyspnoea in patients?; 3) do obstructive and restrictive lung diseases share some common underlying mechanisms?

**Dyspnoea is perceived as a sense of effort** During voluntary increase in ventilation, the motor cortex increases the outgoing motor signal to respiratory muscles and conveys a copy (central corollary discharge) through cortical interneurones to the sensory/association cortex, which is informed of the voluntary effort to increase ventilation. It is also likely that the sense of the respiratory effort arises from the simultaneous activation of the sensory cortex and muscle contraction: a variety of muscle receptors provides feedback to the central nervous system about force and tension, and information from these receptors may conceivably underlie the sense of effort. For clinical purposes the perceived magnitude of respiratory effort is expressed by the ratio of the tidal oesophageal pressure ($P_{oes}$) to the maximal pressure generation capacity of the respiratory muscles ($P_{I,max}$). In healthy subjects, volitional respiratory effort is matched with lung/chest wall displacement (i.e. change in tidal volume percentage vital capacity) via concurrent afferent proprioceptive information, transmitted via vagal, glossopharyngeal, spinal and phrenic nerves, that monitors displacement and is processed and integrated in the sensory cortex. The result is a harmonious neuromechanical coupling (NMC) with avoidance of respiratory discomfort or distress.

**Dyspnoea is perceived as a sense of air hunger** Under some clinical and experimental circumstances the relationship between dyspnoea and effort is less apparent. If normal subjects suppress their ventilation to a level below that dictated by chemical drive ($CO_2$), dyspnoea increases without corresponding increases in indices of respiratory effort. Likewise, in experimental and clinical conditions where peripheral stretch receptors are inhibited, the sensory cortex is not informed of the ventilatory response. In these circumstances, dyspnoea is perceived as a sensation of air hunger whose
intensity depends on a mismatching between the level of chemical stimulated drive and ongoing inhibition from pulmonary mechanoreceptors signalling the current level of ventilation. In turn, dyspnoea arises and may qualitatively change when peripheral afferent feedback is altered and inspiratory motor output either increases or stabilises.

**Pathophysiology**

**COPD** Two clusters of dyspnoea are commonly selected by patients with COPD during physical activity.

The cluster respiratory effort is commonly selected by patients with COPD. Acute mechanical loading and functional respiratory muscle weakness decrease $P_{oes \% P_{I,max}}$, and further increase $P_{oes \% P_{I,max}}$. Furthermore, because of the limbic system activation, the corollary discharge may be sensed as abnormal, thus evoking a sensation of distress. The other cluster is unsatisfied inspiration. Structural abnormalities (chronic bronchitis and emphysema) via their physiological negative consequences, i.e., expiratory flow limitation and dynamic hyperinflation, result in dyspnoea. A patient’s physical activity is indeed characterised by a mismatch between increase in neural output to the respiratory muscles and lung/chest wall displacement. We call this mismatch neuroventilatory dissociation (NVD). In a clinical setting, the slope that defines NVD (i.e., effort versus displacement) is steeper and shifted upward compared with healthy subjects. The steeper the slope, the greater the intensity of dyspnoea (fig. 1). In particular, patients experience intolerable dyspnoea during exercise because tidal volume expansion is constrained from below (by the effects of dynamic lung hyperinflation) as there is no space to breathe. This so-called dyspnoea threshold seems to be at the level at which the inspiratory reserve volume approaches 0.5 L. In turn, unsatisfied inspiration reflects a discrepancy between high ventilatory drive and ventilation less than that dictated by the respiratory drive. The data support the central importance of mechanical restriction in causing dyspnoea in COPD patients.

**Neuromuscular disorders (NMD)** Patients with NMD exhibit heightened neuromotor output, which is sensed as increased respiratory muscle effort and, as such, is likely to be the principal mechanism of dyspnoea in NMD. Nonetheless, a significant positive relationship between increased dyspnoea per unit increase in ventilation and dynamic elastance affects the coupling between respiratory effort and displacement (fig. 2).

**Interstitial lung disease (ILD)** One of the characteristic features of ILD is a reduction in lung compliance and lung volumes. The mechanical response of the respiratory system is similarly restricted in patients with ILD as in those with COPD: tidal volume expansion is constrained from above (reflecting the reduced total lung capacity and inspiratory reserve volume), which results in greater reliance on an increase in breathing frequency to increase ventilation. Differences in dynamic ventilatory mechanics, including possible expiratory flow limitation in some patients, account for distinct qualitative perception in ILD patients, namely inspiratory difficulty and
rapid shallow breathing. Because of increase in both dynamic elastance and efferent respiratory drive, inspiratory difficulty may have its psychophysical basis in the conscious awareness of a dissociation between respiratory effort and the mechanical response, i.e. inability to expand tidal volume appropriately in the face of an increased drive to breathe. In turn, the possibility has also been put forward that intensity of exertional dyspnoea in ILD is more closely linked to mechanical constraints on volume expansion than to indexes of inspiratory effort per se.

Chronic heart failure (CHF) The key message that has emerged from therapeutic intervention studies in patients with CHF is that exertional dyspnoea alleviation is consistently associated with reduced excessive ventilatory demand (secondary to reduced central neural drive), improved respiratory mechanics and muscle function and, consequently, enhanced neuromechanical coupling of the respiratory system during exercise. Pressure support is reported to reduce the tidal inspiratory pleural pressure-time slope without affecting submaximal dyspnoea ratings but allows patients to exercise for additional minutes without experiencing any significant rise in dyspnoea. The available data suggest that increased ventilatory demand, abnormal dynamic ventilatory mechanics and respiratory muscle dysfunction are instrumental in causing exertional dyspnoea in patients with severe cardiac impairment.

Obesity An increase in respiratory neural drive is deemed to be the reason for the similar increase in dyspnoea in obese and lean subjects. However, different underlying mechanisms may affect dyspnoea in obese subjects. Exercise performance is impaired compared with healthy normal-weight subjects when corrected for the increased lean body mass, but normal when expressed as a percentage of predicted for ideal body weight in subjects who hyperinflate the lungs to the same extent as those obese subjects who deflate the lungs, with both volume subgroups reaching similar dyspnoea scores. In “hyperinflators”, dynamic hyperinflation along with a decrease in inspiratory reserve volume increases respiratory muscle loading, respiratory drive and perception of respiratory discomfort. In contrast, “deflators” exhibit a negative relationship between resting end-expiratory lung volume (EELV) and perceptual respiratory response during exercise: the lower the EELV the greater the Borg score. A low resting EELV has three important consequences linked together during exercise: 1) decrease in expiratory reserve volume, 2) dynamic airway compression, and 3) changes in transmural airway pressure resulting in airway dynamic compression. Thus, an alteration in the central drive to the respiratory muscles in response to afferent activity from upper airway mechanoreceptors may also contribute to the unpleasant respiratory sensation in obese subjects.

Diabetes A study on respiratory muscle effort and load has helped elucidate the pathophysiology of dyspnoea during hypoxic stimulation of ventilation in type I diabetes mellitus. The study shows that because of an increase in dynamic elastance, the greater perception of dyspnoea is associated with changes in inspiratory effort, which is out of
proportion with changes in tidal volume in patients with no smoking history.

**Conclusions**

We are still a long way from understanding the symptom of dyspnoea. Although mechanical factors are important contributors to dyspnoea, the precise mechanisms of dyspnoea remain obscure. One approach to the study of this symptom is to identify the major qualitative dimensions of the symptom in an attempt to uncover different underlying neurophysiological mechanisms. The remarkable similarity in choices of qualitative descriptors (work/effort, inspiratory difficulty/unsatisfied inspiration, air hunger, rapid breathing) for exertional dyspnoea in patients with restrictive and obstructive syndromes raises the intriguing possibility that they share some common underlying mechanisms.

**References**

CHEST PAIN

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Chest pain is a frequent symptom of illness and a common reason for seeking medical attention. Rapid assessment is crucial so that life-threatening disease, such as cardiac chest pain, aortic dissection and oesophageal rupture, can be identified and managed appropriately. A basic history often points to the cause and is used in triage of patients attending emergency rooms. Questions are typically asked about the character, location, radiation, severity, exacerbating and relieving factors of the pain, and its relationship to movements such as breathing or coughing. Objective assessment using a questionnaire, such as the McGill Pain score can be useful. Occasionally, it is difficult to tease out differences between cardiac, gastrointestinal and respiratory causes of pain.

The pathophysiology of chest pain is complex and not completely understood but involves peripheral nociceptors, either small Aδ myelinated or unmyelinated C afferent fibres that project via sympathetic and parasympathetic nerves into the dorsal horn of the spinal cord. These neurones synapse with spinothalamic fibres which ascend, cross the spinal cord and terminate in the contralateral ventero-posterior thalamic nucleus. Thalamo-cortical neurons project via the posterior limb of the internal capsule to the somatosensory cortex. The diaphragm has dual nociceptive sensory innervation from both the phrenic nerve and the lower six intercostal nerves, therefore diaphragmatic irritation can present with pain referred to the shoulder or upper abdomen. The trachea and large airways have afferent fibres that project along the vagus nerve. Respiratory chest pain can therefore originate from the chest wall, pleura, large airways and mediastinum, but visceral “lung” pain is unusual.

Pleural pain is often described as sharp, stabbing and made worse by movement such as deep respiration. The pain is often unilateral, reflecting the site of the disease. A pleural rub may be heard. Pleuritic pain with sudden onset prompts a diagnosis of pulmonary emboli, infarction or pneumothorax, whereas pleuritic pain building over a few hours may suggest infection such as pneumonia or pleurisy. Onset over days suggests empyema, malignancy or tuberculosis.

Tracheobronchitis can present with a midline burning pain made worse with respiration. Massive mediastinal lymphadenopathy can cause an indistinct, heavy central chest pain. Similarly, chest pain associated with pulmonary hypertension can be difficult to distinguish from cardiac chest pain. Nondescript, heavy chest pain is quite common in exacerbations of bronchiectasis.

Chest wall pain is usually well localised, reproduced with movement and associated with tenderness. Costocondritis and Tietze’s syndrome are inflammatory disorders of thoracic joints that present with chest wall pain and can be confused with chest wall trauma.

Key points

- Chest pain can be a feature of a wide range of pathology
- An accurate history is essential to direct appropriate investigation of patients presenting with chest pain
pain and tenderness. Bornholm disease (epidemic pleurodynia or devil’s grip), often associated with Coxsackie B virus, can present with epidemics of chest wall pain of sudden onset.

Neuralgic pain can be sharp and knife-like or dull and heavy, and there may be associated sensory symptoms. Pain in a dermatomal distribution requires examination of overlying skin for the characteristic vesicular rash of herpes zoster.

ECG is essential for immediate assessment of cardiac chest pain. Further investigation may include exercise ECG, stress echocardiography or myocardial perfusion scan. Angiography offers the opportunity for therapeutic angioplasty and stent insertion.

Chest radiographs are useful to identify consolidation, pneumothorax, pleural effusion, and bony abnormalities such as vertebral fractures. Contrast computed tomography scanning has made identification of pulmonary emboli, aortic dissection and oesophageal rupture straightforward, and can identify abnormalities often missed on plain radiographs. Nuclear medicine scans have a role in both diagnosis and management of pulmonary emboli. Bone scintigraphy is useful in evaluation of ‘bony’ pain. Magnetic resonance examination is of particular use in visualising nerve roots. Direct endoscopic visualisation of either the upper gastrointestinal tract (oesophagogastroduodenoscopy) or major airways (bronchoscopy) allows epithelial inspection and offers the opportunity for direct microbiological, cytological and histological sampling.

Reference

Physical findings in the context of the history

The purpose of clinical assessment is to make an accurate diagnosis. Making an accurate diagnosis in cases of respiratory disease can be challenging not only because of the diversity of respiratory ill-health, but also because symptoms of respiratory disease are shared with disorders of other body systems.

Breathlessness (a sensation of difficult, laboured or uncomfortable breathing) may have a physiological or psychological explanation but it is extremely important that every time we are faced with a patient complaining of shortness of breath we consider the following points.

Is this patient breathless because of:

- Heart disease?
- Lung disease?
- Pulmonary vascular disease?
- A systemic disorder (anaemia, obesity or hyperthyroidism), or
- Respiratory muscle weakness

It is vital that we go through this checklist both with new presentations of the symptom of breathlessness and also in those with established disease, and we need to bear this list in mind when examining the patient. The patient with chronic obstructive pulmonary disease might this time be breathless, not because of an exacerbation, but because they have gone into atrial fibrillation; or the patient with known heart failure may this time be breathless because of a complicating pneumonia.

Asking specifically about the onset of the symptom of breathlessness can be helpful in the differential diagnostic process and this is summarised in table 1.

Cough

A practical approach to the assessment of cough and breathlessness is summarised in fig. 1.

Physical examination

In the vast majority of cases, the taking of the medical history should lead to the
construction of a list of differential diagnoses. The examination is then an opportunity either to confirm normality or to discover abnormalities consistent with one or other of one’s differential diagnoses. Key features, as with all clinical examination, depend upon inspection, palpation, auscultation and percussion.

**Inspection**

On inspection the key points to observe are:

- General appearance (breathlessness? cachetic?)
- Respiratory rate
- Appearances of the hand (finger clubbing? tremor? tobacco staining? flapping tremor suggestive of CO₂ retention?)
- Does the chest wall move symmetrically?
- Are there any chest wall deformities (scoliosis, pectus excavatum) or scars?
- Any abnormal vessels suggestive of superior vena cava obstruction (fig. 2)?
- Nasal stuffiness or obstruction should be noted.
- A note should be made of the neck/collar size and also of obvious jaw abnormalities and oropharyngeal abnormalities.

<table>
<thead>
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<th>Table 1. Breathlessness: differential diagnosis according to onset</th>
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<tr>
<td><strong>Within minutes</strong></td>
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<tr>
<td><strong>Over hours or days</strong></td>
</tr>
<tr>
<td><strong>Over weeks</strong></td>
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<tr>
<td><strong>Over months</strong></td>
</tr>
<tr>
<td><strong>Over years</strong></td>
</tr>
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</table>

LVF: left ventricular failure; MI: myocardial infarction; SBE: subacute bacterial endocarditis; COPD: chronic obstructive pulmonary disease.

**Palpation**

This involves the following:

- Assessment of chest expansion, where we may be able to elicit reduced expansion symmetrically suggestive of hyperinflation, or reduced movement on one side suggesting localised pathology on that side.
- Determining the position of the trachea by inserting the index and middle fingers in the supra sternal notch.
- Examining the cervical and supra clavicular lymph nodes for enlargement.
- Assessing vocal fremitus by asking the patient to loudly and deeply repeat the words ‘99’ whilst you compare both sides of the chest. Voice sounds are better transmitted through consolidated lung than normal lung and poorly transmitted through pleural effusions.

**Percussion**

Percussion is often poorly undertaken and the key features are to make the movement of your finger as a stroke from the wrist and strike firmly at right angles upon the finger of the other hand which lies along the intercostal space, and to do so in a symmetrical manner systematically comparing both sides of the chest at a point equidistant...
Figure 1. Diagnosis and management of respiratory disease. ACE: angiotensin-converting enzyme; DVT: deep vein thrombosis; FH: family history; VTE: venous thromboembolism; BMI: body mass index; COPD: chronic obstructive pulmonary disease; ENT: ear–nose–throat.
from the midline. The percussion note may be hyper-resonant symmetrically in patients with underlying hyperinflated lungs or asymmetrically in a large pneumothorax, or may be dull in cases of consolidation or pleural effusion.

Auscultation

Listening to the breath sounds involves the following:

- Checking for the presence of bronchial breathing, which is the presence of breath sounds that are similar to those heard over the large central airways in a more peripheral location. Bronchial breathing is classically heard over a consolidated lung (and in association with dullness to percussion), but is also sometimes heard over the upper aspect of a pleural effusion and sometimes over a collapsed lung.

- Determining whether there are or are not any abnormal added sounds, which may be musical sounds (wheezing) or crackles. In cases of wheezing, it is important to determine whether the wheezing is poly- and bilateral, as in asthma or COPD, or monophonic and localised, as may be found in cases of lung cancer or bronchial stenosis or inhaled foreign bodies.

- Crackles may be fine and occur in cases of interstitial lung disease or acutely in cases of pulmonary oedema, or coarse, as often heard in patients with bronchiectasis.

- Pleural rubs sound like a squeaky noise, are usually localised and clearly vary in intensity with respiration. Care in interpreting a noise as a pleural rub is necessary in very thin patients where the diaphragm of the stethoscope may move over the ribs.

- Vocal resonance is found under the same circumstances as vocal fremitus, and when found in conjunction with bronchial breathing is highly suggestive of consolidation. Some physicians find detection of whispering pectoriloquy (WP) a more definite sign; to elicit WP, one asks the patient to whisper ‘99’ and, when it is present, for example, in cases of consolidation, the whispered sound is heard clearly over the chest wall when transmitted through consolidated lung whereas a normally air-filled lung would muffle the whispered sound and make it indistinct.

Finally, one should remember that disorders of other systems may coexist and, whilst examining the chest, one should especially look for evidence of heart and pulmonary vascular disease, noting signs of peripheral oedema and elevation of the jugular venous pressure.

References

# CHAPTER 3:
PULMONARY FUNCTION TESTING

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Ventilation is constrained by the mechanical properties of the airways, lung and chest wall. The latter two set up the volume at which the movement of gas is accomplished at rest and with daily activities, such as exercise, phonation, laughing, changes in body posture and others. However, with the occurrence of cardiopulmonary diseases, lung volumes may also be modified as a result of dynamic mechanisms within the airways and changes in breathing pattern in addition to static changes in lung and chest wall properties.

**Determinants of lung volumes in health and disease**

Tidal volume (VT) is the volume of gas inspired during each breath (fig. 1) necessary to preserve gas exchange. In healthy subjects, inspiration is switched off by neural reflexes, whereas expiration is terminated near the relaxation volume (VR) as a result of static or dynamic mechanisms (see section dedicated to functional residual capacity). Except during exercise, when a lack of increase in VT with ventilation is a functional marker of ventilatory limitation, and perhaps in patients undergoing assisted ventilation, VT has little clinical usefulness in clinical practice.

Total lung capacity (TLC) is the volume of gas contained in the lungs after a deep breath. It is determined by the maximum force exerted by the inspiratory muscles to balance lung and chest wall elastic recoils (figs 1 and 2). In healthy conditions, TLC tends to remain fairly stable with ageing, presumably because the natural decrease of the force of the inspiratory muscles and/or the increase in chest wall stiffness are balanced by the progressive loss of lung elastic recoil.

In contrast, TLC tends to increase in emphysema and sometimes in chronic bronchitis and severe asthma. Though the decrease in lung elastic recoil is presumably the most important mechanism of the increase in TLC under these conditions, an increased force of the inspiratory muscles and chest wall remodelling may also play a role. Surprisingly, for the same level of airflow obstruction, TLC tends to increase during spontaneous long-lasting but not acutely induced bronchospasm. This is presumably because of the different time course necessary to produce airflow obstruction and hyperinflation. That this may be so is shown by a study documenting that when a resistive valve was implanted in the dog trachea, it took time for TLC to increase. Thus it is

**Key points**

Measurement of lung volumes in clinical practice has been proven to be important to assist in the following.

- Diagnosis of pulmonary defects.
- Evaluation of candidates for lung volume resection surgery.
- Prognosis of COPD and interstitial lung diseases.
- Evaluation of the bronchomotor response to constrictor and dilator agents as well as to physical exercise.
Possible that breathing at high lung volumes for long periods of time as a result of severe chronic airflow obstruction may also contribute to the increase in TLC.

TLC decreases in all conditions characterised by an increase in lung elastic recoil (e.g., pulmonary fibrosis, cardiac failure), chest wall stiffness (e.g., neuromuscular diseases, obesity, ascitis and pregnancy) or thoracic space competition (e.g., pleural effusions, pneumothorax).

Measuring TLC is of great importance in clinical practice as it allows identification of the restrictive pulmonary defects. In addition, TLC is also useful in the evaluation of an emphysematous patient as a candidate for lung volume resection surgery or for follow-up of interstitial lung diseases.

Residual volume (RV) is the volume of gas that remains in the lungs after a complete expiration. In young healthy individuals, RV is mostly determined by the balance between the force of the expiratory muscles and the outward recoil of the chest wall (figs 1 and 2). In the elderly, it increases as a result of airway closure.

In restrictive diseases, RV decreases in proportion to the increase in lung elastic or chest wall recoils and/or loss of lung parenchyma.

In obstructive pulmonary diseases, RV is higher than predicted because of premature airway closure, loss of lung elastic recoil, and stiffness of chest wall. Additional mechanisms may dynamically contribute to elevate RV in obstructive lung diseases. For instance, in patients with acutely induced or chronic airflow obstruction, RV achieved after a forced expiration is always higher than after a slow expiration. This is mainly because of two mechanisms. First, during forced expiration in airflow obstruction, expiratory flow limitation (EFL) occurs soon after initiation of the manoeuvre, especially within the airways that are already narrowed. In contrast, during a slow expiration, pleural pressure will exceed the critical pressure necessary to generate maximal flow, and thus EFL late on expiration and at a lower lung volume. Secondly, some airways could close near TLC early on expiration as a result of the disease, thus preventing the subtending alveolar units from emptying and contributing to increased RV.

Also, the effects of volume history of the manoeuvre preceding the expiration may

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Figure 1. Lung volume plotted versus time. VT: tidal volume; EVC: slow expiratory vital capacity; IRV and ERV: inspiratory and expiratory volume reserves, respectively; IC: inspiratory capacity; RV: residual volume; FRC: functional residual capacity; TLC: total lung capacity.

Figure 2. Quasi-static pressure-volume curves of the chest wall and the lung (dashed lines) related to pleural pressure (Ppl) generated during maximum inspiratory and expiratory static efforts (Pimax and Pemin, respectively; continuous lines). Volume is expressed as % of total lung capacity (TLC). TLC is the volume at which Pimax equals the inward elastic recoils of both lung and chest wall. Residual volume (RV) is the volume at which Pemin overcomes the outward elastic recoil of the chest wall. Functional residual capacity (FRC) is the volume at which inward lung recoil equals outward chest wall recoil (arrows with opposite direction). % pred: % predicted.
affect RV. For instance, in healthy subjects or mild-to-moderate asthmatics exposed to a bronchoconstrictor agent, a manoeuvre initiated from TLC will generate greater flow and lower RV than a manoeuvre initiated from end-tidal inspiration. The opposite occurs in chronic airflow obstruction. This suggests that RV is also modulated through the changes in airway calibre caused by large lung inflations. How the deep inspiration manoeuvre affects lung and airways mechanics is still a matter of debate. When a deep breath is taken, the inflating stimulus is transmitted to the lung as well as the airways through the elastic network of lung parenchyma. According to Froeb and Mead (1968), the effects of volume history on airway size depend on the mechanical characteristics of lung parenchyma and airways. Both tissues may lose energy or pressure and deform with stretching, a phenomenon named hysteresis. Since lung elastic recoil and transmural pressure are the forces that determine airway size, any change relative to one of these will necessarily entail a change in flow and RV. As shown in figure 3, if airway hysteresis exceeds parenchymal hysteresis, airway volume will be greater during deflation than inflation and RV will be achieved at a lower lung volume. This generally occurs when constriction is mostly limited to the airways and little affects lung parenchyma, such as with induced airway narrowing. In contrast, when lung parenchyma hysteresis is larger than airway hysteresis, airway volume will be reduced on expiration compared with inspiration and RV.

![Diagram](image)

**Figure 3.** Effects of deep breath on maximum expiratory flow and residual volume according to the relative hysteresis theory of Froeb and Mead (1968). a) Pressure-volume loops of lung parenchyma and airways on inspiration and expiration. The area inside the loop is called hysteresis. b) Partial and maximal flow-volume loops (dotted and continuous lines, respectively). Upper panels of a) and b): both hystereses are similar, so that the constrictor and dilator forces after the deep breath remain equal compared to before inflation. As a result, forced flow and residual volume during the maximum forced expiratory manoeuvre are the same of the partial manoeuvre. Central panels of a) and b): airway hysteresis prevails over lung hysteresis, so that the constrictor force is reduced after the large inflation. Consequently, for a given lung volume, maximum flow will exceed partial flow and residual volume will decrease more after a maximal compared to partial manoeuvre. Lower panels of a) and b): lung parenchyma hysteresis prevails over airway hysteresis, so that the dilator force will decrease after the deep breath. Under these conditions, forced expiratory flow and residual volume after a maximal manoeuvre will decrease and increase, respectively, compared to a partial manoeuvre. exp: expiration; insp: inspiration.
achieved at a higher volume. This is what presumably occurs in chronic airflow obstruction or severe ASM shortening. Finally, when airway and lung parenchyma hystereses change by similar extent, airway size will be similar before and after a deep breath and so will RV. The effects of volume history may be easily assessed in vivo by comparing forced expiratory manoeuvres initiated from total lung capacity and a volume below it (fig. 3b), or by changes in airflow resistance soon after taking a deep breath.

Vital capacity (VC) is the difference between TLC and RV. Because RV is dependent on volume and flow histories in addition to airway, parenchyma, and/or chest wall components of the diseases as discussed above, VC will depend on the type of respiratory manoeuvre from which it is taken and the underlying disease. In general, the largest VC is that obtained during a full inflation from RV (achieved after a slow expiration from end-tidal inspiration) to TLC (inspiratory vital capacity), followed by the slow expiratory vital capacity from TLC to RV (EVC), and the VC measured during a forced expiratory manoeuvre (forced vital capacity). A decrease of VC does not allow differentiation between restriction and obstruction, as it may be due to a decrease in TLC or an increase in RV, or both.

In clinical practice, VC is of central importance for the diagnosis of obstructive pulmonary defects.

Functional residual capacity (FRC) is the volume of gas remaining in the lungs at the end of a tidal expiration in a seated or upright position (fig. 1). Its mechanical determinants are the inward elastic recoil of the lung balancing the outward recoil of the chest wall (fig. 2). In supine position, the abdominal content is displaced towards the chest cavity, thus reducing FRC. Also during speech, singing, laughing or exercise FRC tends to decrease to favour these activities.

In obstructive pulmonary diseases, FRC tends to increase for a series of reasons. For instance, an increase in breathing frequency or in time constant of the respiratory system as a result of either an increase in airflow resistance or a decrease in lung compliance, will lead to an expiratory time relatively too short to allow the respiratory system to empty fully. Presumably, the occurrence of EFL during tidal expiration may also contribute to an increase in FRC to a lung volume where EFL is minimal. Under these circumstances, the dynamic compression of the airways downstream from the flow limiting segment may evoke neural reflexes that prematurely activate the inspiratory muscles to avoid breathing for too long a time under EFL conditions. On the other hand the increase in FRC in airflow obstruction is beneficial as it allows breathing at a volume where the airways are larger, thus decreasing the resistive work of breathing. On the other hand, however, breathing at high lung volume is associated with an increase in the elastic work of breathing and causes dyspnoea.

A decrease in FRC occurs in restrictive respiratory diseases due to an increase in lung elastic recoil (e.g. in pulmonary fibrosis, atelectasis, lung resection, alveolar liquid filling, cardiac diseases) or in chest wall elastance (e.g. in chest wall and pleural diseases, respiratory muscle paralysis, obesity).

Inspiratory capacity (IC) is the volume difference between TLC and FRC. In pulmonary diseases, it tends to decrease as a result of an increase in FRC (obstructive conditions) or a decrease in TLC (restrictive diseases), or both. In clinical practice, changes in IC with acute interventions on airway calibre, such as bronchoprovocation or reversibility tests, or during exercise, reflect mirror-like changes in FRC, assuming that TLC remains unmodified.

IC has no role in the diagnosis of ventilatory defects.

Expiratory and inspiratory reserve volumes are the volumes available to VT to expand when necessary (fig. 1). Though of little interest at rest, they play a critical role during exercise. For instance, in healthy subjects the increase in VT with exercise is achieved at the expenses of a decrease in end-expiratory lung volume.
(EELV) and an increase in end-inspiratory lung volume (EILV). In contrast, in airflow obstruction, the increase in VT is limited by the premature and sustained increase in EELV that may eventually contribute to cause dyspnoea.

**Measurements of lung volumes in clinical practice: technical aspects**

VC, VT, IC, EILV and EELV can be measured by simple spirometry. In contrast, TLC, RV and FRC need to be measured with special techniques described below.

Gas dilution techniques (nitrogen washout and helium dilution) are based on the principle of the conservation of mass, that is the amount of gas resident in the lungs at the beginning of the test can be calculated as the product of concentration and volume of eliminated nitrogen or diluted helium. Both methods yield measurements of lung volumes that communicate with open airways only. In severely obstructed patients, an underestimation of the true lung volume may be a result of some regions with long time constants.

Body plethysmography allows rapid and reproducible measurements of absolute lung volumes. The test is based on Boyle's law, in that lung volume can be calculated from the relationship between changes in mouth pressure (assumed equal to alveolar pressure) and box pressure (constant-volume plethysmography) or volume (constant-pressure plethysmography) during gentle panting manoeuvres against a closed shutter. As opposed to gas dilution techniques, plethysmography measures the whole intrathoracic gas, thus including nonventilated and/or poorly ventilated lung regions. This method may overestimate lung volumes in cases of severe airflow obstruction if the panting frequency >1 Hz.

**Conclusions**

Measuring lung volumes is now an integrative part of lung function assessment. In addition to assist in the diagnosis of the ventilatory defects, it helps explain the presence of respiratory symptoms and hypoxia in cardiopulmonary diseases, has clinical prognostic implications in both obstructive and restrictive diseases, and plays an integral role in the functional evaluation for lung volume reduction surgery in emphysema.

**References**

Pulmonary ventilation is determined by the resistive and elastic properties of the lungs and chest wall and by the driving pressure of the respiratory muscles. Both the lungs and chest wall are elastic structures. The lungs have a very small resting volume. Above this volume the lungs are distended, exerting an inward elastic recoil pressure ($P_L$) that rises markedly with lung volume ($V_L$). The chest wall has a much higher resting volume, exhibiting outward and inward elastic recoil pressure ($P_{CW}$) below and above its resting volume, respectively.

At end-expiratory volume during quiet breathing (functional residual capacity (FRC)) in a healthy subject the respiratory muscles are relaxed and the lungs and chest wall reach the combined resting state (fig. 1). In this situation, the inward $P_L$ is counterbalanced by the outward $P_{CW}$ and the alveolar pressure ($P_{alv}$) equals atmospheric pressure. Inspiration is produced by activation of inspiratory muscles. The outward muscular pressure ($P_{mus}$) expands the chest wall, thereby lowering pleural pressure ($P_{pl}$). This drop in $P_{pl}$ expands the lung and decreases $P_{alv}$ to subatmospheric values. The mouth–alveolar pressure gradient drives inspiratory flow. During quiet breathing in a normal subject, expiration is achieved by relaxing inspiratory muscles. The net inward elastic recoil of the total respiratory system ($P_{RS} = P_L + P_{CW}$) tends to return the system to the overall equilibrium volume, increasing $P_{alv}$ to above mouth pressure ($P_{mo}$) and driving expiratory flow. The activation of the expiratory muscles results in a faster expiration.

**Airway resistance**

The airflow generated by the pressure gradient between the mouth and the alveoli is determined by airway resistance ($R_{aw}$), defined as

$$R_{aw} = (P_{mo} - P_{alv})/V$$
where $V'$ is the gas flow.

In healthy adults, $R_{aw}$ measured at FRC is about 2 hPa·s·L⁻¹. Intrathoracic airway calibre increases as lungs expand, resulting in a hyperbolic dependence of $R_{aw}$ on lung volume. Therefore, an approximately linear relationship is obtained by computing airway conductance ($G_{aw} = 1/R_{aw}$). Since large lungs have wider airways, the specific airway resistance computed as

$$sR_{aw} = R_{aw} / V$$

provides a resistance measurement normalised for differences in lung size. Similarly, specific conductance is defined as

$$sG_{aw} = G_{aw} / V$$

**Body plethysmography**

Measurement of $R_{aw}$ requires the recording of airflow and driving pressure. Airflow can be recorded with a pneumotachograph connected to the mouth. Mouth pressure is simply atmospheric pressure or, alternatively, it can be readily measured with a pressure transducer. As the alveolar airspace is not directly accessible, $P_{alv}$ can be estimated by means of a whole-body plethysmograph (Fig. 2). This technique involves the subject sitting inside a closed cabin breathing the gas from the box. The mouth can be occluded with a shutter coupled to the mouthpiece. First, the shutter is opened and the ratio between $V'$ and the pressure within the box ($P_{box}$) is measured during breathing ($V'/P_{box}$).

During inspiration the air moves from the box to the lung. The inspired gas takes on a higher volume in the lungs than in the box due to the decrease in pressure ($P_{alv} < P_{box}$), the increase in temperature ($37°C$) and the addition of water vapour. The calibration ratio of the plethysmograph ($k = P_{alv}/P_{box}$) is experimentally determined by closing the shutter at FRC and recording $P_{mo}$ and $P_{box}$ during gentle respiratory efforts against the occlusion. Under zero airflow conditions, $P_{alv} = P_{mo}$ and

$$k = P_{alv}/P_{box}$$

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**Figure 1.** Mechanical behaviour of the respiratory system. $V'$: gas flow; $P_{alv}$: alveolar pressure; $V_L$: lung volume; $P_L$: lung elastic recoil pressure; $P_{CW}$: chest wall elastic recoil pressure; $P_{mus}$: outward muscular pressure.

**Figure 2.** Measurement of airway resistance by body plethysmography. $V'$: gas flow; $P_{mo}$: mouth pressure; $P_{alv}$: alveolar pressure; $V_L$: lung volume; $P_{box}$: pressure within the box.
Therefore, 

\[ R_{aw} = P_{alv}/V' = k \cdot P_{box}/V' \]

Body plethysmography measurements of \( R_{aw} \) are usually computed at low respiratory flows (<0.5 L) recorded during shallow panting to minimise the effects of temperature changes during inspiration and expiration. Alternatively, measurements can be made during quiet breathing after computer correction for changes in the physical conditions of the gas.

Whole-body plethysmography is the procedure most commonly used to measure \( R_{aw} \). An added advantage of this technique is that it provides a FRC measurement for the computation of \( sR_{aw} \). However, the device is bulky and expensive and is not suited to measurement in supine patients.

**Interrupter technique**

Airway resistance can also be measured outside the box with a pneumotacograph–shutter system. The subject breathes at rest through the pneumotacograph. When airflow reaches a given threshold the mouth is briefly (~0.1 s) occluded with the shutter. During flow interruption the pressure is equilibrated within the different lung compartments. Therefore, \( R_{aw} \) can be computed as the ratio between the flow just before occlusion and the mouth pressure recorded during flow interruption. \( R_{aw} \) is usually computed as the mean of flow interruptions performed in several breathings.

The interrupter technique can be implemented in handy devices and requires only minimal patient cooperation. However, due to progressive equilibration between mouth and alveolar pressure the computed value of \( R_{aw} \) depends on the time lag between the start of occlusion and \( P_{mo} \) measurement. Slow pressure equilibration in patients with airflow obstruction results in an underestimation of \( R_{aw} \).

**Forced oscillation technique**

In addition to the airflow resistance of the airways, lung and chest wall tissues also exhibit resistive load because of internal frictional resistance to motion. Resistance of the total respiratory system (\( R_{ts} \)) is the sum of airway and tissue resistance. The tissue component of \( R_{ts} \) is generally small in comparison with \( R_{aw} \).

\( R_{ts} \) can be measured during quiet breathing by the forced oscillation technique (FOT). This technique is based on applying a small amplitude (± 1 hPa) pressure oscillation to the patient’s mouth or nose with a loudspeaker or a small pump. \( R_{ts} \) is computed as the ratio of forced pressure oscillation and in-phase flow. The ratio between forced pressure and the out-of-phase flow defines the reactance (\( X_{rs} \)) that provides a combined measurement of the inertial and elastic properties of the respiratory system. Forced oscillation is applied at frequencies (>4 Hz) higher than the breathing rate to facilitate the separation of forced oscillation from tidal breathing. The use of multifrequency oscillation (usually 4–32 Hz) provides a measurement of the frequency dependence of respiratory mechanics.

Current FOT devices are portable and easy to use. The technique does not require any special collaboration from the patient and measurements can be performed in supine. Changes in \( R_{ts} \) during the breathing cycle can be precisely monitored. Moreover, FOT can be coupled to mechanical ventilators. Therefore, FOT is especially useful for epidemiological studies, measurements in infants and monitoring respiratory mechanics in patients during sleep and mechanical ventilation.

**Lung compliance**

The elastic behaviour of the lung is described by the \( P_l-V_l \) relationship. Lung deformability is measured as lung compliance (\( C_l \)), defined as the change in volume divided by the change in pressure.

\[ C_l = \Delta V_l/\Delta P_l \]

The change in volume can readily be measured with a spirometer connected to the mouth. The measurement of \( \Delta P_l \) requires the simultaneous recording of \( P_{pi} \) and \( P_{alv} \). Pleural
pressure is usually estimated from the oesophageal pressure ($P_{soe}$) recorded with a small balloon attached to the tip of a catheter introduced through the nose into the lower oesophagus. Alveolar pressure is estimated in the mouth during brief flow interruptions. In practice, the subject performs a full inspiration followed by a very slow expiration to FRC. A shutter attached to the spirometer performs successive brief (~1 s) occlusions during expiration. The $P_L$–$V_L$ relationship is curvilinear, with $C_L$ decreasing markedly with volume.

$C_L$ is habitually computed in the range of tidal volume at rest (between FRC and FRC+0.5 L). In the normal adult, $C_L$ is about 0.2 L·hPa$^{-1}$. The elastic behaviour of the lung can also be characterised by lung elastance ($E_L$), defined as the reciprocal of $C_L$ ($E_L = 1/C_L$).

Chest wall compliance is computed as $C_{CW} = \Delta V/\Delta P_{CW}$

In healthy subjects, the value of $C_{CW}$ is comparable to that of $C_L$. Since the elastic pressure of the respiratory system is $P_{rs} = P_L + P_{CW}$, the compliance of the respiratory system ($C_{rs}$) is related to the compliance of the lungs and chest wall components as

$$1/C_{rs} = 1/C_L + 1/C_{CW}$$

$C_{rs}$ or $C_{CW}$ can only be measured during complete respiratory muscle relaxation, which is extremely difficult to achieve in conscious patients.

**Measurement of respiratory mechanics in mechanical ventilation**

Respiratory mechanics can be measured in sedated mechanically ventilated patients by recording airflow and pressure at the airway opening ($P_{ao}$). The driving pressure required to overcome the elastic and resistive loads ($E_{rs}$ and $R_{rs}$, respectively) of the respiratory system is

$$P_{ao} = R_{rs} \cdot V' + E_{rs} \cdot V$$

where $V$ is volume. $R_{rs}$ and $E_{rs}$ can be computed by least squares fitting of this equation to $P_{ao}$, $V'$ and $V$ recordings.

In patients ventilated with a constant flow waveform, $R_{rs}$ and $E_{rs}$ can also be measured by performing a post-inspiratory pause. Flow interruption results in a sharp drop in pressure from the peak value at end inspiration ($P_{max}$) to $P_1$, followed by a slow decay to a plateau ($P_2$). The sudden decrease in $P_{ao}$ is associated with the resistive load of the airways. Therefore, $R_{aw}$ is estimated as

$$R_{aw} = (P_{max} - P_1)/V'$$

A higher value of resistance due to the contribution of tissue viscoelasticity and gas redistribution within the lungs is computed from the pressure drop to the plateau ($P_{max} - P_2$).

The additional performance of a post-expiratory pause allows $E_{rs}$ to be computed as the ratio of pressure and volume changes at the end of the post-inspiratory and post-expiratory pauses.

**Respiratory muscle strength**

Since direct measurements of muscular pressure are not clinically available, respiratory muscle performance is commonly assessed by measuring maximal pressures generated at the mouth during maximal inspiratory and expiratory efforts against an occluded airway (or occluded except for a small leak). Maximum expiratory pressure ($P_{E,max}$) is measured at total lung capacity (TLC). Maximum inspiratory pressure measurements ($P_{I,max}$) are taken at either FRC or residual volume (RV). Alternatively, inspiratory muscle strength can be assessed during sniffing with one nostril occluded with a plug. Maximum pressure (sniff $P_{di}$) is recorded into the occluded nostril during a rapid forceful inspiratory sniff performed at FRC.

The clinical testing of maximal respiratory pressures is quick and simple but measurement is dependent on effort. The test is useful for excluding significant respiratory muscle weakness.

**References**

Apart from spirometry, the transfer factor of the lung for carbon monoxide (TL,CO) is the most frequently performed pulmonary function test. It focuses on the integrity of the alveolar (gas exchanging) part of the lung. The TL,CO can detect abnormalities limited to the pulmonary microcirculation, the only routine test which can do so. It helps to think of the TL,CO as a measure of the anatomy of the alveolar region, whereas blood gas measurements (arterial oxygen (P_a,O_2) and carbon dioxide (P_a,CO_2) tension) measure a physiological efficiency, which involves airways and larger blood vessels, as well as alveolar structures. For example, the TL,CO is normal in asthma (alveoli are uninvolved), but the P_a,O_2 may be considerably reduced.

**Definition**

The transfer factor (called the diffusing capacity of the lung for carbon monoxide (DL,CO) in the USA) measures the surface area available for gas exchange. It is closely related to the oxygen diffusing capacity (DL,O_2). TL,CO is the quantity of inhaled CO absorbed, per unit time and per unit CO partial pressure. The pressure gradient is the alveolar-plasma carbon monoxide tension (P_CO) difference. CO is chosen for alveolar-capillary exchange because, after diffusing into capillary blood, CO binds to haemoglobin (Hb) as carboxy-Hb, but at an extremely low partial pressure (P_CO). Plasma P_CO is so low that it is not usually measured, but it may reach significant levels in current smokers. CO uptake is independent of blood flow, but it is dependent on the number of Hb-binding sites, i.e. on capillary volume. “Transfer” is the better term, because chemical reaction as well as “diffusion” is involved.

**Technique**

Nearly all clinical laboratories use the single breath (sb) technique of OGILVIE et al. The TL,CO is measured during a 10-s breath-hold at maximal inspiration (volume = total lung capacity (TLC)).

Breath-holding at TLC optimises the distribution of the inhaled marker gases (He and CO), and makes TL,CO independent of ventilation. The breathing manoeuvre is shown in fig. 1. The subject is asked to: 1) exhale slowly to residual volume; 2) make a signal; 3) inspire rapidly to full inflation; and 4) breath-hold. The breath-hold is assisted by automatic closure of the inspiratory and expiratory valves for a preset time (9–11 s), after which exhalation occurs rapidly (there is no need for a forced expiration) and an alveolar sample taken, from which water vapour and CO_2 are absorbed before He and CO concentrations are analysed.

**Calculation of the TL,CO**

The key point is that the TL,CO is the product of two measurements, the alveolar volume (V_A) and the rate of alveolar uptake of CO, given by the transfer coefficient of the lung for CO (K_CO). During the breath-hold at
maximal inspiration, $V_A$ should equal TLC minus anatomical dead space (97–98% TLC). In practice, $V_A$ in normal subjects = 94% TLC with a lower confidence limit (-1.64 SD) of 83%. The 10-s breath-hold is insufficient time for complete gas mixing; in airflow obstruction, the measured $V_A$ may be much less than 80% of the actual TLC (measured by multi-breath gas dilution or plethysmography).

The $k_{CO}$ is the rate of alveolar uptake of CO during the breath-hold (the slope in fig. 2). It is a rate constant with units of $s^{-1}$ or $min^{-1}$. When normalised to barometric pressure (minus water vapour pressure) ($Pb^*$), $k_{CO}/Pb^* = K_{CO}$ (min$^{-1}$·kPa$^{-1}$). The final step in the calculation of $T_{L,CO}$ is the multiplication of $K_{CO}$ by $V_A$ (in mmol: 1 mmol = 22.4 mL standard temperature, pressure and dry).

$$K_{CO} \times V_A = T_{L,CO} \text{ (mmol·min}^{-1} \cdot \text{kPa}^{-1})$$

$$T_{L,CO}/V_A = K_{CO} \text{ (mmol·min}^{-1} \cdot \text{kPa}^{-1} \cdot \text{L}^{-1})$$

but the units are equivalent to (min$^{-1}$·kPa$^{-1}$).

If $V_A$ remains constant, $T_{L,CO}$ and $K_{CO}$ will change equally (as % predicted). There are formulae to correct $T_{L,CO}$ for anaemia, so the Hb level should always be known. Oxygen breathing with an increase in $P_{A,O_2}$ reduces $T_{L,CO}$ and $K_{CO}$ by competitive antagonism between $O_2$ and $CO$; it is the basis of the Roughton–Forster equation which partitions $1/T_{L,CO}$ (transfer resistance) into $1/DM$ (alveolar–capillary membrane resistance) and $1/\theta_Vc$ (transfer resistance of red cells).

Figure 1. Transfer factor of the lung for carbon monoxide ($T_{L,CO}$) setup and breathing protocol. The breath-hold time is set automatically, and is calculated from $0.33 \times$ inspired time to 1 L expiratory time. $F_{A,CO}$: alveolar carbon monoxide fraction; $F_{A,He}$: alveolar helium fraction; RV: residual volume.
When VA is reduced, TL,CO and KCO may change in opposite directions (table 1) if the cause is a) reduced alveolar expansion, e.g. extrapulmonary restriction, or b) a reduction in aerated alveolar units, e.g. pneumonectomy or consolidation or atelectasis. Other causes of a reduced VA are c) diffuse alveolar damage (emphysema or fibrosis) (TL,CO and KCO both reduced) and d) airflow obstruction (VA low due to poor gas mixing). In d), TL,CO and KCO are variable, being low in emphysema and normal or high in asthma.

Causes of a low KCO (and TL,CO):
- diffuse alveolar damage (fibrosis, emphysema)
- pulmonary vascular diseases
- chronic heart failure
- anaemia

Causes of a high KCO:
- extrapulmonary restriction
- loss of aerated units
- increased pulmonary blood flow
- acute alveolar haemorrhage
- polycythaemia

**Implications of KCO x VA = TL,CO**

1. Transfer factor of the lung (TL)/VA does not correct TL,CO for a low VA because a) TL/VA may rise when VA falls, and b) TL/VA = KCO = the rate constant for alveolar uptake of CO.
2. The same TL,CO (say 60% predicted) can arise from different combinations of KCO and...
VA, such as a) high $K_{CO}$ and low VA (extrapulmonary restriction), b) low $K_{CO}$ and normal VA (pulmonary vasculopathy), or c) low-ish $K_{CO}$ and low-ish VA (fibrosis).

References

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<td>$P_{A,O_2}$ increase</td>
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$P_{A,O_2}$: alveolar oxygen tension; $V_A$: alveolar volume.
CONTROL OF VENTILATION

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Key points

- The slope of the $V'_{E-P_{ET,CO2}}$ relationship ($\Delta V'_{E}/\Delta P_{ET,CO2}$) is driven by central “chemoreceptor” CO$_2$ responsiveness and, if $P_{a,O2}$ is not excessive, also that of peripheral chemoreceptors.

- The hyperoxic rebreathing method appreciably reduces the time demands of the steady-state, constant-concentration inspirate approach for measuring $\Delta V'_{E}/\Delta P_{ET,CO2}$, although $\Delta V'_{E}/\Delta P_{ET,CO2}$ obtained by this method reflects only the activity of the central chemoreflex.

- The isocapnic $V'_{E-P_{ET,CO2}}$ response is curvilinear, and reflects solely the activity of the carotid chemoreceptors. It can be determined by steady-state, constant-concentration inspirates or by rebreathing.

- Expressing the $V'_{E}$ response as a function of $S_{a,O2}$ yields a linear profile of hypoxic responsiveness; the actual $V'_{E}$ stimulus, however, is $P_{a,O2}$ not $S_{a,O2}$.

- The “Dejours” hypoxia-withdrawal test is a further means of estimating hypoxic $V'_{E}$ responsiveness. Abruptly administering 100% O$_2$ from a prior hypoxic background will acutely suppress carotid body hypoxic responsiveness and cause $V'_{E}$ to fall transiently and rapidly; the maximum decrease in $V'_{E}$ as a fraction of the total hypoxic $V'_{E}$ provides the hypoxic index.

The ventilatory control system is highly complex, involving the transmission of primary humoral stimuli from their sites of generation to the sensing elements; the integration of chemoreceptor afferent activity within brainstem "respiratory centres"; the generation of respiratory motor-discharge patterns; neuromuscular transmission at the respiratory muscles; and, finally, the generation of appropriate pulmonary pressure gradients to generate the required airflow and ventilation. Consequently, while the inhalation of hypercapnic or hypoxic gas mixtures, either singly or in combination, is widely utilised to assess the normalcy of ventilatory "chemoreflex" sensitivity, interpretation of the response should be made in the context of the entire "input-output" relationship. Subjects with increased airways resistance or impaired respiratory muscle function, for example, may have an abnormally low overall ventilatory CO$_2$ or hypoxic response despite normal chemoreceptor responsiveness.

Ventilatory response to inhaled CO$_2$

The relationship between minute ventilation ($V'_{E}$) and arterial (a) or alveolar (A; typically end-tidal (ET)) carbon dioxide tension ($P_{CO2}$), with the subject sequentially inhaling a series of progressively greater hypercapnic inspirates (e.g. 3–6%), each for sufficiently long to establish a steady state, is used to estimate overall ventilatory CO$_2$ responsiveness. The resulting $V'_{E-P_{ET,CO2}}$ relationship is typically linear in healthy, normoxic individuals, with a slope ($\Delta V'_{E}/\Delta P_{ET,CO2}$) averaging $\sim 2$–3 L·min$^{-1}$·mmHg$^{-1}$. This slope reflects the CO$_2$ responsiveness of both the central "chemoreceptors", located predominantly on the ventral medullary surfaces, and also, if
arterial oxygen tension (P$_{a,O_2}$) is not excessive, the peripheral chemoreceptors (predominantly, if not exclusively, the carotid bodies in humans). At P$_{a,O_2}$ levels of ~90 mmHg, the central component accounts for 70–75% of the response with the peripheral component accounting for the remainder. However, as the “peripheral” component of CO$_2$ responsiveness increases with reductions of P$_{a,O_2}$ below normal, ΔV′E/ΔPET,CO$_2$ increases with greater (but constant) degrees of hypoxaemia and decreases with greater (but constant) degrees of hyperoxia. This results in a “fan” of hypoxia-dependent CO$_2$ response slopes reflecting altered response “sensitivity” (also termed “potentiation”), with little-or-no change in the extrapolated zero V′E intercept on the PCO$_2$ axis (fig. 1). By contrast, sustained metabolic acidemia or alkalaeemia results in a parallel shift in the CO$_2$ response relationship (i.e. no change in CO$_2$ “sensitivity”) with a reduced or increased zero V′E intercept, respectively.

The increasing V′E/PET,CO$_2$ slope with greater levels of simultaneous hypoxia reflects a progressively greater carotid body response component; it is crucial, therefore, to maintain P$_{a,O_2}$ constant (iso-oxia) during the test. Above a P$_{a,O_2}$ of ~200 mmHg, the carotid body component is effectively inactivated and hence the sufficiently hyperoxic CO$_2$ response entirely reflects that of the “central” component. Interpreting the result depends on the relationships between the typically measured PET,CO$_2$ (or, less typically, the P$_{a,CO_2}$) and the PCO$_2$ (and local [H$^+$]) at each set of chemoreceptors; these relationships depend on factors such as the local-tissue perfusion, CO$_2$ production, CO$_2$ capacitance, H$^+$ buffering capacity and metabolic rate. The equilibrium process is rapid at the carotid body chemoreceptors, but is considerably delayed at the sites of central chemoreception.

It has been has proposed that three or more levels of inspired (I) PCO$_2$ should be used for the slope characterisation. Each level is maintained for ~8 min, with the average V′E and PET,CO$_2$ over the final 3 min providing the steady-state value. Consequently, the demands of the test are time consuming, although transiently “overshooting” I,CO$_2$ beyond the required level can reduce the time required to attain the new V′E steady-state level.

This concern is obviated, to a considerable extent, by the rebreathing method of READ and LEIGH, which takes a small fraction of the time to perform while providing effectively the same ΔV′E/ΔPET,CO$_2$ values as for the steady-state method. The subject re-breathes from a 6–7 L bag initially containing ~7% CO$_2$ balance O$_2$. The high initial P$_{a,CO_2}$ is designed to raise the P$_{a,CO_2}$ rapidly to, or close to, the mixed-venous level such that the subsequent rebreathing provides an effectively linear increase in P$_{a,CO_2}$; the high inspired oxygen tension (P$_{I,O_2}$) maintains P$_{a,O_2}$ above levels for which variations in carotid chemosensitivity would influence the response slope. The rebreathing relationship is shifted to the right of the steady-state relationship, as a result of both the transit delay between the lungs and the sites of chemoreception and the kinetics of the V′E response. Consequently, as the test is designed to provide a constant rate of change of PCO$_2$ at the chemoreceptor sites,
the rate of change of $V' E$ is compared with the rate of change of $PET,CO_2 (ΔV'E/ΔPET,CO_2)$. This is currently the more common means of assessing $CO_2$ responsiveness. It is important to recognise, however, that the $CO_2$ responsiveness obtained by this hyperoxic method reflects only the activity of the central chemoreflex.

One must be careful, however, not to assume that hypoxia does not influence central chemoreceptor responsiveness; it does indirectly by increasing cerebral blood flow. This tends to "wash out" $CO_2$ from the region, narrowing the difference between the local tissue $P_{CO_2}$ and $P_{a,CO_2}$.

Beginning at a value below the spontaneous control condition, $CO_2$ responsiveness is not characterised by the extrapolated dashed lines in fig. 1. Rather, there is a region of virtual insensitivity to increasing $P_{CO_2}$, if previously lowered by, for example, acute hyperventilation or sufficient hypoxia. The transition from the "insensitive" to the "sensitive" region is considered to reflect a ventilatory recruitment threshold. The difference between this threshold and the lower $PET,CO_2$ at which apnoea ensues is thought to be important in conditions such as sleep apnoea. Also, as this threshold is lower in hypoxia than in hyperoxia, it can be used to further understand the interaction between peripheral and central chemoreceptor mediation. As a practical expedient, the difference in $PET,CO_2$ between these conditions at resting ventilation can be used as an index of the threshold change (Duffin has suggested $PET,O_2$ values of 150 and 50 mmHg for this assessment).

**Estimation of ventilatory response to hypoxia**

The ventilatory response to hypoxia, if defined under isocapnic conditions, is considered solely to reflect the activity of the carotid chemoreceptors. Both constant-concentration inspirates and rebreathing techniques have been successfully utilised for the characterisation.

The pattern of the ventilatory response to a step decrease of $P_{a,O_2}$ is not monotonic, even with $PET,CO_2$ being maintained constant by controlling the inspired level (i.e. isocapnic hypoxia): there is an initial increase to a peak, usually well within 5 min, followed by a slow reduction (termed "hypoxic ventilatory decline") to a final steady-state value (fig. 2a). The initial increase is considered to be the carotid body component and the subsequent decline is thought to result from the hypoxia-mediated increase in cerebral blood flow. This reduces the degree of central chemoreceptor stimulation as a result of cerebral $CO_2$ wash-out, although an involvement of altered neurotransmission has also been proposed. If the hypoxic step is limited to the initial, or primary, response phase, then the resulting $V'E-P_{a,O_2}$ relationship over a range of increasingly hypoxic inspirates is curvilinear, with the $V'E$ rate of change approaching infinity at a $P_{a,O_2}$ of $-30$ mmHg. Naturally, at higher isocapnic $P_{CO_2}$ levels the curvature constant of the response is increased as a result of greater hypoxic-hypercapnic interaction at the carotid bodies. It is recommended that the subject be switched to air or even a mildly hyperoxic mixture between successive hypoxic steady states to avoid possible depression of brainstem respiratory neurones. If, instead of isocapnia being maintained in this test, $P_{a,CO_2}$ is allowed to decrease spontaneously as ventilation increases (poikilocapnia), then both the peak initial response and the final level achieved after the hypoxic ventilatory decline are reduced.

A rebreathing test, notionally similar to the "Read–Leigh" test of $CO_2$ sensitivity, yields considerably greater data density in a significantly shorter period, although the requirement for isocapnia throughout the test does demand a degree of sophistication in obviating, by means of a $CO_2$-absorbing system, the otherwise progressive hypercapnia. The resulting curvilinear response to the progressive isocapnic hypoxia is shown in fig. 2b for two subjects differing markedly in hypoxic sensitivity. There is little, from a physiological standpoint, to choose
between an exponential and a hyperbolic characterisation of the response. The conflicting issues regarding the most appropriate index for hypoxic response characterisation appear to be obviated (on empirical grounds) by the demonstration that the curvilinear $V^E_{9E}$–$P_{a,O2}$ relationship can be transformed into a linear relationship by substituting arterial $O_2$ saturation ($S_{a,O2}$) for $P_{a,O2}$ (fig. 2c):

$$V^E_{9E} = G \cdot S_{a,O2} + V^E_{9E}(0)$$

where $V^E_{9E}(0)$ is the control $V^E_{9E}$ and the slope parameter $G$ is the hypoxic responsiveness quantifier. $G$ has been shown to average $\sim 1.5 \pm 1.0$ (average $\pm$ SD) L·min$^{-1}$-% decrease of $S_{a,O2}$ in normal subjects. At higher isocapnic levels, $G$ is increased as a result of the potentiating effect of $CO_2$ on carotid sensitivity, which sums with the further central $CO_2$–$H^+$ stimulation.

In addition to the ease of measuring $S_{a,O2}$ noninvasively by pulse oximetry, and averting any assumption regarding the difference between $P_{ET,CO2}$ and $P_{a,O2}$, the linearity of the $V^E_{9E}$ response makes this rebreathing method a very practical means of assessing hypoxic ventilatory responsiveness. It is important to recognise, however, that the ventilatory stimulus is $P_{a,O2}$; $S_{a,O2}$ is merely a practical expedient, with uncertainties regarding the influence of conditions altering the haemoglobin affinity for $O_2$. 

Figure 2. Ventilatory time-course to prolonged isocapnic step-decrease in end-tidal oxygen tension ($P_{ET,O2}$; a). Ventilatory response to progressive isocapnic hypoxia (in two subjects) as a function of $P_{ET,O2}$ (b) and oxygen saturation ($SO_2$; c; figure reproduced from Rebuff and Slutsky (1981), with permission from the publisher). Ventilatory time-course to an hyperoxic step-increase in an exercising hypoxic subject with alveolar proteinosis (d; figure reproduced from Wasserman et al. (1989), with permission from the publisher). $P_{ET,CO2}$: end-tidal carbon dioxide tension; $V^E$: minute ventilation; $P_{a,O2}$: oxygen tension.
The current degree of a subject’s hypoxic ventilatory drive may be estimated by the hypoxia-withdrawal test of DEJOURS. If a particular level of $P_{a,O_2}$ is established by inhalation of a hypoxic gas mixture, or noting the spontaneous $P_{a,O_2}$ if the subject is already hypoxaemic (as in fig. 2d for an exercising subject with alveolar proteinosis), then the abrupt administration of 100% $O_2$ will acutely suppress carotid body hypoxic responsiveness and cause $V^E$ to fall transiently and rapidly. The maximum decrease in $V^E$ as a fraction of the total hypoxic $V^E$ provides the hypoxic index. In addition to the assumption (probably justified in humans) that the consequently high level of $P_{O_2}$ actually "silences" the carotid bodies, the validity of the Dejours’ test depends upon the $V^E$-decrement reaching its nadir prior to the subsequently increased $P_{a,CO_2}$ (caused by the reduced $V^E$) influencing central sites of $CO_2$ responsiveness. As the nadir of the response commonly occurs ~20–25 s after the hypoxic–hyperoxic transition, there is some uncertainty regarding this latter point. Although this test is quite easy to perform and provides a useful qualitative estimate of hypoxic responsiveness, it remains to be precisely standardised and quantified.

The peripheral-chemosensory potentiation of the $CO_2$ response by hypoxia may also be used to provide an index of hypoxic ventilatory responsiveness, as follows: 1) from the linear difference between the hyperoxic and the hypoxic $CO_2$ response, and 2) the increase in $V^E$ between the hyperoxic (peripheral chemoreceptors "silenced") and the hypoxic ($40 \text{ mmHg } P_{a,O_2}) CO_2$ response relationship, measured at a standard target level of 40 mmHg $P_{a,CO_2}$ ($\Delta V_{40}$).

**Conclusions**

While these approaches provide indices of acute ventilatory responsiveness, laboratory-based tests of more chronic blood-gas and acid–base regulatory challenges are less well standardised.

**References**

The fundamental function of the lung is to contribute to the homeostasis of the system by ensuring that pulmonary uptake of oxygen \( (V_O2) \) and clearance of carbon dioxide \( (V_{CO2}) \) match with whole-body bioenergetic requirements. We must look at pulmonary function as the first step of the oxygen transport chain from the atmosphere to mitochondria.

Arterial blood gas (ABG) analysis provides direct measurements of partial pressures of oxygen \( (P_{a,O2}) \) and carbon dioxide \( (P_{a,CO2}) \) and pH in arterial blood. In clinical practice, ABG analysis is needed to assess the severity and causes of pulmonary gas exchange impairment and acid–base (A–B) disequilibrium. ABG analysis is one of the most useful diagnostic tests, not only in the critical care setting, but also in general clinical practice, to assess patients with respiratory diseases and those with other disorders with potential impact on pulmonary gas exchange and A–B disturbances (diabetes, heart failure, renal failure). Moreover, ABG analysis is mandatory to establish the diagnosis of respiratory failure.

Modern equipment to perform ABG assessment uses electrodes to measure \( P_{a,O2} \), \( P_{a,CO2} \) and pH. Other variables, such as bicarbonates (actual \( HCO_3^- \) and standard \( HCO_3^- \)), base excess (BE) and oxyhaemoglobin saturation \( (S_a,O2) \) are computed using well-defined equations.

A simple and practical two-step approach for ABG interpretation in the clinical setting is illustrated in figure 1. The first step aims at the analysis of pulmonary gas exchange status based primarily on \( P_{a,O2} \) and \( P_{a,CO2} \), while the second step addresses the assessment of A–B status using \( P_{a,CO2} \), pH and, eventually, \( HCO_3^- \) (or BE).

### Step 1: Evaluation of lung gas exchange

Healthy subjects at sea level breathing room air (inspired oxygen fraction \( (F_{I,O2}) \) 0.21) show \( P_{a,O2} \) values close to 90–95 mmHg. \( P_{a,O2} \) values <80 mmHg are considered arterial hypoxaemia and \( P_{a,O2} \) <60 mmHg indicates...
hypoxaemic respiratory failure. Because of the characteristics of the oxyhaemoglobin dissociation curve, a \( P_{a,O2} \) of 60 mmHg corresponds to a \( S_{a,O2} \) of ~90% and is located at the upper end of the steepest portion of the curve. \( P_{a,O2} \) values <60 mmHg will have a substantial impact, reducing arterial O2 content and compromising tissue oxygenation. The accepted reference interval for \( P_{a,CO2} \) is 35–45 mmHg. By convention, hypercapnic respiratory failure is established at \( P_{a,CO2} \).50 mmHg.

Abnormal levels of respiratory gases in arterial blood are generally due to impaired pulmonary gas exchange. Intrapulmonary factors that may cause arterial hypoxaemia are listed in table 1. Pulmonary ventilation–perfusion (\( V/Q \)) inequality is the most frequent determinant of hypoxaemia and hypercapnia in the clinical scenario. However, the identification of pulmonary shunt (perfusion of unventilated pulmonary units, \( V/Q=0 \)) as the main cause of hypoxaemia in a patient with severe pneumonia has relevant therapeutic implications. It is of note, however, that alterations of extrapulmonary factors such as cardiac output, \( F_{I,O2} \), \( V_O2 \), and minute ventilation are also determinants of \( P_{a,O2} \) and \( P_{a,CO2} \).

When \( P_{a,CO2} \) values are close to 40 mmHg, \( P_{a,O2} \) is an excellent indicator of the efficacy of the lung as an oxygen exchanger, but patients with abnormal \( P_{a,CO2} \) values (hypercapnia or hypocapnia) may benefit from the integrated reading of \( P_{a,O2} \) and \( P_{a,CO2} \) values indicated in table 1. Such an integrated view can be numerically obtained by computing the alveolar-arterial oxygen gradient (\( P_{A-a,O2} \)) using the following simplified formula:

\[
P_{A-a,O2} = \left( \left( P_B - P_{H2O}\right) \times F_{I,O2} - P_{a,CO2} / R \right) - P_{a,O2}
\]

where \( P_B \) is barometric pressure, \( P_{H2O} \) is airway water vapour partial pressure and \( R \) is respiratory quotient (the ratio \( VCO2 \) and \( VO2 \), ~0.8 at rest).

At sea-level, the normal expected \( P_{A-a,O2} \) value is <15 mmHg in young subjects and <20 mmHg in the elderly. Table 1 shows the contribution of \( P_{A-a,O2} \) in the identification of the mechanisms of alteration of ABG.

To further understand the cause of arterial hypoxaemia, the effect of supplemental oxygen breathing on \( P_{a,O2} \) should be examined, keeping in mind that in the normal lung \( P_{A-a,O2} \) widens when breathing additional oxygen. While hypoxaemia due to pulmonary \( V/Q \) inequalities and diffusion defects is usually corrected by increasing inspired oxygen concentrations, this does not correct respiratory failure due to shunt.

A simple, but less accurate, way to compute \( P_{A-a,O2} \) is to use the rule of “130”. It is assumed that in a healthy subject, at sea-level \(( FI,O2 = 0.21 \) ), the sum of \( P_{a,O2} \) and \( P_{a,CO2} \) should be ~130 mmHg. Consequently, the difference between 130 and the sum of \( P_{a,O2} + P_{a,CO2} \) is a surrogate of \( P_{A-a,O2} \). The

Table 1. Arterial–alveolar oxygen gradient \((P_{A-a,O2})\) in the evaluation of the causes of arterial hypoxaemia.

<table>
<thead>
<tr>
<th>Cause</th>
<th>( P_{a,O2} )</th>
<th>( P_{a,CO2} )</th>
<th>( P_{A-a,O2} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoventilation</td>
<td>( \downarrow )</td>
<td>( \uparrow )</td>
<td>( \leftrightarrow )</td>
</tr>
<tr>
<td>( V/Q ) mismatch</td>
<td>( \downarrow )</td>
<td>( \leftrightarrow \ \uparrow )</td>
<td>( \uparrow )</td>
</tr>
<tr>
<td>( O_2 ) diffusion limitation</td>
<td>( \downarrow \ \downarrow )</td>
<td>( \leftrightarrow \ \downarrow \uparrow )</td>
<td>( \uparrow \ \uparrow )</td>
</tr>
<tr>
<td>Shunt</td>
<td>( \downarrow \ \downarrow )</td>
<td>( \leftrightarrow \ \downarrow \uparrow )</td>
<td>( \uparrow \ \uparrow )</td>
</tr>
</tbody>
</table>
The following examples illustrate the use of the rule. A patient with $P_{a,O2}$ 70 mmHg and $P_{a,CO2}$ 60 mmHg ($130 - (P_{a,O2} 70 + P_{a,CO2} 60) = 10$ mmHg) is hypoventilating a lung that is functionally "normal", with a $P_{A-a,O2}$ within the reference interval. On the other hand, a patient with hypoxaemic respiratory failure and hypocapnia ($130 - (P_{a,O2} 50 + P_{a,CO2} 20) = 60$ mmHg) shows worse pulmonary oxygen exchange (higher $P_{A-a,O2}$).

**Table 2. Respiratory failure**

**Hypoxaemic respiratory failure**
- $P_{a,O2} < 60$ mmHg, $P_{a,CO2}$ normal or low, at sea-level ($F_{I,O2} 0.21$)
  - Hypoxaemia due to pulmonary $V/Q$ mismatching ($P_{a,O2}$ rises with $F_{I,O2}$)
  - Chronic respiratory diseases (only pulmonary fibrosis shows oxygen diffusion limitation with $V/Q$ mismatch)
  - Hypoxaemia due to intrapulmonary shunt (lung units with $V/Q = 0$) ($P_{a,O2}/F_{I,O2} < 200$ mmHg)

**Hypercapnic respiratory failure**
- $P_{a,CO2} > 50$ mmHg and $P_{a,O2}$ low, at sea-level ($F_{I,O2} 0.21$)
  - "Normal" lung ($P_{A-a,O2}$ gradient preserved)
  - Reduced alveolar ventilation due to extrapulmonary factors
  - Advanced chronic respiratory disease or severe exacerbation
  - Hypoxaemia due to pulmonary $V/Q$ mismatch

---

**Figure 2. Arterial carbon dioxide tension ($P_{a,CO2}$)–pH nomogram for the diagnosis of acid–base disorders.**

$P_{a,CO2}$–pH values that fall into acute or chronic, respiratory and nonrespiratory (or metabolic) "bands" should be considered as "simple" disorders (Case 1: $P_{a,CO2}$ 70 mmHg, pH 7.19, acute respiratory acidosis). $P_{a,CO2}$–pH values that fall between respiratory and metabolic "bands" should be considered as "mixed" disorders (Case 2: $P_{a,CO2}$ 40 mmHg, pH 7.20, acute respiratory and metabolic acidosis). N: normal.
than a patient with respiratory failure and hypercapnia \((130 - (P_{a,O2} 50 + P_{a,CO2} 50) = 30 \text{ mmHg})\). The computation of the \(P_{A-a,O2}\) (and the use of the rule of 130) is not useful clinically when \(F_i,O2\) increases. Calculating the \(P_{a,O2}/F_i,O2\) ratio is recommended to assess the efficacy of the lung as an oxygen exchanger in critical care when comparing ABG measurements taken at different \(F_i,O2\) levels. Lung injury is defined as \(P_{a,O2}/F_i,O2 < 300\) while acute respiratory distress syndrome (ARDS) is associated with a \(P_{a,O2}/F_i,O2\) ratio \(< 200\) (table 2).

### Step 2: Diagnosis of A–B disorders

Arterial pH is highly regulated to be maintained between 7.38–7.42. In the clinical assessment of A–B equilibrium, two main determinants of arterial pH must be taken into account, namely: the respiratory component \((P_{a,CO2})\) and the metabolic component. Hypercapnia (high \(P_{a,CO2}\)) generates respiratory acidosis (low pH) whereas hypocapnia (low \(P_{a,CO2}\)) is associated to respiratory alkalosis (high pH). In simple acute respiratory disorders, for each 10 mmHg variation in \(P_{a,CO2}\), the expected change in pH is 0.07 for acidosis and 0.08 for alkalosis, while in simple chronic respiratory disorders it is 0.03 for both acidosis and alkalosis.

The metabolic component refers to the impact of nonvolatile molecules generating acidosis or alkalosis. The variable most often used to assess the metabolic component is bicarbonate \([HCO_3^-]\), computed through the Henderson–Hasselbalch equation:

\[
\text{pH} = 6.1 + \log \left( \frac{[HCO_3^-]}{0.03 \times P_{a,CO2}} \right)
\]

In the past, the role of simple rules associating changes in \(P_{a,CO2}\) with changes in pH (and \(HCO_3^-\)) was emphasised as useful for the diagnosis of simple and mixed A–B disorders. A graphical illustration of this approach is shown in figure 2.

Table 3 displays some examples of simple A–B disorders.

The first two rows in table 3 indicate simple, uncompensated, A–B disorders. The first row may correspond to a chronic obstructive pulmonary disease patient with an episode of severe exacerbation showing acute hypercapnia leading to respiratory acidosis.

### Table 3. Examples of simple acid–base disorders

<table>
<thead>
<tr>
<th></th>
<th>pH</th>
<th>(P_{a,CO2})</th>
<th>([HCO_3^-])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory acidosis</td>
<td>↓</td>
<td>↑</td>
<td>←</td>
</tr>
<tr>
<td>Respiratory alkalosis</td>
<td>↑</td>
<td>↓</td>
<td>←</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

\(P_{a,CO2}\): arterial carbon dioxide tension; \([HCO_3^-]\): bicarbonate concentration.

### Table 4. Respiratory disorders

<table>
<thead>
<tr>
<th></th>
<th>Respiratory acidosis</th>
<th>Respiratory alkalosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system depression, neuromuscular disorders</td>
<td></td>
<td>Anxiety, central nervous system disorders</td>
</tr>
<tr>
<td>Chest wall abnormalities</td>
<td></td>
<td>Hormones/drugs (catecholamine, progesterone, hyperthyroidism, salicylate)</td>
</tr>
<tr>
<td>Lung diseases</td>
<td></td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypoxia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liver diseases</td>
</tr>
</tbody>
</table>
The second example fits with any situation leading to hyperventilation and low $P_{a,CO_2}$ that generates respiratory alkalosis (e.g. interstitial oedema in heart failure). The third row indicates an example of acidosis due to a metabolic disturbance (e.g. exercise-related increase in blood lactate, ketoacidosis, renal failure). Finally, the fourth example of A–B disequilibrium corresponds to a metabolic alkalosis that may be seen in patients with liquid depletion and low intracellular and serum potassium concentrations (e.g. excessive diuretic therapy).

Common causes of A–B disorders are illustrated in tables 4 and 5. It is of note that although they may begin as simple disorders (respiratory or metabolic), they often evolve to become mixed A–B abnormalities.

Table 5. Metabolic disorders

<table>
<thead>
<tr>
<th>Metabolic acidosis</th>
<th>Normochloraemic acidosis (or high anion gap acidosis)</th>
<th>Ketoacidosis</th>
<th>Lactic acidosis</th>
<th>Renal failure</th>
<th>Toxins</th>
<th>Hyperchloraemic acidosis (or normal anion gap acidosis)</th>
<th>Extra-renal loss of Na⁺</th>
<th>Renal tubular acidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic alkalosis</td>
<td>Chloride-responsive type</td>
<td>Gastric fluid loss</td>
<td>Volume contraction</td>
<td>Chloride-resistant type</td>
<td>Mineral corticoid disorders</td>
<td>Milkalkali and Bartter syndromes</td>
<td>Hypoalbumin</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3. Comprehensive approach to interpreting arterial blood gases. $V/Q$: ventilation/perfusion; $V_A$: alveolar ventilation; $P_{A,O_2}$: alveolar-arterial oxygen gradient; $P_{a,O_2}$: arterial oxygen tension; $P_{a,CO_2}$: arterial carbon dioxide tension; AG: anion gap; Cl⁻: chloride; U: urinary.
Conclusion

In clinical practice, the correct interpretation of ABG provides unique information on the characteristics and severity of lung gas exchange impairment and on A-B abnormalities. It represents a fundamental step towards an appropriate diagnosis of the patient and the adoption of the treatment strategy. Figure 3 summarises the interpretative “integrative” approach to be used in the evaluation of ABG. As a first step (Step 1), the combined reading of $P_a,O_2$ and $P_a,CO_2$ values, on room air and during supplemental oxygen breathing, should be used to identify the causes and the severity of arterial hypoxaemia (blue squares and blue circles). As a second step (Step 2), the combined reading of $P_a,CO_2$ and pH is needed for the correct diagnosis of A-B disorders (red squares). Furthermore, the study of serum electrolytes, and in particular serum chloride, may be of great help in the identification of the causes of metabolic disorders (red squares; further step, Step 3).

References

EXERCISE TESTING

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The ability to exercise largely depends on the integrated physiological responses of the respiratory, cardiovascular and skeletal muscle systems. In healthy individuals exercise tolerance is influenced by age, sex and level of fitness. In patients with lung diseases, exercise tolerance is typically reduced and limited by symptoms, such as dyspnoea and leg fatigue.

Cardiopulmonary exercise testing (CPET), i.e. the study of ventilatory and pulmonary gas exchange variables during symptom-limited incremental exercise, is considered the “gold standard” for evaluating the degree and the causes of exercise intolerance in disease states. Moreover, CPET has been extensively utilised in patients with chronic obstructive lung disease (COPD), cystic fibrosis (CF), interstitial lung diseases (ILD) and pulmonary vascular disorders (PVD). In COPD and CF, exercise tolerance is mainly limited by pulmonary mechanic abnormalities (e.g. reduction in ventilatory capacity, dynamic hyperinflation); in ILD exercise tolerance is limited by ventilatory constraints and pulmonary gas exchange abnormalities (e.g. arterial oxygen desaturation); in PVD, both circulatory (e.g. reduced adaptation in cardiac output) and pulmonary gas exchange abnormalities contribute to exercise intolerance.

Some causes of exercise intolerance in lung diseases:

- ventilatory limitation to exercise,
- dynamic hyperinflation,
- increased work of breathing,
- pulmonary gas exchange abnormalities,
- excessive perception of symptoms,
- impaired cardiovascular response to exercise,
- reduced oxygen delivery, and
- peripheral muscle weakness/dysfunction.

Exercise protocols

The symptom-limited maximal incremental exercise protocol is recommended as a first step in the evaluation of exercise tolerance. Minute ventilation ($V_e$), cardiac frequency ($f_c$), oxygen uptake ($V_{O2}$), CO₂ output ($V_{CO2}$) and the end-tidal O₂ and CO₂ are the primary variables measured, typically on a breath-by-breath basis using computerised systems. Additional required measurements include: ECG, blood pressure, dyspnoea and leg discomfort, exercise-related arterial O₂ desaturation and dynamic hyperinflation. Careful selection of patients minimises the likelihood of serious complications during maximal incremental exercise testing. Myocardial infarction (within 3–5 days), unstable angina, severe arrhythmias, pulmonary embolism, dissecting aneurism, pulmonary embolism, dissecting aneurism.

Key points

CPET is considered the gold standard for:

- an objective measure of exercise capacity
- identifying the mechanisms limiting exercise tolerance
- establishing indices of the patient’s prognosis
- evaluating the effects of therapeutic interventions
and severe aortic stenosis represent absolute contraindication to CPET. Resting lung function measurement and ECG are usually obtained before CPET. Cycle and treadmill exercise have been utilised interchangeably, although the former is largely utilised as the work rate for incremental and endurance tests is easier to quantify. As the exercise period should last 10–12 min, the work rate increment should be selected carefully. In patients with lung diseases the usual rate of workload increase is 10 Watt·min⁻¹, although slower or faster rates are possible in the very sick and in fitter patients, respectively. The maximal incremental exercise test is also utilised to determine the appropriate work rate to be used in an endurance protocol.

Constant work rate (CWR) tests, on either a cycle ergometer or a treadmill, are utilised for the measurement of exercise “endurance” tolerance and ventilatory and pulmonary gas exchange kinetics. CWR exercise results in steady-state responses when work rate is of moderate intensity (i.e. below the lactate threshold, \( h_L \)); conversely, high intensity CWR exercise (i.e. above the \( h_L \)) results in steady states either being delayed or not attained at all.

Walking tests, such as the 6-min walking test (6-MWT) have been increasingly utilised for the assessment of exercise tolerance in chronic lung diseases. The object of this test is to walk as far as possible for 6 min. The test should be performed indoors along a 30-m flat, straight corridor; encouragement significantly increases the distance walked. Measurements of arterial \( O_2 \) saturation by pulse oximetry (\( S_{pO_2} \)), \( f_C \) and exertional symptoms are recommended during the 6-MWT.

**Indications to CPET**

In patients with lung diseases, exercise testing is mainly utilised for functional and prognostic purposes. Other indications include detection of exercise-induced bronchoconstriction, selection of candidates for surgery including lung transplant, and evaluation of the effects of therapeutic intervention including pulmonary rehabilitation.

**Exercise variables and indexes**

**Peak oxygen uptake (\( V'_{O_2,peak} \))** The classical criterion for defining exercise intolerance and classifying degrees of impairment is the \( V'_{O_2,peak} \). With good subject effort on an incremental test, \( V'_{O_2,peak} \) reflects a subject’s maximal aerobic capacity (“maximum” \( V'O_2 \)). This index is taken to reflect the attainment of a limitation in the \( O_2 \) conductance pathway from the lungs to the mitochondria. Values \(<80\%\) predicted are considered abnormal while values \(<40\%\) of the predicted indicate severe impairment.

**Lactate threshold (\( h_L \))** The \( h_L \) is the highest \( V'O_2 \) at which arterial lactate is not systematically increased, and is estimated using an incremental test. It is considered an important functional demarcator of exercise intensity. Sub-\( h_L \) work rates can normally be sustained for prolonged periods. \( h_L \) is dependent on age, sex, body mass and fitness. Noninvasive estimation of \( h_L \) requires the demonstration of an augmented \( V'CO_2 \) in excess of that produced by aerobic metabolism, and its associated ventilatory sequelae.

**\( O_2 \) pulse** The \( O_2 \) pulse is the product of the stroke volume and difference between the arterio-mixed venous \( O_2 \) content (\( C_{aO_2}-C_{vO_2} \)). Given the Fick equation (\( V'O_2 = cardiac output \cdot (C_{aO_2}-C_{vO_2}) \)), the \( O_2 \) pulse can be calculated as follows:

\[
O_2 \text{ pulse} = V'O_2/f_C
\]

In patients with ILD, the \( O_2 \) pulse at peak exercise is lower and its rate of increase with increasing work rate is usually reduced because of the reductions in stroke volume and \( C_{aO_2} \). In PVD, the \( O_2 \) pulse is characteristically low at peak exercise and may not increase during incremental exercise, reflecting the abnormal \( CO \) adaptation.

**Heart rate reserve (HRR)** The peak cardiac frequency (\( f_C,\text{peak} \)) achieved on a symptom-limited exercise test decreases with age. The most commonly used equation to predicted peak cardiac frequency (\( f_C,\text{peak pred} \))
HRR is defined as the difference between $\dot{f}_{C,peak\ pred}$ and $\dot{f}_{C,peak}$. In healthy individuals, HRR is virtually zero; a high HRR is usually observed in patients with COPD, CF and ILD.

**$\dot{V}^{'E}/\dot{V}^{'}CO_2$ slope and ventilatory equivalent for CO$_2$** It is conventional to express the ventilatory response to exercise relative to $\dot{V}^{'}CO_2$. It can be measured as the slope of the $\dot{V}^{'}E$-$\dot{V}^{'}CO_2$ relationship ($\Delta \dot{V}^{'}E/\Delta \dot{V}^{'}CO_2$) over its linear region, i.e. typically extending from "unloaded pedalling" to the respiratory compensation point. In normal individuals, $\Delta \dot{V}^{'}E/\Delta \dot{V}^{'}CO_2$ values of $\sim 23-25$ have been reported.

The adequacy of the ventilatory response to exercise is also expressed by the ratio $\dot{V}^{'}E/\dot{V}^{'}CO_2$ that represents the litres of ventilation necessary to clear 1 L of CO$_2$. Up to the respiratory compensation point, $\dot{V}^{'}E/\dot{V}^{'}CO_2$ declines curvilinearly as the work rate increases. It is common practice to record the value at $\dot{hL}$ ($\dot{V}^{'}E/\dot{V}^{'}CO_2@\dot{hL}$) or the minimum value ($\dot{V}^{'}E/\dot{V}^{'}CO_2,min$). These have each been proposed to provide noninvasive indices of ventilatory inefficiency. In normal individuals, $\dot{V}^{'}E/\dot{V}^{'}CO_2@\dot{hL}$ values of 25–28 have been reported. Several factors may increase $\Delta \dot{V}^{'}E/\Delta \dot{V}^{'}CO_2$ and $\dot{V}^{'}E/\dot{V}^{'}CO_2@\dot{hL}$, e.g. hypoxaemia, acidosis, increased levels of wasted ventilation and pulmonary hypertension.

**Breathing reserve (BR)** BR provides an index of the proximity of the ventilation at the limit of tolerance ($\dot{V}^{'}E,max$) to the maximal achievable ventilation (MVV, estimated from the subject’s resting forced expiratory volume in 1 s $\times$ 40). BR can be defined as $\dot{V}^{'}E,max$ as a percentage of MVV (i.e. $1-\dot{V}^{'}E,max$/MVV). In COPD, CF and ILD, BR is usually reduced or absent at peak CPET exercise (fig. 1). Analysis of the flow–volume loops is also emerging as an important tool to assess the degree of airflow and ventilatory limitation during exercise in patients with COPD.

**Dynamic hyperinflation** In normal subjects, end-expiratory lung volume (EELV) decreases with increasing work rate by as much as 0.5–1.0 L below functional residual capacity. Changes in EELV during exercise can be estimated by asking the subject to perform an inspiratory capacity manoeuvre at a selected point in the exercise test. In COPD, particularly in the advanced phases of the disease, EELV increases during exercise (i.e. dynamic hyperinflation) in spite of expiratory muscle activity.

**Arterial O$_2$ desaturation** During exercise, $\dot{S}p,O_2$ is normally maintained in the region of $\sim 97–98\%$. However, arterial oxygen desaturation can be observed in patients with moderate-to-severe ILD and in patients with primary pulmonary hypertension.

**Tolerable limit of exercise (Tlim) and “isotime” measurements** Tlim is expressed as a function of time measured during CWR protocols. In clinical practice, high-intensity ($\sim 70–80\%$ Watt max) CWR protocols are utilised for the evaluation of interventions. In addition to Tlim, measurement of pertinent physiological variables (e.g. $\dot{V}^{'}E$, inspiratory capacity, dyspnoea) at standardised time ("isotime") are obtained.
CPET response patterns

Ventilatory response  The ventilatory response to exercise in patients with lung disorders is abnormal. Conventionally, the ratio of $V^e$ at peak exercise to the estimated MVV represents the assessment of the ventilatory limitation or of the prevailing ventilatory constraints. Ventilatory limitation is commonly judged to occur when $V^e$/MVV exceeds 85%. In lung diseases, the increase in $V^e$/MVV may reflect the reduction in MVV but also the increase in $V^e$. The ventilatory response during exercise is influenced by metabolic rate ($V^cO_2$), the arterial carbon dioxide tension ($P_{a,CO_2}$) and the physiological dead space fraction of the tidal volume ($V^d/V^t$). The relationship existing among these variables is described by the following equation:

$$V^e = 863 \times V^cO_2/P_{a,CO_2} \times (1-V^d/V^t)$$

(where 863 is a constant, $P_{a,CO_2}$ is the arterial carbon dioxide partial pressure in Torr and $V^d/V^t$ is the dead space ($V^d$) expressed as a fraction of the tidal volume ($V^t$)). In lung diseases, for a given $V^cO_2$ and $P_{a,CO_2}$, $V^e$ is usually increased because of a higher $V^d/V^t$. $\Delta V^e/\Delta V^cO_2$ or $V^e/V^cO_2@V_{OL}$ are often utilised in the functional assessment of patients with lung diseases (e.g. COPD, ILD, PVD). $V^e/V^cO_2$ is usually increased, particularly in patients with PVD.

Pulmonary gas exchange  The efficiency of pulmonary gas exchange can be assessed by studying the magnitude of alveolar-arterial $O_2$ partial pressure difference ($P_{a-a,O_2}$), at rest and during exercise. Normally, arterial $O_2$ partial pressure ($P^aO_2$) does not decrease during exercise, and $P_{a-a,O_2}$ at peak exercise usually remains below 20–30 Torr. In most patients with ILD and PVD, pulmonary gas exchange efficiency is impaired, as indicated by an abnormally large $P_{a-a,O_2}$ (>30 Torr) at peak exercise accompanied by arterial $O_2$ desaturation. These changes reflect regional ventilation-perfusion ratio ($V^A/Q^V$) dispersion and alterations in pulmonary capillary transit time resulting from the recruited pulmonary-capillary volume becoming inadequate for the high levels of pulmonary blood flow.

Cardiovascular response  CPET has proved very useful in the detection and quantification of cardiovascular abnormalities during exercise. The characteristic findings are a reduced $V^O_2,peak$, reduced $h_{LV}$, steeper $f_{C-V^O_2}$ relationship (with a reduced HRR at peak exercise), and a shallower profile (or even flattening) of the $O_2$ pulse increase with increasing $V^O_2$. An abnormal cardiovascular response to exercise is observed in PVD and in particular in patients with idiopathic pulmonary arterial hypertension.

Exercise testing in prognostic evaluation  Exercise tolerance is well recognised as a valuable predictor of mortality in healthy subjects. This also appears to be the case in chronic pulmonary diseases. Exercise testing has become an essential component in the prognostic evaluation of patients with lung diseases.

Several studies have confirmed that $V^O_2,peak$ is superior to other indexes in the risk stratification of patients with end-stage lung diseases; many centres, however, utilise field tests for prognostic purposes.

Table 1. Cardiopulmonary exercise testing prognostic indices

<table>
<thead>
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<th>COPD</th>
<th>ILD</th>
<th>CF</th>
<th>PVD</th>
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<tbody>
<tr>
<td>↓ $V^O_2,peak$</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>↑ $V^e/V^cO_2$</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial $O_2$</td>
<td>↓+</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; CF: cystic fibrosis; PVD: pulmonary vascular disorders; ↓: decreased; $V^O_2,peak$: peak oxygen uptake; ↑: increased; $V^e$: minute ventilation; $V^cO_2$: CO2 output.

ERS Handbook: Respiratory Medicine
Evaluating the effects of therapeutic interventions

High-intensity endurance CWR protocols, performed on a cycle ergometer or on a treadmill, to the Tlim have been successfully utilised in COPD patients for the evaluation of the effects of therapeutic interventions (e.g. bronchodilators, oxygen, heliox, rehabilitation).

References

Bronchial provocation testing (BPT) may be done with several different aims in mind, as part of research and in the clinical setting, and with several different chemical substances. It may be done to test specific bronchial responsiveness (BR) to an allergen using the allergen bronchial provocation test, or to test nonspecific BR using a bronchial provocation test to histamine (a mediator substance) or metacholine (a transmitter substance), as well as several other different substances (table 1).

Methods of BPT

Testing BR has been divided into direct and indirect methods. Metacholine BPT and histamine BPT represent direct methods, using a transmitter substance (metacholine) or a mediator (histamine) as test agents. Indirect methods include exercise testing (which may also be regarded as a bronchial provocation test, but which otherwise is regarded to fall outside the present topic), inhaled AMP, mannitol and eucapnic voluntary hyperventilation tests. The indirect tests commonly act by causing mediator or transmitter release and their effect on inflammatory cells and nerves.

Previously, BPT was done qualitatively by inhaling the test substance at a 10-fold increase in concentration; however, during the last 25 yrs a quantitative assessment by doubling the concentration/dose of the test substance has been done.

Key points

- BPT with metacholine/histamine is a sensitive measure of asthma, but not so specific when compared with other chronic lung diseases.
- BPT with indirect measures (exercise, adenosine monophosphate, hypertonic saline, mannitol, eucapnic voluntary hyperpnoea) are specific, but not sensitive.
- Indirect measures of BR (exercise, etc.) respond rapidly (over 1–4 weeks) to inhaled steroids.
- Direct measures of BR (metacholine, histamine) respond slowly (over 3 months or more).
- Direct measures of BR (metacholine, histamine) are presently the most exact monitoring tool for asthma.
Taking bronchial provocation with metacholine as an example, fig. 1 shows the reduction in forced expiratory volume in 1 s (FEV₁) caused by inhaling doubling doses of metacholine, with interpolation on the x-axis to determine the concentration of metacholine to cause a 20% decrease in FEV₁ (PC₂₀). Later, a simplification of the test was introduced by inhaling single doubling doses of metacholine, determining PD₂₀ (the dose of the test agent causing a reduction in FEV₁ of 20%). As it is easier and quicker to determine PD₂₀ as compared with PC₂₀, PD₂₀ may be recommended for clinical routine use.

The test is performed under standardised conditions, with specified nebulisation rates for the tidal breathing method (PC₂₀), inhaling the test agent for 2 min, then measuring FEV₁, and then inhaling the doubling concentration. The test is stopped when FEV₁ is reduced by ≥ 20%, and the PC₂₀/PD₂₀ determined by interpolating on the semi-logarithmic dose–response curve (fig. 1).

When determining BR by measuring PD₂₀, the cumulative inhaled dose is determined. This is done by inhaling doubling doses of the test substance. The delivering device most often used at present as is an inspiration-triggered nebuliser, such as the Spira nebuliser (Spra Respiratory Care Centre, Hameenlinna, Finland) or the Aerosol Provocation System (APS) (Jaeger, Wuerzburg, Germany). Alternatively a hand-held DeVilbiss nebuliser (DeVilbiss Healthcare, Somerset, PA, USA) may be used.

Determination of PC₂₀ or PD₂₀ are used both for BPT with metacholine and histamine as well as with AMP, and may be used for allergen BPT. A BPT with mannitol was recently developed and launched commercially by inhaling cumulative doses of mannitol through a powder inhaler. Here a 15% reduction in FEV₁ (PD₁₅) is used as the cut-off point.

Eucapnic voluntary hyperventilation (EVH) may also be seen as a bronchial provocation test. In this test, the subject inhales dry air with 5% CO₂ for 6 min at a preferred ventilation rate of 85% of maximum voluntary ventilation (MVV), often calculated

<table>
<thead>
<tr>
<th>Bronchial responsiveness</th>
<th>Test method</th>
<th>Bronchial provocation test substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific</td>
<td>Direct</td>
<td>Allergen bronchial provocation test</td>
</tr>
<tr>
<td>Nonspecific</td>
<td>Direct</td>
<td>Metacholine</td>
</tr>
<tr>
<td></td>
<td>Indirect</td>
<td>Histamine</td>
</tr>
<tr>
<td></td>
<td>Indirect</td>
<td>Exercise test</td>
</tr>
<tr>
<td></td>
<td>Indirect</td>
<td>Inhaled AMP</td>
</tr>
<tr>
<td></td>
<td>Indirect</td>
<td>Inhaled mannitol</td>
</tr>
<tr>
<td></td>
<td>Indirect</td>
<td>Eucapnic voluntary hyperventilation</td>
</tr>
</tbody>
</table>

AMP: adenosine monophosphate.
as FEV1 × 30, but tolerating a ventilation rate down to 65% of MVV (FEV1 × 22). A reduction in FEV1 ≥ 10% is taken as a positive test. EVH test has been shown to be particularly sensitive for asthmatic athletes, in particular endurance athletes.

**Clinical relevance of BPT**

Previously, allergen BPT was often used qualitatively to diagnose asthma, and to demonstrate the reaction of the airways to the allergen. This has changed during recent years through fear of worsening the asthma after such a bronchial provocation test. A long-lasting worsening of nonspecific bronchial hyperresponsiveness was demonstrated after performing an allergen bronchial provocation test, thus the allergen bronchial provocation test is now mostly a tool in research projects, and is not used in clinical practice.

Conversely, the different measures of nonspecific bronchial hyperreactivity are often used, both in a research context, but also in a clinical setting. With the diagnosis of asthma in mind, the direct measures of bronchial hyperreactivity are seen as most sensitive for bronchial asthma, whereas indirect measures are considered to be more specific and less sensitive. In asthma patients from an outpatient clinic compared with healthy subjects, histamine BR was found to be more sensitive but less specific in discriminating asthmatics from healthy subjects. Compared with exercise testing, metacholine bronchial provocation tests were more sensitive, but were markedly less specific for discriminating between asthma and other chronic lung diseases; when adding cold air inhalation to exercise, a sensitivity comparable with metacholine was reached, while maintaining the sensitivity. In a general population of university students, a PC20 > 8 mg·mL⁻¹ ruled out current asthma, whereas a value <1 mg·mL⁻¹ was diagnostic of current asthma symptoms.

Other differences are also found between direct and indirect BR. Indirect BR is rapidly influenced by treatment with inhaled steroids, with the first effects already appearing after 1 week, whereas metacholine BR needed several months of inhaled steroids treatment to show an effect.

Results of BPT may be used to monitor the effect of treatment in asthma. It has been shown that metacholine BPT is superior to clinical assessment and lung function measurements in the follow-up of asthma patients. By monitoring the effect of treatment of asthma with inhaled steroids by follow-up using metacholine BPT as compared with follow-up based upon clinical symptoms and lung function measurements, it was shown that follow-up by metacholine BPT improved asthma control and had a positive effect upon airways remodelling, as assessed by bronchial biopsies.

Thus, BPT with various substances and performed in a standardised measure is probably, at the present time, the best tool for the continuing follow-up of asthma patients.

**References**

Recently, noninvasive techniques such as induced sputum and exhaled breath analysis have been successfully established to reveal an inflammatory status and to find oxidative stress indicators in the airways involved in the pathogenesis of lung diseases. These techniques allow longitudinal sampling of various lung biomarkers of inflammation in the same individual, providing a possibility to monitor the lung damage process and evaluate treatment strategies in patients with respiratory diseases, including children.

**Induced sputum**

Induced sputum is one of the most referenced methods used to determine airway inflammation in asthma, chronic obstructive pulmonary disease (COPD) and chronic cough both in research and in clinical practice. The induced sputum technique is a relatively noninvasive method allowing sampling of low airway secretions from patients who are not able to produce sputum spontaneously.

**Procedure** Sputum induction consists of inhalation of nebulised saline solution (isotonic or hypertonic) over different time periods and subsequent expectoration of secretions into a Petri dish.

The subject is asked to inhale 200 mg of salbutamol before induction, and forced expiratory volume in 1 s (FEV1) is monitored before and after each inhalation to either prevent or detect possible bronchoconstriction.

---

**Key points**

- Sputum and exhaled breath analysis are useful noninvasive tools to appraise airway inflammation, particularly in a longitudinal sense.
- Healthy sputum is rich in macrophages and neutrophils but poor in eosinophils, lymphocytes and epithelial cells.
- Many inflammatory mediators can be measured in the fluid phase of sputum.
- Although further validation of many assays is needed, exhaled breath analysis can reveal markers of both asthma and COPD.

After collection, sputum sample is processed according to a standardised method and centrifugation is required to separate sputum cells from the fluid phase.

**Safety issues** Sputum induction is a simple, safe and well-tolerated procedure even in patients with severe lung diseases and exacerbations. It is recommended to use experienced personnel and to apply standard operating procedures taking into consideration the degree of airway obstruction, to use a modified protocol for subjects with severe airway obstruction, and to assess lung function and symptoms during the procedure. Sputum induction is considered
to be safe if the fall in FEV1 is within 5% of baseline after waiting 15 min. Excessive airway constriction may occur in asthmatics and patients with COPD if they show a fall in FEV1 of > 20%. This adverse effect can affect 11% of asthmatics and patients with COPD.

**Cell counts in different diseases** A sputum sample from a healthy subject is rich in macrophages and neutrophils and poor in eosinophils, lymphocytes and epithelial cells. These reference parameters can be used for comparison with cell counts obtained from patients with airway inflammation pathology.

Asthma is characterised by sputum eosinophilia, which predicts a favourable response to corticosteroids. However, non-eosinopilic asthma accounts for 25–55% of steroid-naive asthmatics and it is associated with a poor response to corticosteroids.

In COPD, neutrophils are usually increased and they are associated with reduced FEV1, suggesting that neutrophilic airway inflammation is functionally relevant. Up to 40% of subjects with COPD have a high eosinophil count, which appears to predict a response to corticosteroid therapy.

In up to 40% of subjects with chronic cough, a sputum eosinophil count >3% is shown. These subjects with cough and sputum eosinophilia have an objective response to corticosteroid treatment. Conversely, patients without sputum eosinophils do not respond.

Many inflammatory mediators can be measured in the fluid phase of sputum. These mediators belong to the class of granulocyte proteins, leakage markers, cytokines and chemokines, eicosanoids and proteases.

Table 1 summarises cellular and fluid phase markers of airway inflammation in different pulmonary diseases.

**Reproducibility and validity** The method of induced sputum induction is reproducible, sensitive and valid. The reproducibility is documented within sample, between samples and between examiners for all types of cells. A standardised methodology of sputum induction and processing was issued in 2002.

### Table 1 Biomarkers in induced sputum

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Asthma</th>
<th>COPD</th>
<th>Cystic fibrosis</th>
<th>Sarcoidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cellular phase</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCC</td>
<td></td>
<td></td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>CD8+</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fluid phase</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECP, MPO, albumin, fibrinogen, nonkinase plasminogen activator, plasmonogen activator inhibitor, neurokinin A, IL-8, IL-13, Cys-LTs, 8-isoprostane, MMP9/TIMP ratio</td>
<td>IL-8, IL-6, TNF-α, IL-10, leptin, MPO, HNL, NE, ECP, EPO, LTB-4, GRO-α, MCP-1, GM-CSF, MMP-1, -8, -9, -12, hyaluronan</td>
<td>IL-8, NE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

↑: increased level; COPD: chronic obstructive pulmonary disease; TCC: total cell count; ECP: eosinophil cationic protein; MPO: myeloperoxidase; IL: interleukin; Cys-LTs: cysteinyl leukotrienes; MMP9: matrix metalloproteinase-9; TIMP: tissue inhibitor of metalloproteinases; TNF: tumour necrosis factor; HNL: human neutrophil lipocalin; NE: neutrophil elastase; EPO: eosinophil peoxidase; LTB-4: leukotriene B-4; GRO-α: growth related oncogen-α; MCP-1: monocyte chemotactic protein-1; GM-CSF: granulocyte-macrophage colony-stimulating factor; MMP: metalloproteinases.
by the European Respiratory Society Task Force in order to provide guidance for the reproducibility of the results obtained.

Examination of samples obtained from patients with different respiratory diseases demonstrated significant differences in cell counts, confirming the validity of the technique. Reference values and the distribution of cell counts in induced sputum were established on a large number of samples from healthy subjects.

**Exhaled breath**

Measuring biomarkers in breath is important in monitoring airways inflammation and oxidative stress. Exhaled breath analysis can be defined as analysis of exhaled gases and/or exhaled breath condensate (EBC).

Variable-sized particles or droplets that are aerosolised from the airway lining fluid, distilled water that condenses from gas phase out of the nearly water-saturated exhalate, and watersoluble volatiles that are exhaled and absorbed into the condensing breath are the main components of EBC.

**Sample collection and analysis** The method of exhaled breath analysis is completely noninvasive, and it is suitable for longitudinal studies and for monitoring the response to pharmacological therapy.

Sample collection is noninvasive, simple and easy to perform in patients of any age. Homemade and commercially manufactured condensers are available.

Breath analysis consists of direct (on line) and indirect (off line) reading methods. Breath analysis is immediately available in the on-line method. The use of indirect methods generally involves collecting and trapping the breath sample and subsequently transferring it to an analytical instrument for analysis.

Various kinds of breath samples include mixed expired air and end expired air. End-exhaled-

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Clinical significance in asthma</th>
<th>Clinical significance in COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>F2-isoprostanes</strong></td>
<td>Increased reflecting the severity of the disease and the degree of inflammation</td>
<td>Increased reflecting the severity of the disease and the degree of inflammation</td>
</tr>
<tr>
<td><strong>Leukotrienes</strong></td>
<td>Elevated in both adults and children</td>
<td>Elevated in steroid-naive and steroid-treated patients and correlate with the degree of airway inflammation</td>
</tr>
<tr>
<td><strong>Prostanoids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>Decreased and normalises with glucocorticoid therapy</td>
<td></td>
</tr>
<tr>
<td><strong>Hydrogen peroxide</strong></td>
<td>Increased in both adults and children</td>
<td>Increased in patients with exacerbations</td>
</tr>
<tr>
<td><strong>Nitrite/nitrate, nitrosothiol, nitrotyrosine</strong></td>
<td>Increased and correlate with eosinophilic inflammation, reduced by corticosteroid therapy</td>
<td>Increased in early stages of exacerbations</td>
</tr>
<tr>
<td><strong>FeNO</strong></td>
<td>Increased and falls after treatment with corticosteroids</td>
<td>Increased during exacerbations and falls after inhaled steroids in stable COPD</td>
</tr>
</tbody>
</table>

COPD: chronic obstructive pulmonary disease; FeNO: exhaled nitric oxide fraction.
Air represents the alveolar air concentration and mixed-exhaled-air represents the gas mixture coming from the dead space of the bronchial tree and the alveolar gas-exchange space.

The analysis of sample and measurement of different biomarkers are usually performed by immunoassays mass spectrometry, high-performance liquid chromatography, nuclear magnetic resonance spectra, luminometry, spectrophotometry and pH-meter.

**Biomarkers** Several biomolecules can be detected in exhaled air of healthy subjects and patients with different inflammatory lung diseases (table 2).

**Validity** Immunoassays for many biomarkers still need to be validated by reference analytical techniques. Concentrations of markers are often close to the detection limit of the assays making analytical data less reliable. Dilution of airway lining fluid may influence the results of biomarker analysis in EBC. A confident dilution marker for EBC has not been standardised yet. However, dilution markers can be avoided by: 1) testing for multiple biomarkers and calculating ratios among them; and 2) identification of a substance that serves as an on-off indicator of an abnormality.

Standardisation and validation of exhaled breath analysis is important, and special attention should be given to technical issues of flow dependence, time dependence, influence of respiratory patterns, origin of markers in EBC, and possible nasal, saliva and sputum contamination.

The latest achievements in standardisation and validation of exhaled breath analysis have been presented in ATS/ERS recommendations.

**Conclusions**

Noninvasive methods such as induced sputum and exhaled breath analysis have been successfully introduced in clinical practice and research to study airway inflammation involved in the pathogenesis of respiratory diseases.

**References**

- Brightling CE. Clinical applications of induced sputum. *Chest* 2006; 129; 1344-1348.
## CHAPTER 4:

**OTHER DIAGNOSTIC TESTS**

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<td>BRONCHOALVEOLAR LAVAGE</td>
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Bronchoscopy is an essential tool for the pulmonologist that allows inspection and sampling of the airways. The procedure is usually performed with or without conscious sedation.

**Equipment**

The flexible bronchoscope has evolved from a fibreoptic instrument to videobronchoscopes, which are now almost universally used in most centres (fig. 1). The videobronchoscope consists of a video chip at the distal end, an instrument channel and optical fibres that illuminate the airways. The images obtained are then transmitted to a monitor. The distal end of the bronchoscope can be angled through to 180°. This, in combination with manual rotation movements, allows the bronchoscope to be manipulated in the airways.

**Indications**

Bronchoscopy provides diagnostic information in patients with suspected lung cancer, diffuse lung disease and in patients with persistent infection or local pulmonary infiltrates.

Investigation of symptoms
- Haemoptysis
- Persistent cough
- Recurrent infection

Investigation of suspected neoplasia
- Unexplained paralysis of vocal cords or hemi-diaphragm
- Stridor
- Localised monophonic wheeze
- Suspicious sputum cytology
- Unexplained pleural effusions
- Mediastinal tissue diagnosis and staging
- Assess suitability for surgery
- Staging of lung cancer

Assessment of persistent or recurrent infection
- Identification of organisms
- Evaluate airways if recurrent or persistent infection

Assessment of diffuse lung disease

Therapeutic bronchoscopy was traditionally performed for malignant disease. However, there are now a number of therapeutic procedures for emphysema and asthma:
- Clearance of airway secretions
- Removal of foreign body
- Palliation of endobronchial airway obstruction by tumour ablation or insertion of stents

**Key points**

- Bronchoscopy provides diagnostic information in suspected lung cancer and diffuse lung disease and in patients with persistent infection or local pulmonary infiltrates.
- Bronchoscopy also has therapeutic uses in tumour treatment, as well as asthma and emphysema.
Bronchoscopic lung volume reduction for emphysema

Bronchial thermoplasty for asthma

**Patient preparation**

Patients should be given a full explanation of the procedure accompanied by written information. Below is a simple pre-procedure check list:

- Patient information – verbal and written
- Informed consent
- Full blood count and clotting – before transbronchial lung biopsy
- Electrocardiogram (ECG) if history of cardiac disease
- Ensure patients do not eat or drink for at least 4–6 h before the procedure
- Ensure patients have someone to take them home following the procedure if they receive sedation
- Patients are advised not to drive or operate machinery for at least 24 h after any sedation

Patients are monitored by continuous oximetry throughout the procedure. Those with pre-existing cardiac disease or hypoxia that is not fully corrected by oxygen therapy should undergo continuous ECG monitoring.

**Procedure**

The oro-pharynx is anaesthetised with 4% xylocaine and the nasal passage with 2% lidocaine gel. Venous access should always be secured before the procedure, and oxygen administered *via* a single nasal cannula. Bronchoscopy can be performed with or without light sedation (fig. 2).

In the nasal approach, the bronchoscope is lubricated with 2% lidocaine gel and passed through the nares under direct vision. It is then inserted into the nasopharynx until the epiglottis is visualised.

In the oral approach, the patient is asked to bite gently onto a mouth-guard; the bronchoscope is then inserted through this mouth-guard into the posterior pharynx, to the level of the epiglottis.

The movement of the vocal cords is assessed, and they are then anaesthetised using 2-mL aliquots of 2% lidocaine. When the coughing has subsided, the bronchoscope is advanced through the widest part of the glottis, taking care not to touch the vocal cords. The subglottic area of the trachea is very sensitive, and patients initially feel as though they are choking. Further 2-mL aliquots of 2% lidocaine are administered in the trachea, carina, and right and left main bronchi. The airways are carefully inspected down to the subsegmental level for the presence of endobronchial lesions and mucosal abnormalities (fig. 3). Narrowing of the bronchial tree as a result of external compression from large lymph nodes or masses is also noted.

**Bronchoscopic sampling**

Bronchoscopy also provides an opportunity to obtain a variety of samples which may aid diagnosis.
Bronchial washings

The specimens are obtained by injection of 20 mL of normal saline into the affected segment of the lung, followed by aspiration.

Bronchial brushings

A fine cytology brush may be used to scrape cells from the surface of any visible lesion or from segments when the lesion is not visible at bronchoscopy. The bronchial brush specimen may be smeared onto a slide and fixed before cytological analysis, or shaken into saline for cytospin preparations.

Bronchial biopsy

Any endobronchial abnormalities should be biopsied. At least four samples should be obtained and placed in 10% formal saline solution. The diagnostic yield for polypoid lesions should be high (>90%), but is less for submucosal lesions.

Bronchoalveolar lavage (BAL)

This is used in the assessment of diffuse lung disease. The bronchoscope is wedged into the segment of interest and 50-60-mL aliquots of warm saline are injected into the segment. The fluid is then slowly aspirated using low-pressure suction or direct hand suction. A total of 150-250 mL is instilled and aspirated.

Transbronchial lung biopsy

Used to obtain parenchymal lung tissue for the evaluation of diffuse lung diseases. It is particularly useful when a broncho-centric component is visible on computed tomography (CT) scans. The closed biopsy forceps are advanced into a specific bronchial segment and advanced until met with resistance. The forceps are then withdrawn a short distance and the jaws opened. The patient is asked to take a deep breath and the open forceps are advanced further. When there is further resistance, the patient is asked to breathe out and a biopsy sample is taken during expiration. Samples are obtained from the periphery of the lung.

Transbronchial fine-needle aspiration (TBNA)

Mediastinal and hilar lymph nodes can be sampled by TBNA. The site of aspiration is planned on the basis of a cross-sectional CT. The needle is inserted at the desired point perpendicular to the airway wall. The needle is moved back and forth after penetration of the airway wall and suction applied with a 20-mL syringe. Samples collected can then be used to prepare slides or placed in cytolyte or saline solution for cytological analysis. This is useful in the staging and diagnosis of suspected lung cancer. This should be performed prior to any other aspects of bronchoscopy so as not to carry over cells from endobronchial lesions into TBNA specimens and hence falsely upstage the patient. Needle aspiration of submucosal lesions may also improve diagnostic yield. Overall TBNA is a low risk procedure with a good yield.

Complications

The adverse effects of flexible bronchoscopy may be due to the sedation, the local anaesthesia or the procedure. The overall incidence of complications is about 2%. Mortality from the procedure is less than 0.02%.

Sedative drugs may depress respiration and have cardiovascular effects (e.g. hypotension). Lidocaine may very rarely cause bradycardia, seizures, bronchospasm or laryngeal spasm.

The procedure may cause bronchospasm, laryngospasm, hypoxaemia or cardiac arrest.
arrhythmias, particularly in patients with pre-existing cardiac disease or hypoxia not corrected by oxygen supplementation. Infection can be introduced by the bronchoscope. Therefore, it is essential to clean and disinfect all instruments before use. Haemorrhage and pneumothorax may follow transbronchial lung biopsy. The risk is 5–7%, and this is increased with paroxysmal coughing. Hypoxia and precipitation of respiratory failure are the main complications of bronchoalveolar lavage particularly as the procedure is often performed in patients with diffuse lung disease.

**Advanced diagnostic procedures**

The airway is illuminated by blue light during fluorescence bronchoscopy. Normal tissue is visible as fluorescent green, whereas abnormal areas appear brown and red in colour. This absence of autofluorescence occurs in dysplasia, carcinoma in situ and invasive carcinoma, and may enable the earlier detection of endobronchial tumours. It is currently used as a research tool but may also be useful in routine practice. Narrow band imaging emphasises the blood vessels and increased capillary loops in the mucosa, which is associated with dysplasia and carcinoma in situ. Magnification of images and presentation at high definition further enhances the ability of the operator to detect subtle abnormalities.

Endobronchial ultrasound guided transbronchial fine needle aspiration (EBUS–TBNA) is performed with an integrated linear array ultrasound bronchoscope. It provides excellent ultrasound images of the mediastinum and tissue adjacent to the airways and allows ultrasound-guided sampling of mediastinal lymph nodes or peribronchial tumour masses. The sensitivity of this technique is high. Its use is rapidly expanding and is establishing an important role in the diagnosis and staging of lung cancer. A radial or mini probe system can be used for localising peripheral pulmonary masses. These probes are passed through the instrument channel of a flexible bronchoscope into the desired segment with a guide sheath.

The probe is manipulated in the airways with or without radiological guidance. Once the abnormal area is identified the sheath is maintained in position, the radial ultrasound probe is removed and washings, brushings and biopsies obtained via the guide sheath.

**Therapeutic procedures**

The therapeutic role of bronchoscopy is rapidly increasing. It is well established in the treatment of endobronchial tumour obstruction. A variety of techniques such as cryotherapy, electrocautery or laser can be utilised by flexible bronchoscopy to rapidly debulk tumours, which are obstructing the main airways. Several clinical series have demonstrated that these techniques are very effective in palliating symptoms and improving the quality of life for patients with endobronchial tumour occlusion. They also reduce the risk of post-obstructive pneumonia. Where the airway wall structure has been extensively damaged or there is extrinsic compression from the tumour, endobronchial stents can be used to support the airways. Metal self-expanding stents can be inserted via a flexible bronchoscopy and are available in both uncovered and covered formats.

Brachytherapy is localised radiotherapy administered to an area of tumour infiltration. A blind-ending catheter is inserted through the instrument channel of the bronchoscope into the desired airway. The bronchoscope is then removed whilst maintaining the catheter in the appropriate position. The catheter can then subsequently be loaded with a remote device which is used to insert radiotherapy beads and hence deliver local radiotherapy. This technique can also be used to treat endobronchial obstruction. However, there is a risk of acute localised oedema following the procedure and treatment carries a significant risk of severe haemorrhage.

More recently a number of innovations have been developed for the bronchoscopic treatment of patients with severe emphysema with significant hyperinflation. Endobronchial valves, such as zephyr valves and intra-bronchial valves, can be used for
bronchoscopic volume reduction. Other developments include biological polymers, endobronchial coils and airway stents. A novel treatment for patients with moderate to severe asthma is also delivered bronchoscopically. A special catheter is used to apply radiofrequency energy to the airways in order to destroy airway smooth muscle.

Weblinks
- www.interventionalbronchoscopy.co.uk.
What it is and when to use it

Bronchoalveolar lavage (BAL) involves using a fibreoptic bronchoscope to wash a subsegment of the lungs with sterile physiological saline to sample components from the peripheral air spaces in health and disease. These include immune and inflammatory cells, other pathological cells or features, cytokines, enzymes, lipids or other secreted products, inhaled environmental or occupational agents, and infections. Since the 1960s, BAL has been used extensively in research and to assist in the diagnosis of peripheral lung diseases, notably diffuse interstitial lung diseases (ILDs), occupational lung diseases, rare lung diseases, thoracic malignancies and lower respiratory tract infections (table 1). Numerous publications, including guidelines from the European Respiratory Society (ERS), confirm that BAL cytological or microbiological findings can often increase diagnostic confidence. However, BAL itself is rarely specifically diagnostic and must be interpreted together with clinical, physiological, radiological and other multidisciplinary investigations.

Prior to 2000, BAL was routinely included in the diagnostic work-up of parenchymal lung diseases. Currently, for ILDs, specialists consider that high-resolution computerised tomography (HRCT) patterns are often sufficiently diagnostic to avoid the need for BAL or lung biopsy. A recent American Thoracic Society/ERS consensus terminology for the idiopathic interstitial pneumonias (IIPs) has also changed the way specialists diagnose and manage this subgroup of ILDs. However, BAL is still indicated whenever the preliminary clinical investigations plus HRCT fail to establish a confident diagnosis, or where additional information is needed to confirm, strengthen or to exclude a diagnosis.

How to obtain a sample

This chapter will only describe the BAL procedure recommended in Europe for routine cytological investigation of adults with lung diseases where infection is not suspected. A modified procedure to minimise contamination with irrelevant microorganisms and target sites of maximal involvement is used for the specialist diagnosis of lower respiratory tract infections.

A standardised procedure must be followed in order to minimise variability due to the unknown dilution factor during lavage and many other potential sources of variability. There is still no globally agreed standard for the general conduct of BAL in adults for cytological and other purposes, but the ERS...
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<td>Drug-induced eosinophilic pneumonia</td>
<td>Eosinophils very high</td>
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| Other pulmonary eosinophilias                                 |     |     |
| Idiopathic eosinophilic pneumonia                             | Eosinophils very high |     |
| Allergic diseases: asthma; Churg–Strauss syndrome; bronchopulmonary aspergillosis | Mild to moderate increases in eosinophils plus lymphocytes |     |
| Parasitic infections: schistosomiasis; stronguloides          | Eosinophils often high |     |

| Acute respiratory distress syndrome                           | Neutrophils very high |     |

| Idiopathic interstitial pneumonias                             |     |     |
| Idiopathic pulmonary fibrosis                                 | Moderate increases in neutrophils ± eosinophils |     |
| Nonspecific interstitial pneumonitis                          | Mild increases in lymphocytes plus neutrophils ± eosinophils |     |
| Cryptogenic organising pneumonia                              | Moderate increases in lymphocytes plus neutrophils |     |
| Lymphoid interstitial pneumonia                               | Increases in lymphocytes |     |
| Respiratory bronchiolitis associated interstitial lung disease | Mainly macrophages containing smoking-particles plus a few neutrophils |     |
| Desquamative interstitial pneumonia                           | Macrophages containing smoking particles plus moderate increases in neutrophils ± eosinophils or lymphocytes |     |
| Acute interstitial pneumonia                                  | Neutrophils very high |     |
has long promoted BAL standardisation in a series of European guidelines. The earliest on technical aspects and clinical applications contain useful information but need some updating. However, updated guidelines for a standardised BAL procedure in adults were published in 1999. A protocol using this European standard procedure is as follows.

1) Perform BAL under local anaesthesia using fibreoptic bronchoscopy as part of pre-treatment assessment.
2) Proceed initially as for routine fibreoptic bronchoscopy: generally semi-supine patient positioning; pre-medication with a sedating compound; local anaesthesia with lidocaine removing any excess prior to lavage.
3) For lavage, gently wedge the tip of the bronchoscope into an appropriate subsegmental bronchus. The recommended standard site is right middle lobe in diffuse lung diseases and healthy controls, but the area of greatest radiographic abnormality in localised lung diseases.
4) Sequentially introduce then aspirate standard aliquots (4–60 mL) of sterile physiological saline pre-warmed to body temperature through the application tube of the bronchoscope. Do not exceed total introduction volume of 240 mL.
5) Aspirate each aliquot, keeping dwell time to the minimum using very low suction pressure (3.33–13.3 kPa/25–100 mmHg) to avoid airway collapse.
6) Collect the recovered fluid into a container to which cells are poorly adherent, e.g. siliconised glass or a non-cell adherent plastic designed for suspension tissue cultures. Place the recovered fluid into a container to which cells are poorly adherent, e.g. siliconised glass or a non-cell adherent plastic designed for suspension tissue cultures. Keep the container sealed to prevent contamination of BAL with blood or bronchial secretions.
7) Record the lavage site, total BAL fluid introduction volume and number of aliquots and the total recovery volume. Do not exceed total introduction volume of 240 mL.
8) Aspirate each aliquot, keeping dwell time to the minimum using very low suction pressure (3.33–13.3 kPa/25–100 mmHg) to avoid airway collapse.
9) Send the BAL sample to the laboratory to enable processing to commence within 1 h because BAL cells deteriorate rapidly within 1 h. Also send a patient protocol with age, sex, provisional diagnosis and other factors that influence BAL findings including smoking history (current, ex- or non-smoker), current medications and associated diseases. If biopsies are needed, perform these after BAL to avoid contamination of BAL with blood or bronchial secretions.
10) If biopsies are needed, perform these after BAL to avoid contamination of BAL with blood or bronchial secretions.

### Table 1. Continued

| Systemic connective tissue diseases |  
|-----------------------------------|-----------------------------------|
| Systemic sclerosis                | Moderate increases in neutrophils ± eosinophils or lymphocytes |
| Sjögren’s syndrome                | Moderate increases in neutrophils ± lymphocytes |

| Granulomatous lung diseases |  
|----------------------------|-----------------------------------|
| Sarcoidosis                | Moderate increases in lymphocytes ± mild neutrophils |
| Hypersensitivity pneumonitis/ extrinsic allergic alveolitis | Lymphocytes very high. Neutrophils and mast cells also increased after recent exposure |
| Chronic beryllium disease | Moderate to high increases in lymphocytes |

* using differential percentage BAL cell counts (see text for full explanation). * excluding infections.
BAL is safe and side-effects are low and as for fibreoptic bronchoscopy alone, except for an increased risk of minor post-lavage pyrexia, which can be minimised by keeping total BAL introduction volumes to < 300 mL.

**Processing of samples for cytology**

BAL cells deteriorate rapidly in saline and laboratory processing should commence within a maximum of 1 h after BAL sample collection. To delay deterioration, BAL cells should be transferred into serum-free minimum essential medium containing 25 mM HEPES buffer (MEM-HEPES), which maintains pH7 in an open system.

Non-cell adherent containers and pipettes must be used for all laboratory procedures. The processing procedure is as follows. 1) Measure the total volume of the BAL sample. 2) Record any abnormality in the gross appearance of the fluid, e.g. milky appearance suggestive of alveolar lipoproteinosis, very bloody suggestive of acute haemorrhagic conditions. 3) Mix sample to ensure even suspension then divide into measured aliquots for different departments if required (e.g. ≥ 20 mL for BAL cytology and flow cytometry, 10 mL for microbiology, 20 mL for electron microscopy). 4) For BAL cytology, the fluid aliquot should be mixed and a cell viability test conducted, e.g. trypan blue. Then make a total count of nucleated cells (per mL) using an improved Neubauer counting chamber and white cell counting stain, e.g. Kimura stain. If the original BAL sample is too dilute for an accurate cell count, the count should be performed after separating the cells by centrifugation and resuspending them in higher concentration. 5) Centrifuge the BAL sample at low speed (300 × g at 4°C for 10 min) to separate the cells and other insoluble components from the supernatant fluid. Aspirate the supernatant and aliquot it for storage at -70°C. Then wash the BAL cell pellet in MEM-HEPES and resuspend in a small volume (1-2 mL) to achieve a more concentrated suspension. Perform a total cell count/mL and calculate the number/mL and total in the original BAL fluid. 6) Adjust the volume of the cell suspension to a standard 1.5 × 10^6 cells/mL to make cytocentrifuge slide preparations. Use 100-μL aliquots (1.5 × 10^5 cells) per slide (spin at 90 × g for 4 min). Prepare at least six slides per patient. After air drying, fix two slides in methanol (not formalin which impairs staining of mast cells). Stain with May–Grünwald–Giemsa for differential cell counting. Use other slides for special stains, e.g. Gomori–Grocott silver stain for fungi and *Pneumocystis carinii*, and Perl stain for haemosiderin-laden macrophages.

Mucus contamination of BAL samples, if very excessive, can cause serious technical problems in processing. When there is such heavy contamination from the upper airways, BAL results must be interpreted with caution. Mucus can be removed by filtering the lavage through cotton gauze or nylon mesh, but this can cause loss of adherent cells, dust fibres and other components. An alternative to avoid such loss is to remove mucus by treating the BAL cell pellet with the mucolytic dithiothreitol.

Some workers consider that when BAL cells are in tissue culture medium, processing can be delayed for 24 h to enable long distance transport to centralised processing centres. However, this is not advisable because granulocytes are short lived and apoptotic changes start within 9 h. Therefore, it is advisable to transfer BAL cells into tissue culture medium within 1 h and make cytocentrifuge preparations within 1-4 h. Staining of airdried preparations can be delayed for ≥ 24 h if necessary. It is essential that BAL is conducted by clinical and laboratory personnel who are highly trained in the procedure, applications and interpretation.

**Differential cell counting and other cytological appearances**

The standard approach to counting BAL cells in cytocentrifuge preparations is to express the count of each type as a percentage of the total BAL cells (differential percentage cell count). This proportionate approach is not affected by the unknown BAL dilution factor.
Differential cell counts are performed and other cytological features identified by examining May–Gruenwald–Giemsa stained cytocentifuge slide preparations by light microscopy. First, low-power magnification (×10 and ×25 objectives) is used to search the entire preparation and semi-quantitatively grade (0–5) any mucus and erythrocytes, and identify any unusual cytological features, such as inorganic dust particles or fibres, globules of lipoprotein, giant cells, malignant cells or microorganisms. Secondly, higher-power magnification (×40 or ×60 objectives) is used to count all the immune and inflammatory cells and any other type of nucleated cells employing random-field counting methodology until a total of >400 cells have been counted. The count for each cell type is then expressed as a percentage of the total cells counted (differential percentage BAL cell count). For diagnostic purposes, all nucleated cells, not only inflammatory cells, must be included in the count to ensure that important information is not omitted (e.g. malignant cells, giant cells and epithelial cells). The presence of >5% of bronchial epithelial cells indicates excessive contamination from the upper airways, and such samples are inadequate as a reliable indicator of alveolar events.

Abnormal cell appearances must also be reported, including proportions of foamy macrophages, multinucleate macrophages, giant cells, macrophages containing smoking-related particles, macrophages containing refractile or bi-refrangent particles indicative of inorganic dusts, or macrophages heavily laden with haemosiderin confirmed by Perl staining, indicating possible pulmonary haemosiderosis.

When neutrophil counts are very high it is important to check for intracellular bacteria, which can indicate active bacterial pneumonia.

Fungal spores or hyphae may also be seen, and their presence should be confirmed using Gomori–Grocott silver stain, which can also detect Pneumocystis carinii.

Normal cell counts and the effect of smoking

BAL cells from healthy nonsmokers are mainly macrophages and a few lymphocytes, but proportions of other cell types are very low. Smoking causes increases in BAL macrophages up to four-fold higher (total and per mL) in healthy smokers compared with nonsmokers; smokers also have slight increases in neutrophils. Thus, smoking must be taken into account when defining normal ranges and interpreting any BAL studies. Published normal ranges show considerable variability when cell counts are expressed per mL or absolute total numbers. However, results are very similar when expressed as differential percentage counts, consistent with these not being influenced by dilution.

The following normal ranges can be employed for diagnostic BAL cell counts: macrophages >80% in nonsmokers and >90% in smokers; lymphocytes ≤20% in nonsmokers and ≤10% in smokers; neutrophils ≤3% in nonsmokers and ≤4% in smokers; eosinophils ≤0.5% in nonsmokers and ≤3% in smokers; mast cells ≤0.5% in nonsmokers and smokers; plasma cells 0%; and ciliated or squamous epithelial cells ≤5%. Smoking-related inclusions are frequent in macrophages from smokers.

Main applications in the diagnostic work-up of peripheral lung diseases

Although this chapter describes BAL procedures, it would be incomplete not to include a summary indicating how BAL is used in routine clinical investigation to increase confidence in the diagnosis of many parenchymal lung diseases. A quick guide showing the main types of increased BAL inflammatory cells and other cytological features in a wide range of lower respiratory diseases is given in table 1.

References

- American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of Idiopathic Interstitial

FINE-NEEDLE BIOPSY

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Percutaneous (or transthoracic) fine-needle biopsy (PFNB) is a technique that allows cytohistological diagnosis of thoracic lesions. While the first reports on the use of transthoracic needle biopsy date back to the end of the 19th century, the modern era of PFNB did not begin until the mid-1960s when NORDENSTROM (1965) introduced the use of fine needles (diameter <20 Gauge).

Indications
PFNB is indicated when a cytohistological diagnosis is required of peripheral lung lesions (nodules, mass or infiltrates) following a negative bronchoscopy. PFNB is also indicated for expansive lesions of the chest wall or for diagnosis of mediastinal masses, especially those located in the anterior mediastinum.

Contraindications
Absolute contraindications are: contralateral pneumonectomy, bleeding disorders, uncooperative patient, uncontrollable cough, and suspected arteriovenous malformation or hydatid cyst. Relative contraindications that may increase the risk of complications are: respiratory failure, severe chronic obstructive pulmonary diseases, pulmonary arterial hypertension and unstable ischaemic heart disease.

Technique
Guidance systems Biplane fluoroscopy is the traditional guidance system for PFNB. Its main advantage is the real-time visualisation of the needle during the whole procedure. In recent years, computed tomography (CT) has become the most common means of guidance. Although performing a CT scan is more time-consuming, it has several advantages: 1) it helps determine the safest needle trajectory avoiding vascular structures, fissures, bullae and necrotic areas of the tumour; 2) it allows an approach to lesions not visible on fluoroscopy; and 3) it avoid radiation exposure to the operators. However, there are no studies that demonstrate a better sensitivity of CT compared with fluoroscopy. Ultrasound can also be used as guidance system when the lesion is in contact with the thoracic wall.

Type of needle Commercially available needles are either: 1) aspiration needles that yield material satisfactory for cytological evaluation (Chiba, Franseen, Westcott, Nordenstrom); or 2) histology needles that yield a tissue core (Trucut, Menghini, Silverman). Needle diameter should be <20 Gauge and generally 20-22 Gauge needles are utilised. The use of an histology needle is recommended when either a benign

Key points
• PFNB is indicated when a cytohistological diagnosis of peripheral lung lesion is required.
• The most common guidance system for PFNB is CT scan. Biplane fluoroscopy and ultrasound can also be used.
• The sensitivity of PFNB for lung cancer is 85–95%.
• The most frequently reported complication is minor pneumothorax (25%).
lesion or a malignancy other than cancer (i.e. lymphoma) is suspected.

**Results**

The reported sensitivity of PFNB ranges from 60–97%. In patients with lung cancer, a diagnosis by PFNB is generally established in 85–95% of cases. Lower sensitivities are reported for benign lesions (4–14%). Sensitivity may be affected by the size and location of the lesion, number of needle passes, size of the needle, availability of immediate cytological assessment and experience of the operator. False-positive results are rare and the specificity of the technique is extremely high. However, it is important to emphasise that a nondiagnostic PFNB does not rule out the possibility of malignancy.

**Complications**

The most frequently reported complication is minor pneumothorax, with an incidence of ~25%. Major pneumothorax, requiring chest tube drainage, occurs in 5% of cases. Haemoptysis occurs in 5–10% of cases and is generally mild and self-limited. Rare complications include air embolism (0.07%), haemothorax, empyema, tumour implantation along the needle tract and haemopericardium.

**References**

MEDICAL THORACOSCOPY/PLEUROSCOPY

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Thoracoscopy was first used 100 yrs ago, primarily as a diagnostic procedure, but soon also as a therapeutic technique for lysis of pleural adhesions by means of thoracocautery (‘Jacobaeus operation’) to facilitate pneumothorax treatment of tuberculosis. At the end of the last century, the addition of the term ‘medical’ was necessary in order to distinguish this procedure from ‘surgical’ thoracoscopy, which is much more invasive, using general anaesthesia, a double-lumen endotracheal tube and multiple points of entry. Surgical thoracoscopy is better described as video-assisted thoracic surgery (VATS), whereas medical thoracoscopy can be performed under local anaesthetic or conscious sedation in an endoscopy suite using nondisposable rigid (or semi-rigid) instruments. It is therefore considerably less invasive and less expensive.

Medical thoracoscopy/pleuroscopy (MT/P) are invasive techniques that would be used only when other more simple methods fail. Today, it is considered to be one of the main areas of interventional pulmonology. As with all technical procedures, there is certainly a learning curve before full competence is achieved. Therefore, appropriate training is mandatory. Actually, the technique is very similar to chest-tube insertion by means of a trocar, the difference being that, in addition, the pleural cavity can be visualised (fig. 1) and biopsies can be taken from all areas of the pleural cavity including the chest wall, diaphragm, mediastinum and lung.

There are two different techniques of diagnostic and therapeutic thoracoscopy, as

Key points

- MT/P has the advantage compared with VATS that it can be performed under local anaesthesia or conscious sedation, in an endoscopy suite using nondisposable rigid (or semi-rigid) instruments. Thus, it is considerably less expensive.
- The leading indications for MT/P are pleural effusions, both for diagnosis – mainly in exudates of unknown aetiology – or for staging in diffuse malignant mesothelioma, lung cancer, and for talc poudrage, the best conservative method today for pleurodesis.
- MT/P can also be used efficiently in the management of early empyema and pneumothorax.
- In the above indications, MT/P can replace most surgical interventions, which are more invasive and more expensive.
- MT/P is a safe procedure, even easier to learn than flexible bronchoscopy, provided sufficient experience with chest-tube placement has been gained.
- MT/P as part of the new field of interventional pulmonology should be included in the training programme of chest physicians.
performed by the pneumologist. The one, very similar to the technique first described by Jacobaeus for diagnostic purposes, uses a single entry with a rigid 9-mm thoracoscope with a working channel for accessory instruments and an optical biopsy forceps under local anaesthesia. This single-entry technique has now been modified by the introduction of an autoclavable semi-flexible pleuroscope (Olympus), which has the advantage that handling is very simple, similar to a flexible bronchovideoscope.

The other technique uses two entries, one with a 7-mm trocar for the rigid examination telescope and the other with a 5-mm trocar for accessory instruments, including the biopsy forceps. For this technique, neuroleptic or general anaesthesia is preferred.

For cauterisation of adhesions and blebs, or in case of bleeding after biopsy, electrocoagulation should be available. For pleurodesis of effusions, 4–6 g of a sterile, dry, asbestos-free talc is insufflated through a rigid or flexible suction catheter with a pneumatic atomiser. In pneumothorax patients, 2–3 g of talc is sufficient. After thoracoscopy, a chest tube is introduced through which immediate suction is started carefully.

MT/P is a safe examination if the contraindications are observed and if certain standard criteria are fulfilled. An obliterated pleural space is an absolute contraindication. Relative contraindications include bleeding disorders, hypoxaemia and an unstable cardiovascular status, and persistent uncontrollable cough. The most serious, but fortunately least frequent, complication is severe haemorrhage due to blood-vessel injury during the procedure. However, this and also pulmonary perforations, can be avoided by using safe points of entry and a cautious biopsy technique. Reported mortality rates (<0.001) are very low. The most frequent complication is nonspecific, transient fever.

Pleural effusions are by far the leading indication for MT/P, both for diagnosis, mainly in exudates of unknown aetiology, and for staging in diffuse malignant mesothelioma or lung cancer, and for treatment by talc pleurodesis in malignant or other recurrent effusions, or in cases of empyema. Spontaneous pneumothorax for staging and for local treatment is also an excellent indication. For those who are familiar with the technique, other (mainly diagnostic) indications are biopsies from the diaphragm, the lung, e.g. in interstitial lung diseases, the mediastinum and the pericardium. In addition, MT/P offers a remarkable tool for research as a ‘gold standard’ in the study of pleural effusions.

Figure 1. a) Diagram of a computed tomography scan showing several malignant lesions of the parietal pleura for which biopsies can be taken under visual control through the thoracoscope. b) Tuberculous pleural effusion. After drainage of 800-mL serous effusion, typical sago-like nodules on the reddened inflamed posterior chest wall, firm adhesions between right lower lobe (1) and chest wall (2). Reproduced from Loddenkemper et al. (2010), with permission from the publisher.
Malignant pleural effusions represent the leading diagnostic and therapeutic indication for MT/P. MT/P has a much higher diagnostic sensitivity and specificity in malignant pleural effusions than closed needle biopsy and pleural fluid cytology (fig. 1). Biopsies can be taken under direct visual control not only of the costal pleura, but also of the visceral and diaphragmatic pleura. An additional advantage is that the diagnostic procedure can easily be combined with the therapeutic procedure of talc poudrage for pleurodesis. MT/P is helpful in the staging of lung cancer, diffuse malignant mesothelioma and metastatic cancers. In lung cancer patients, thoracoscopy can determine whether the tumour spread to the pleura is secondary to venous or lymphatic obstruction or is parapneumonic. As a result, it may be possible to avoid exploratory thoracotomy or to determine operability. In diffuse malignant mesothelioma, MT/P provides an earlier diagnosis and a better histological classification due to larger and consequently more representative biopsies, as well as a more precise staging.

In tuberculous pleural effusion, MT/P has a high diagnostic sensitivity of almost 100% (fig. 2). It provides much more often a bacteriological confirmation of the diagnosis of TB and thus the possibility to perform susceptibility tests. In parapneumonic pleural effusion (empyema), MT/P offers the possibility to remove fibrinopurulent membranes and break up loculations, thus creating one single pleural cavity for successful local treatment.

In other pleural effusions, when the origin remains indeterminate, the main diagnostic value of MT/P lies in its ability to exclude, with high probability, malignant or tuberculous disease. In pneumothorax patients, MT/P allows talc poudrage for pleurodesis, which is highly effective in recurrence prevention.

References

Thoracentesis (pleural tap; fig. 1) is a frequently performed procedure that is used to remove and analyse pleural fluid. Its goals may be diagnostic and/or therapeutic.

Diagnostic thoracentesis should be performed on almost all patients with a pleural effusion of unknown origin. Its main purpose is to differentiate between transudate and exudate. The number of diagnoses established by pleural fluid analysis varies with the population being evaluated. Careful history and physical examination, radiological evaluation, and ancillary blood tests are crucial in establishing a pre-test diagnosis.

The main purpose of therapeutic thoracentesis is to relieve dyspnoea and respiratory insufficiency caused by pleural effusion.

Patient position
A sitting position is preferred in conscious patients, as this will help the fluid to settle in the posterior and basal regions of the lung (usually the 7th to 8th intercostal spaces, although clinical examination may reveal different locations of the fluid).

Once a comfortable position for operating on the patient is achieved, the site for the puncture must be selected. This is decided according to the results of the physical examination and the radiological findings, which will indicate characteristics such as the size and localisation of the main effusion and whether it is free-organised, free-floating or encapsulated. Ultrasound examination is valuable to assess fluid presence accurately.

The puncture should be guided by ultrasound or attempted one intercostal space further down from where dullness on percussion starts. At least in pleural effusions of smaller size, ultrasound guidance is strongly recommended.

The thoracentesis set
The thoracentesis set is detailed in table 1.

Procedure
1. Under sterile conditions, the selected region of puncture is disinfected with povidone iodine or alcohol, and a sterile draping, preferably with a centre hole, is taped to the patient's back.

2. Local anaesthesia is injected stepwise, at first with an intradermal injection producing a small wheal, then infiltrated subcutaneously and into the intercostal muscle down to the parietal pleura at the upper rim of the lower rib in order to avoid the intercostal nerve and vessels. During the injection, alternating aspiration is performed until the parietal pleura is penetrated and pleural fluid is

Key points
- Thoracentesis may be diagnostic or therapeutic in patients with a pleural effusion.
- Ultrasound examination is valuable in guiding the procedure.
- There are no absolute contraindications, and complications are rare, but the possibility should be taken into account.
aspirated. Then 20–60 mL of pleural fluid should be aspirated for fluid analysis.

Diagnostic thoracentesis can occasionally be carried out without local anaesthesia if the adult patient is calm, the puncture is anticipated to be easy, the subject is not obese and the operator is experienced.

3. For therapeutic thoracentesis, a catheter should be used, which is immediately connected to a closed three-way stop-cock. This allows aspiration syringes to be changed or facilitates connection to a suction device.

4. As soon as the procedure is finished, the needle or the catheter is removed and pressure is applied to the wound for a few minutes, followed by a sterile dressing.

5. Chest radiography should be carried out to exclude the development of a pneumothorax, unless the procedure has been performed under ultrasound guidance without any problems.

Contraindications

Diagnostic thoracentesis has no absolute contraindications provided that it is done with caution by experienced persons. The following are relative contraindications.

- Altered coagulation. A decision must be taken as to whether thoracentesis is really needed. If so, it may be necessary to reverse anticoagulation or to administer fresh frozen plasma or platelets.
Mechanical ventilation with positive pressure at the end of expiration. Whenever possible, mechanical ventilation is suspended briefly. If this is not possible, thoracentesis must be carried out with caution using ultrasound guidance.

Local skin infections such as cellulitis or Herpes zoster.

Small effusions (this should be done under ultrasound control).

Complications

As with any invasive investigation, complications may occur, but these are rare. Patients have to be informed about possible complications when asked to give their informed consent. The most important are:

- Pneumothorax. This is usually only small if caused by entrance of air into the pleural cavity through the needle or the aspiration system. It can become larger if the lung is injured by the needle.
- Hypotension. This may be induced by a vasovagal reaction when the parietal pleura is punctured. It can be avoided by careful local anaesthesia and prevented by administering atropine (not routinely necessary).
- Bleeding. This can be prevented by avoiding the lower rim of the upper rib and by excluding coagulopathies.
- Haemopneumothorax. This is rare when the above-described technique is observed and the patient has no bleeding disorder.
- Re-expansion pulmonary oedema. This can be prevented by removing <1–1.5 L of pleural fluid.

Additional recommendations

1. The region from the mid-clavicular line to the sternum should be avoided, as here the vessels are located in the centre of the intercostal space.

2. Sterile conditions are mandatory during the whole procedure to prevent infection which may lead to empyema.

3. For diagnostic purposes, 20 mL of pleural fluid is usually sufficient to assess the appearance of the fluid and for chemical, cytological, and bacteriological analysis. Recent work recommends ~60 mL for cytology in case of suspected malignancy.

References

Interventional pulmonology encompasses both diagnostic and therapeutic bronchoscopic, thoracoscopic and other techniques that go beyond everyday “simple” procedures performed by pulmonary clinicians. In the context of pulmonary function testing and interventional pulmonology, this chapter will be limited towards the effects on interventional bronchoscopy of pulmonary function tests.

Interventional bronchoscopy here is limited to all (rigid and flexible) bronchoscopic procedures designed to reopen obstructed central airways (including laser, electrocautery, cryotherapy, brachytherapy and photodynamic therapy) or to establish airway patency (airway stenting).

The literature on interventional bronchoscopy has, during the past few decades, mainly focused on the “technicality” of the various procedures; data pertaining to the functional assessment and evaluation are relatively scarce. Certainly in the “pioneer era” of interventional pulmonology, patients were referred in a (very) late stage of disease, with severe dyspnoea and/or stridor or signs of post-obstructive disease, requiring prompt intervention without additional testing. In stable and nonlife-threatened patients with or without symptoms, however, additional testing before proceeding an intervention may be helpful in patient selection, and post-procedure testing may focus the usefulness and efficacy of an intervention. Thus, as more centres successfully perform various interventional bronchoscopic techniques, the need is increasing for a critical evaluation and selection of patients in order to understand the physiological effects of these interventions and gain an evidence-based, algorithmic integration of these techniques in the overall care of these patients. Alternatively, abnormalities observed during pulmonary function testing may prompt the clinician to suspect an upper (or central) airway stenosis (UAS).

In patients suffering from malignant airway stenosis, which is not candidate for, or unresponsive to, “classical” oncological treatments, the main interest of interventional pulmonological treatment should lie in the improvement of quality of life and the avoidance of death by suffocation.

**Key points**

- Symptoms of central airway stenosis occur late, after at least 50% (on exercise) or 80% (at rest) of the tracheal lumen is obstructed.
- The diagnostic accuracy of spirometric indices and visual flow-volume loop criteria in detecting central airway stenosis is relatively poor.
- Interventional bronchoscopic techniques have been shown to significantly improve objective pulmonary function and quality of life.

In patients suffering from malignant airway stenosis, which is not candidate for, or unresponsive to, “classical” oncological treatments, the main interest of interventional pulmonological treatment should lie in the improvement of quality of life and the avoidance of death by suffocation.

**Pulmonary function tests in UAS**

Inspection of the maximal inspiratory and expiratory flow-volume loop is currently the most widely used method to detect/suspect...
the presence of UAS (figs 1–3). However, significant changes in spirometry appear relatively late in the course of the stenosing process. The airway cross-sectional area indeed has to be reduced by \( \geq 50\% \) in order to cause breathing impairment, a clinical observation that recently has been corroborated by a fluid dynamics study of tracheal stenosis. There is also a very poor or even absent correlation between the severity of the UAS as determined by the flow loop analysis and its spirometrically derived indices, and breathing symptoms or radiological assessment of UAS. There is also a very poor or even absent correlation between the severity of the UAS as determined by the flow loop analysis and its spirometrically derived indices, and breathing symptoms or radiological assessment of UAS. UAS becomes more easily symptomatic during exercise (from a tracheal diameter \( \leq 8 \text{ mm} \)), whereas at rest the diameter has to be \( \leq 5 \text{ mm} \) before symptoms occur. All of this may explain why the diagnostic accuracy of the various individual spirometric indices and visual flow-volume loop criteria in detecting UAS is relatively poor (receiver-operating-curve analysis \( < 0.52 \)).

Typical flow-volume appearances, however, may be helpful: a typical “coffin” or “box” appearance of the flow-volume curve is suspicious for a fixed UAS due to severe tracheal obstruction; an isolated plateau during expiration is suspicious for an intrathoracic airway stenosis; an isolated plateau of the inspiratory loop suggests extrathoracic obstruction. Obstructive lesions at multiple airway sites and associated abnormalities such as severe chronic obstructive pulmonary disease may cause atypical flow-volume loop characteristics.
UAS may lead to typical flow–volume loop abnormalities and spirometric derived indices, but

- the diagnostic accuracy in detecting UAS of these tests is (very) low;
- symptoms of UAS occur relatively late in the UAS process; and
- symptoms of UAS occur earlier during exercise.

The most commonly used quantitative criteria to detect UAS include maximal expiratory flow at 50% of forced vital capacity (FVC; MEF50%)/maximal inspiratory flow at 50% of FVC (MIF50%) (<0.30 for intrathoracic, and >1 for extrathoracic stenosis), forced expiratory volume in 1 s (FEV1)/maximum expiratory flow (>10 mL·s⁻¹·min⁻¹), MIF50% (<100 L·min⁻¹), and FEV1/FEV0.5 (>1.5). The visual criteria are the presence of a plateau, biphasic shape, or oscillations in the inspiratory or expiratory curves.

**Impact of interventional bronchoscopy on pulmonary function**

In most patients, but not all, pulmonary function significantly improves after restoration of central airway patency. *Eisner et al.* (1999) demonstrated mean improvements of 388 mL for FVC, 1,288 mL for peak expiratory flow, and 550 mL for FEV1 after stenting in nine patients. *Geb et al.* (1992) showed increases in FVC from 64% to 73% predicted, and in FEV1 from 49% to 72% predicted after stenting in 17 patients. *Vergnon et al.* (1995) showed mean improvements in FEV1 (440 mL), peak expiratory flow (920 mL·s⁻¹), maximum expiratory flow 25-75% (470 mL·s⁻¹), and forced inspiratory volume in 1 s (310 mL) after stenting in a total of 24 patients. Improvements were more outspoken in intra- and extrathoracic tracheal stenosis as compared with bronchial stenosis. *Noppen et al.* (2004) showed improvements after tracheal stenting for inoperable benign thyroid disease (FEV1 +540 mL, FVC +730 mL, peak expiratory flow +96 L·min⁻¹) (figs 4 and 5).

*Ernst et al.* (2007) showed improvements in some but not all patients stented for severe tracheomalacia, in respiratory symptoms, quality of life, and in functional status assessed by exercise testing and FEV1. Overall, these retrospective and prospective observational case series, in selected patients, show significant but not homogeneous improvements in a number of functional parameters. Data on physiological effects of repermeabilisation techniques without additional stenting are even more scarce: objective improvements in pulmonary function was seen in 58% of patients after cryotherapeutic debulking of central airways.

![Figure 4. Computed tomography image of the same patient after stenting.](image1)

![Figure 5. The same patient, 1 yr after stent insertion.](image2)
and a trial of 19 patients with major airway obstruction due to lung cancer showed significant improvements in a variety of parameters including FEV1, FVC and ratio of forced expiratory/forced inspiratory flow rate at 50% of vital capacity, after endobronchial radiotherapy.

A breakthrough article by MIYAZAWA et al. (2004) shed more light on the underlying physiological phenomena occurring after airway stenting, including the heterogeneity of response. A total of 64 patients with extrinsic airway stenoses due to advanced malignancy were studied; patients were classified by location of the stenosis (tracheal, carinal, bronchial or multi-site). Pulmonary function tests and CT were performed before and after stenting. Prior to stent insertion, patients underwent endobronchial ultrasound to evaluate the airway walls and ultrathin bronchoscopy to evaluate airway patency distal to the obstruction. Stents were placed at the visualised flow-limiting segments (choke points). Distinctive flow-volume loop patterns were found for each of the four types of stenosis. Most patients showed symptomatic improvement after stenting, and most flow-volume loops returned to normal. All 10 patients with multi-site, extensive stenosis, however, showed persistent choke points, associated with only minor improvements in symptoms and spirometry. Repeat endoscopy in these patients showed upstream displacement of choke points (distally from the inserted stents), and ultrasound showed destructed cartilage at these sites. Additional stenting at these sites then improved symptoms and pulmonary function to levels comparable with the other groups. This additional physiological and imaging information excluded all therapeutic failures.

Conclusions

When patients with UAS present with dyspnoea at exertion, and certainly with dyspnoea at rest, severe central airway stenosis is already present. In these patients, flow-volume loop analysis and spirometry will most probably show aberrations typical for UAS. However, as a screening tool in a general population, these aberrations show a poor accuracy in predicting UAS. In extremely symptomatic, almost suffocating patients, immediate intervention with repermeabilisation/stenting is warranted. In non-life-threatening cases, pre-intervention pulmonary function testing may yield useful information on the type, site and extent of the stenosis, whereas postprocedure testing may be used to focus the response and can be used as a basis for post-procedure follow-up. In the case of a multi-site, extensive airway stenosis, its relatively typical flow-volume loop pattern may be predictive of therapeutic failure of single-site stenting and may predict the necessity of additional stenting at upstream choke points. Interventional bronchoscopic procedures offer immediate (and often longstanding) palliation of respiratory symptoms, improvements in quality of life (and frequently length of life as well), and objective improvements in pulmonary function in the majority of patients. When used judiciously, they have become an invaluable tool in the armamentarium of modern pulmonology.

References

# CHAPTER 5:

**LUNG IMAGING**

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CHEST X-RAY AND FLUOROSCOPY

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Chest radiography is the most frequently used radiological chest imaging technique and also one of the most challenging. The technical aspects of this imaging modality are studied extensively. New approaches to image acquisition and display have been introduced in the past decade. As a general rule, establishing the presence of a lung disease process on the radiograph should constitute the first step in radiological diagnosis of chest disease.

Basic radiographic techniques

Diagnostic accuracy in chest disease is partly related to the quality of the radiographic images themselves. Several variables such as patient position, patient respiration and film exposure factors must be taken into account to ensure image quality (table 1). Positioning of the patient must be such that the X-ray beam is properly centred, the patient’s body not rotated and the scapulas rotated so that they are projected away from the lungs. Patient respiration must be fully suspended, preferably at total lung capacity. Film exposure factors should be such that faint visualisation of the thoracic spine and the intervertebral disks on the postero-anterior (PA) radiograph is possible and that lung markings behind the heart are clearly visible. Exposure should be as short as possible, consistent with the production of adequate contrast. A high-kilo voltage technique appropriate to the film speed should be used.

Projections

PA and lateral projection The most satisfactory routine radiographic views for evaluating the chest are the PA and lateral projections with the patient standing (fig. 1). The combination of these two projections provides very good three-dimensional information. In patients who are too ill to stand up, antero–posterior (AP) upright or supine projections offer alternative but considerably less satisfactory views. The AP projection is of inferior quality because of the shorter focal-film distance, the greater magnification of the heart, and often the restricted ability of these patients to suspend respiration or achieve full inspiration. Based on a review of the literature and recommendations of the American College of Radiology and the American Thoracic Society, recommendations on the use of chest radiographs are summarised in table 2.

Lateral decubitus projection For the lateral decubitus projection, the patient lies on one side and the X-ray beam is oriented...
horizontally. This technique is particularly helpful for the identification of small pleural effusions. <100 mL of fluid may be identified on well-exposed radiographs in this position. Radiography in the lateral decubitus position is also useful to demonstrate a change in position of an air–fluid level in a cavity or a freely moving intracavitary loose body (e.g. fungus ball in aspergilloma).

**Lordotic projection** The lordotic projection can be made in AP or PA projection. For this projection, the patient stands erect and the X-ray tube is angled 15° cephalad. The main advantage of this modification is its reproducibility. The lordotic projection can be used: 1) for improving visibility of the lung apices, superior mediastinum and thoracic inlet, and 2) for identifying the minor fissure in suspected cases of atelectasis of the right middle lobe.

**Oblique projection** Oblique studies are sometimes useful in locating a pleural or chest wall disease process (e.g. pleural plaque); however, in most situations, computed tomography is preferred.

**Inspiratory–expiratory radiography**

Comparison of radiographs exposed in full inspiration and maximal expiration may supply useful information in two specific situations. The first indication is the evaluation of air trapping, either focal or general. With air trapping, diaphragmatic excursion is reduced symmetrically and lung density changes little between expiratory and inspiratory radiographs. The second indication is when a pneumothorax is suspected and when the visceral pleural line is not visible on the standard inspiratory radiograph or the findings are equivocal. In these situations, a film taken in full expiration may show the line more clearly.

**Bedside radiography**

Chest radiography, performed at the bedside with portable apparatus, is one of the most frequently performed radiological examinations; however, this technique is also the examination with the most variation in image quality. The amount of diagnostic information provided by chest examinations done with portable apparatus is high, and many abnormalities are detected. These examinations are useful 76–94% of the time. However, poor image quality and day-to-day variations in film density interfere with the detection of interval changes in patients with pulmonary diseases. The need to improve the image quality of this examination has long been recognised, but it is a difficult problem to solve.

**Digital chest radiography**

There have been many remarkable advances in conventional thoracic imaging over the past decade. Perhaps the most remarkable is the rapid conversion from film-based to digital radiographic systems. Digital radiography (DR) is the common name for different technologies that are characterised by a direct readout matrix that covers the whole exposure.

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**Table 1. Key points to obtaining a good chest radiograph**

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<th>Radiographic appearance</th>
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<td>Frontal view (PA view)</td>
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<td>Area from the lower cervical spine to below the costophrenic angles</td>
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<tr>
<td>Sterno-clavicular joints symmetrical about the midline</td>
</tr>
<tr>
<td>Shadows of the scapulae away from the lung field</td>
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<td>Lateral view</td>
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<td>Soft tissues of the axillae should be included</td>
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<td>Respiration</td>
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<td>End of normal inspiration</td>
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<tr>
<td>Positioning of the patient</td>
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<td>Erect position</td>
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<tr>
<td>Very ill patients: horizontal or semi-erect</td>
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<tr>
<td>Postero-anterior (PA) position</td>
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<tr>
<td>Film exposure factors</td>
</tr>
<tr>
<td>High kilo voltage</td>
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<tr>
<td>Focus-film distance</td>
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<tr>
<td>Must be kept constant for any particular department</td>
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<td>150–180 cm</td>
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Chest X-ray and fluoroscopy
Figure 1. Postero-anterior chest radiograph. Normal lungs are visible as black fields (air) (*) with superposition of multiple white linear structures (vessels and walls of airways). The lunghili consist of bronchi (main stem (1) and lobar bronchi) and vascular structures (pulmonary arteries (2) and pulmonary veins). A normal pleura is not visible on a chest radiograph. In the mediastinum we can visualise the trachea (3) as a translucent tube on the midline, the aortic arch (4), the pulmonary trunk (5), the left border or the heart formed by the left ventricle (6) and the right border of the heart formed by right atrium (7). A normal heart has a normal cardiothoracic index: (a+b)/maximal diameter of the chest (c) must be less than 0.5. The bony components of the chest visible on the frontal view are: the ribs (+), the manubrium sternum (8), the clavicular (9), the scapulae (10) and the vertebral bodies on the midline. The diaphragm (11) is sharply delineated and also the costophrenic angles (12) must be sharp and free. b) Lateral chest radiograph. The lateral chest film can be used to localise better the findings on the frontal view. Numbers and symbols are as for a).

Table 2. Recommendations for the use of chest radiography

<table>
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<th>Indications</th>
<th>No indications</th>
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<td>Signs and symptoms related to the respiratory and cardiovascular system</td>
<td>Routine screening of unselected populations</td>
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<td>Follow-up of previously diagnosed thoracic disease for evaluation of improvement resolution, or progression</td>
<td>Routine pre-natal chest radiographs for the detection of unsuspected disease</td>
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<td>Staging of intrathoracic and extrathoracic tumours</td>
<td>Routine radiographs solely because of hospital admission</td>
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<td>Pre-operative assessment of patients scheduled for intrathoracic surgery</td>
<td>Mandated radiographs for employment</td>
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<tr>
<td>Pre-operative evaluation of patients who have cardiac or respiratory symptoms or patients who have a significant potential for thoracic pathology that may lead to increased peri-operative morbidity or mortality</td>
<td>Repeated radiograph examinations after admission to a long-term facility</td>
</tr>
<tr>
<td>Monitoring of patients who have life support devices and patients who have undergone cardiac or thoracic surgery or other interventional procedures</td>
<td></td>
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Conversion of X-ray intensity into electrical signals can either be direct (selenium-based systems) or indirect (scintillator/photodiode systems). Advantages of DR systems are a high image quality and the potential for dose reduction. This technique is now the preferred imaging modality for bedside chest imaging because of its more consistent image quality. DR is rapidly replacing film-based chest units for in-department PA and lateral examinations. The final aim is to realise a completely integrated digital radiology department throughout the hospital connected to a large digital image archiving system. This concept, referred to as picture archiving and communication systems (PACS), represents the logical culmination of the extensive research that is continuing in this area.

Chest fluoroscopy

Chest fluoroscopy was a popular procedure a generation ago. Patients were examined fluoroscopically in various projections, and multiple spot radiographs were obtained with barium in the oesophagus. Examinations to evaluate pericardial effusion also were frequent. Overall diminution in cardiac pulsation and greater pulsation of the posterior cardiac wall in the lateral projection were thought to be signs of effusion. Other indications for fluoroscopy included the investigation of foreign bodies determined by air trapping and appropriate mediastinal shift and the evaluation of diaphragmatic paralysis. This evaluation of diaphragmatic paralysis is still an indication for fluoroscopy today.

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Computed tomography (CT) is the second most important imaging modality of the chest and is, together with chest radiography, one of the two basic imaging techniques for visualising the lungs. Although there are indications to perform a CT of the chest in patients with normal chest radiography, this examination usually succeeds a chest X-ray on which a lesion is seen or suspected.

Magnetic resonance imaging (MRI) of the chest is, except for visualisation of the heart and great vessels, used less frequently in daily clinical practice. In selected cases, this imaging technique can sometimes add information to what is seen on CT. Since its introduction CT has undergone several technical changes and improvements. The first scanners were “incremental”CT scanners. In order to complete one cross-sectional image, the patient needed to suspend respiration for a few seconds. After that, the table was moved and the next scan was performed. This was repeated about 25 times in order to image the entire thorax.

Spiral scanning (also known as helical or continuous-volume scanning) has radically altered CT scanning protocols (table 1). In this technique, there is continuous patient movement with simultaneous scanning by a constantly rotating X-ray tube and detector system. While the first spiral CT scanners had only one row of detectors, today's scanners have multiple rows (multislice, multiraw or multidetector-row CT). This allows for simultaneous acquisition of multiple images in the scan plane with one rotation of the X-ray tube around the patient. It also offers flexible image reconstruction options such as reconstructing images at various image thickness and two-dimensional and three-dimensional reconstructions.

Thin-section or high-resolution CT (HRCT) is a special type of acquisition technique that uses 0.5–1-mm slice thickness and high-frequency reconstruction algorithms to produce high-detail images. It is used when detailed information about the lung parenchyma is needed. These thin slices can be obtained with the “incremental” acquisition technique in which 1-mm slices are produced with an image interval of 10–20 mm. However, with multislice spiral CT, it has become possible to produce a continuous set of thin slices of the entire chest. Although the quality of the individual images may be somewhat lower when the multislice acquisition is used, the overall information obtained is usually larger. Indeed, instead of a small number of axial slices with an image gap between, a continuous dataset is obtained that allows the

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**Key points**

- CT is the second most important imaging modality of the chest.
- CT diagnosis of lung diseases is based on the study of their appearance and distribution patterns together with a careful analysis of patient data.
- CT interpretation of diffuse and interstitial lung diseases requires a formal multidisciplinary approach.
- MRI is second to CT when it comes to visualising pulmonary structure and pathology.
production of additional slices in different imaging planes. For this reason multislice is replacing the "incremental" technique in most institutions especially when it is the initial CT examination in a patient with a suspected lung problem. An important drawback, however, may be the increased radiation dose. On the other hand, the lung parenchyma is very suitable for reduction of the radiation dose without important quality loss and first reports on the use of low-dose CT in demonstrating lung disease are indeed promising.

As mentioned earlier, CT of the chest is usually performed when the chest radiography is abnormal or suspicious for the presence of pathology, although there are certainly indications for doing this examination even when the chest radiograph does not show any (obvious) abnormalities. Table 2 lists the most frequent indications for a CT of the chest.

Generally the diagnosis of lung disease on a chest CT is based on three elements:

- Recognition of the appearance pattern of the disease, i.e. classifying the abnormalities in a category that is based on their appearance.

- Determination of location and distribution of the abnormalities in the lung: the distribution pattern.

- Careful analysis of the patient data that are available at the time the CT scan is performed.

Although in some cases a diagnosis or a narrow differential diagnosis list can be proposed purely based on the study of the appearance and the distribution pattern of the disease on CT, the abnormalities seen in the lung should be carefully correlated with observations made on other radiological examinations and with all the clinical data available at the time of the CT examination. In particular diffuse and interstitial lung diseases are often very difficult to diagnose.

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Table 1. Advantages of spiral computed tomography scanning

<table>
<thead>
<tr>
<th>Advantage</th>
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<tbody>
<tr>
<td>Sectional imaging without superposition of structures</td>
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<tr>
<td>Rapid acquisition within one breath-hold</td>
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<tr>
<td>Very good blood vessel opacification in vascular studies using limited amount of contrast</td>
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<tr>
<td>No respiratory misregistration between scans improving nodule detection</td>
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<tr>
<td>Fast and high-quality multiplanar and three-dimensional reconstructions</td>
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</tbody>
</table>

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Figure 1. Thin-slice computed tomography of the lung obtained with the multislice spiral acquisition technique in a patient with sarcoidosis. The combination of axial (a) and coronal (b) views allows a better study of the appearance and distribution pattern of the lung lesions.
when the interpretation is based only on the CT presentation. Ideally, cooperation should be established between the clinician responsible for the patient, the radiologist and, when pathological information is present or probably required, the pathologist.

Continuous efforts are being made to improve the image quality and the diagnostic performance of CT imaging of the lung. A further increase in the number of detector rows is feasible and may reduce acquisition time and hence improve image quality. Automated and semi-automated software packages will help to interpret the CT images. Dual-energy CT scanning may become helpful to study pulmonary perfusion in patients with pulmonary embolism.

**Magnetic resonance imaging**

Like CT, MRI produces multiplanar cross-sectional images, but it allows for a greater tissue characterisation because it has a better contrast resolution than CT. It also has the benefit of not using ionising radiation.

Tissue protons are exposed to a strong external magnetic field and realign along the plane of the magnetic gradient. From this position they are deflected momentarily by applying a so-called radio frequency (RF) pulse. As they return to their original alignment, the protons emit a faint electromagnetic signal which is detected by a receiving RF coil. When in addition a suitable gradient is set up along the magnetic field, signal detection can be confined to a pre-selected body plane. Processing of the data then yields a sectional image of the plane of interest.

MRI has an established role in the imaging of the heart and the great thoracic vessels. Concerning the chest wall, the diaphragm, the mediastinum and the lung, MRI was for many years considered a useful problem-solving technique for specific instances when used in addition to CT. These instances include the identification of tumour invasion in the chest wall and the mediastinal structures, differentiation between solid and vascular hilar masses, assessment of diaphragmatic abnormalities and the study and follow-up of mediastinal lymphoma during treatment. As mentioned earlier, however, most centres now use multidetector spiral CT for thoracic imaging, including the areas thought earlier to be the domain of “problem-solving” MRI.

Although it has become clear that MRI will always be second to CT when it comes to visualising pulmonary structure, disease and patterns with high spatial resolution, the many research and development efforts that have been made in recent years have resulted in new and valuable applications that are very promising and that may be implemented in clinical practice. There has been much interest in the role of MRI in the diagnosis of pulmonary embolism as a radiation-free

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**Table 2. Indications for computed tomography of the chest**

<table>
<thead>
<tr>
<th>Abnormal chest radiography</th>
<th>Normal chest radiography</th>
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<tbody>
<tr>
<td>Further evaluation of a chest wall, pleural, mediastinal or lung abnormality seen on a chest radiograph</td>
<td>Detection of diffuse lung disease</td>
</tr>
<tr>
<td>Rule out or confirm a lesion seen on a chest radiograph</td>
<td>Detection of pulmonary metastases from a known extrathoracic tumour</td>
</tr>
<tr>
<td>Lung cancer staging and follow-up</td>
<td>Demonstration of pulmonary embolism</td>
</tr>
<tr>
<td>Assessment of thoracic vascular lesion</td>
<td>Investigation of a patient with haemoptysis</td>
</tr>
<tr>
<td>Investigation of patients with clinical evidence of a disease that might be related to the presence of chest abnormalities (e.g. pulmonary infection in an immunocompromised patient with fever)</td>
<td>Investigation of patients with clinical evidence of a disease that might be related to the presence of chest abnormalities (e.g. pulmonary infection in an immunocompromised patient with fever)</td>
</tr>
</tbody>
</table>
alternative to CT. Studies have shown that direct visualisation of the thrombus in the pulmonary artery is possible, while others have concentrated on the study of lung perfusion, looking for decreased-signal areas in the lung that represent underperfused lung tissue on gadolinium-enhanced MRI. Imaging of pulmonary ventilation by MRI has also become possible. Hyperpolarised $^3$He gas has been used to demonstrate perfusion changes in patients with asthma, chronic obstructive pulmonary disease and cystic fibrosis. Hyperpolarized xenon-129, fluorine and oxygen-enhanced lung MRI are methods of gas imaging that have opened up the field of imaging pulmonary ventilation by MRI. Diffusion-weighted (DW) MRI is another interesting application. This technique provides a measurement that reflects the random Brownian motion of water protons in tissue. This motion causes signal loss that can be measured with the use of diffusion-sensitive sequences and that can be quantified by calculating the apparent diffusion coefficient. In the chest, it has been used successfully to differentiate between malignant and benign lesions.

Most of these techniques remain in the experimental domain, but it can be expected that some of them will reach daily clinical practice.

References


Figure 2. Patient with leftsided malignant mesothelioma. Both CT (a) and MRI (b) show irregular and nodular pleural thickening. There is suspicion of invasion in the diaphragm and spleen. Diffusion-weighted MRI (c) shows increased signal in the spleen (arrowheads) indicating tumour invasion in this structure. In addition an increased signal is seen in the chest wall (arrows) suggesting chest-wall invasion.
• Muller NL. Computed tomography, magnetic resonance imaging, past, present and future. *Eur Respir J* 2002; 35: Suppl. 35, 3s–12s.
NUCLEAR MEDICINE OF THE LUNG

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Nuclear medicine may contribute to the diagnosis of pulmonary embolism (PE) and inflammatory diseases, and the diagnosis and staging of lung cancer. Among several techniques available, pulmonary perfusion and ventilation scintigraphy (PLS and VLS, respectively), gallium-67 scintigraphy and positron emission tomography (PET) scintigraphy are of interest in clinical practice.

Diagnosis of PE

Thanks to its noninvasiveness, safety and low cost, PLS still remains the cornerstone of the diagnosis and follow-up of PE.

Perfusion lung scintigraphy has been proven to be useful for:

- diagnosis of PE
- detection of recurrences under treatment or after its discontinuation
- differential diagnosis between thromboembolic and nonthromboembolic pulmonary hypertension

Two main scintigraphic criteria must be considered for the diagnosis: 1) identification of perfusion defects corresponding to one or more pulmonary segments and 2) diversion of pulmonary blood flow from lower and posterior lung regions. Perfusion defects typically are multiple, wedge-shaped and often bilateral. PLS has a sensitivity of 100% in that it allows exclusion with certainty when the diagnosis is negative. The specificity varies in different reported series, but on average does not reach acceptable values; to increase the specificity, VLS has been introduced, but is cumbersome, time-consuming and poorly available. Nowadays, VLS is only indicated in some individual patients with PE, since similar results can be obtained by using chest radiography. A few years ago, a new classification of perfusion defects was published in order to optimise its diagnostic usefulness in conjunction with chest radiography; such a method has made it possible to obtain a diagnostic accuracy similar to that shown by angio-computed tomography (CT). PLS also plays a leading role in the follow-up of patients with PE, as it helps to monitor the efficacy of treatment in the first days, it allows promptly detection of early and late recurrences and evolution towards pulmonary hypertension, and it may

Key points

- Nuclear medicine of the lung has a role in the diagnosis of pulmonary embolism and inflammatory diseases, and in the diagnosis and staging of lung cancer.
- Perfusion scintigraphy is key in the diagnosis and follow-up of pulmonary embolism as it is safe, cheap and noninvasive.
- Gallium-67 scintigraphy is useful in identifying and localising intrathoracic inflammation and infection.
- FDG PET and PET/CT are used in diagnosis, treatment targeting and treatment in lung cancer.
differentiate between thromboembolic pulmonary hypertension and other types of pulmonary hypertension.

**Diagnosis of inflammatory diseases**

Gallium-67 citrate is the most widely employed positive tracer in order to identify and localise intrathoracic inflammations and infections. To acquire images, a scintillation gamma-camera with a low energy collimator is required. Gallium scintigraphy may help in evaluating the activity of granulomatous disorders and the efficacy of steroid treatment. In patients with sarcoidosis, it shows a high diagnostic sensitivity; in some cases, the presence of highly specific signs, such as pando or lambda signs, allows avoidance of invasive diagnostic tests. Moreover, this tracer may differentiate between sarcoidosis and non-Hodgkin's lymphoma, and detect multiple extrapulmonary sites of sarcoidosis. Also, gallium scintigraphy is indicated in investigating metabolic activity in pulmonary infections and the efficacy of proper therapy. In the diagnosis of pulmonary tuberculosis, gallium scintigraphy may indicate the necessity of a bronchoalveolar lavage and the site where it should be performed. This occurs mostly in cases of suspected re-infection of areas of pleuroparenchymal fibrosis, in cases of suspicion where sputum is repeatedly negative, and in immunocompromised patients. Finally, gallium scintigraphy may be of value in the evaluation of efficacy of chemotherapy in lymphomatous diseases and may help differentiate post-attinic fibrosis from residual tumour foci when a lung density persists after radiotherapy.

**Diagnosis of lung cancer**

PET is a nuclear medicine technique that produces a three-dimensional imaging of functional and biochemical processes within the body. Recently, PET has been combined with CT (PET/CT) (fig. 1); such fusion generally improves diagnostic accuracy by upgrading specificity when compared with PET alone. The most frequently used tracer is 2-[^18]F-fluoro-2-deoxy-D-glucose (FDG), a glucose analogue, whose tissue concentration is directly related to the glucose metabolism. The uptake of FDG may be evaluated by a semiquantitative measurement, the “standardised uptake value” (SUV), i.e. the ratio between the amount of tracer in a specific area and the same amount potentially present if the tracer had been evenly distributed in the body.

FDG PET is proven useful in:

- diagnosing and staging lung cancer
- monitoring the efficacy of treatment
- defining the biological target volume for radiation treatment planning

An indication of increasing clinical relevance of FDG PET and PET/CT is the differentiation of benign from malignant solitary pulmonary nodules by replacing invasive modalities of investigation. A SUV of 2.5 has been reported as a guideline for the cut-off between benign (SUV <2.5) and malignant (SUV >2.5) lesions. A meta-analysis from 40 studies showed a sensitivity of 97% but a lower specificity (78%) due to FDG uptake within inflammatory/ granulomatous lesions. However, a high rate of false-negative FDG results can occur when nodules are <1 cm (sensitivity of 69% for nodules of 5–8 mm). Moreover, some histotypes, such as bronchoalveolar carcinomas and well-differentiated neuroendocrine tumours, usually present a low glucose metabolic activity and cannot be correctly depicted by FDG imaging.

FDG PET is also a standard modality for staging nonsmall cell lung cancer. Several studies have demonstrated that PET is more accurate than CT in the staging of mediastinum (N state). Due to its high negative predicted value, invasive staging procedures (mediastinoscopy) can be omitted in patients with a negative FDG PET for mediastinal lymph node involvement. On the contrary, a positive finding should not preclude mediastinoscopy. Moreover, the addition of FDG PET to the standard work-up can prevent useless thoracotomies and
change therapeutic approach in a significant percentage of patients. PET is useful in disclosing distant metastases (M state) with a high sensitivity and specificity. However, PET cannot replace CT or magnetic resonance imaging for detecting brain metastases. Moreover, the measurement of FDG SUV within the tumour correlates negatively with patient prognosis; early changes of FDG SUV during radiotherapy and chemotherapy can predict therapy efficacy; and PET is more accurate than contrast-enhanced CT for detecting residual tumour after radiotherapy and chemotherapy.

A recent indication of PET/CT is the definition of the “biological target volume” for radiation treatment planning. This approach has the goal of increasing the dose to the tumour and focusing the treatment planning to the biological target, which reveals an elevated glucose metabolism.

Thanks to D. Volterrani, Nuclear Medicine, University of Pisa, Pisa, Italy, for active assistance.

References
TRANSTHORACIC ULTRASOUND

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Transthoracic ultrasonography can be performed with the most basic ultrasound (US) equipment. It is used for the investigation of chest wall abnormalities, pleural thickening and pleural tumours, and the qualitative and quantitative description of pleural effusions. Lung tumours, pulmonary consolidations and other parenchymal pulmonary processes abutting the pleura can also be visualised. Furthermore, US is ideal to guide thoracentesis, drainage of effusions and other thoracic interventions. US is particularly useful in intensive care units where radiographic equipment is unavailable.

Advantages of thoracic US include its mobility, dynamic properties, lack of radiation and low cost.

The ultrasonographic appearance of the normal thorax and the most common pathologies are reviewed in this chapter.

General technical aspects and appearance of the normal thorax

A low-frequency probe (e.g. 3.5 MHz) is routinely used for screening purposes, while detailed assessment of an abnormal chest wall or pleura can be performed with a high-frequency probe (e.g. 8 MHz).

Superficial muscles and fascia planes appear as a series of echogenic layers during the initial surveillance of a normal chest. Curvilinear structures on transverse scans, associated with posterior acoustic shadowing represent the ribs.

The visceral and parietal pleura normally appear as one highly echogenic line.

Movement of the lung with the respiratory cycle in relation to the chest wall on real-time US is called the "lung sliding" sign. Its presence is strong evidence against a pneumothorax.

US cannot visualise normal aerated lung tissue. The large change in acoustic impedance at the pleura–lung interface, however, causes horizontal artefacts that are seen as a series of echogenic parallel lines equidistant from one another below the pleura. These bright but formless lines are known as reverberation artefacts (fig. 1).

Chest wall pathology

Softtissue masses, such as abscesses, lipomas and a variety of other lesions, can be detected by US. These lesions are mostly benign, but variable echogenicity and nonspecific US findings make differentiation between various aetiologies difficult. Supraclavicular and axillary lymph nodes are usually accessible, and US may even help to distinguish benign from malignant lymph nodes. Hypoechoic masses disrupting the normal structure of a

Key points

- Transthoracic US can be used to investigate chest wall abnormalities, pleural thickening and pleural tumours, and to describe pleural effusions.
- Advantages of the technique include its mobility, dynamic properties, lack of radiation and low cost.
rib may represent bony metastases and can be seen on US.

**Pleural pathology**

Transthoracic US is most commonly used to investigate pleural effusions, and is more sensitive than decubitus radiographs at demonstrating minimal or loculated effusions. The US appearance of a pleural effusion depends on its nature and chronicity. Four appearances based on the internal echogenicity are recognised: anechoic; complex but nonseptated; complex and septated; and homogenously echogenic. Transudates are invariably anechoic, unseptated and free flowing, whereas complex, septated or echogenic effusions are usually exudates. Malignant effusions are

![Figure 1. The typical appearance of a normal chest on ultrasound (US). A transverse view through the intercostal space is shown. The chest wall is visualised as multiple layers of echogenicity representing muscles and fascia. The visceral and parietal pleura appear as an echogenic bright line (two distinct lines sliding during respiration are visible on real-time US). Reverberation artefacts beneath the pleural lines imply an underlying air-filled lung. P: pleura; L: lung; R: reverberation artefact.](image1)

![Figure 2. Example of an anechoic pleural effusion is shown in a). It presents as an echo-free space between the visceral and parietal pleura. Compressive atelectasis of the lung may be seen as a tongue-like structure in a large effusion. Note the difference to the effusion on b), which is classified as complex septated. Multiple septa form many compartments in the same effusion. PE: pleural effusion; L: lung; S: septum.](image2)
frequently anechoic. The atelectatic lung inside a large effusion may appear as a tongue-like structure within the effusion. Inflammatory effusions are often associated with strands of echogenic material and septations that show more or less mobility with respiration and the cardiac cycle (fig. 2).

The volume of a pleural effusion can be estimated using the following classification: minimal, if the echo-free space is confined to the costophrenic angle; small, if the space is greater than the costophrenic angle but still within the range of the area covered with a 3.5 MHz curvilinear probe; moderate, if the space is greater than a one-probe range but within a two-probe range; and large, if the space is bigger than a two-probe range.

Both small effusions and pleural thickening may appear as hypoechoic on US, so differentiation might be difficult. An important sign in favour of an effusion is mobility on real-time US.

Figure 3. A peripheral pulmonary lesion is shown schematically without (top) and with (bottom) pleural contact. Only the lesion with pleural contact is visible on ultrasound. Reproduced from Dacon et al. (2005), with permission from the publisher.
Metastatic pleural tumours and malignant mesothelioma can be visualised as polypoid pleural nodules or irregular sheet like pleural thickening. They are often associated with large pleural effusions. Benign pleural tumours are rare. Qureshi et al. found that pleural thickening >1 cm, pleural nodularity and diaphragmatic thickening >7 mm were highly suggestive of malignant disease. In their study, US correctly identified 73% of malignant effusions.

The absence of normal lung sliding, the loss of comet-tail artefacts and exaggerated horizontal reverberation artefacts are reliable signs for the presence of a pneumothorax.

**Pulmonary pathology**

A lung tumour abutting the pleura will be detectable by US (fig. 3). In most cases these tumours present as a hypoechoic mass with posterior acoustic enhancement (fig. 4).

Visceral pleura or chest wall involvement is important for staging of malignant lung tumours. Loss of movement of a visualised tumour with respiration suggests infiltration beyond the parietal pleura.

US can detect pneumonic consolidations provided they have contact with the pleura. Non-infective causes of consolidations with similar appearance on US include pulmonary infarction, haemorrhage and bronchoalveolar carcinoma.

A hypoechoic lesion with a well-defined or irregular wall abutting the pleura might represent a lung abscess. The centre of the abscess is most often anechoic, but may reveal septations and internal echoes.

**Conclusion**

The value of US for chest physicians is firmly established. Basic thoracic ultrasonography is an elegant and inexpensive investigation that extends the physicians’ diagnostic and interventional potential at the bedside in peripheral lung, pleural, and chest wall disease.

**References**


CHAPTER 6:

LUNG INJURY AND RESPIRATORY FAILURE

LUNG INJURY
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RESPIRATORY FAILURE
N. Ambrosino and F. Guarracino

OXYGEN THERAPY AND VENTILATORY SUPPORT
A.K. Simonds

INTENSIVE CARE AND HIGH-DEPENDENCY UNIT
S. Nava and P. Navalesi

ASSESSMENT FOR ANAESTHESIA/SURGERY
M.M. Schuurmans, C.T. Bolliger and A. Boehler
LUNG INJURY

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Acute lung injury (ALI) and its most severe manifestation, the acute respiratory distress syndrome (ARDS), are defined by physiological (i.e. ratio of arterial oxygen tension ($P_{a,O_2}$) to inspiratory oxygen fraction ($F_{i,O_2}$) ≤ 300 mmHg for ALI and ≤ 200 mmHg for ARDS, independent of positive end-expiratory pressure) and bilateral pulmonary infiltrates as radiological criteria. Cardiac failure must be excluded based either on pulmonary artery wedge pressure (<18 mmHg) or on clinical evaluation of left ventricular function if the invasive measurement is unavailable.

These criteria should be re-evaluated after 24 h, since their persistence is essential for the correct diagnosis of ALI/ARDS. Furthermore, timing may be of influence on the development of ALI/ARDS.

Lung oedema may evaluated by computed tomography or other established methods.

ALI/ARDS may be caused by various aetiologies: direct lung injury, e.g. pneumonia, aspiration, toxic inhalation, near drowning or lung contusion; or indirect lung injury e.g. sepsis, burn, pancreatitis or massive blood transfusion. The two aetiologies may coexist.

The exact incidence of ALI/ARDS is not known; its annual mortality rate has been estimated to be >30,000 patients per year in the USA. Despite recent advances in the understanding of the pathophysiology of ARDS, improvements in supportive care, and multiple therapeutic efforts directed at modifying the course of the condition, mortality rates are persistently 35–40%.

The pathophysiology of ALI/ARDS is related to altered pulmonary capillary permeability and increased intrapulmonary shunt, which is associated with impaired gas exchange. ARDS has been divided into three stages in which an initial inflammatory phase (exudative) is followed by fibro-proliferation, which can lead to established interstitial and intra-alveolar fibrosis, the final phase.

Mechanical ventilation itself can seriously damage lung parenchyma (ventilator-induced lung injury). ALI/ARDS often has systematic

Key points

- ALI and its most severe manifestation ARDS are defined as $P_{a,O_2}/F_{i,O_2}$ ≤ 300 mmHg and ≤ 200 mmHg, respectively, in addition to bilateral infiltrates as radiological criteria.
- Principles of protective ventilator settings for patients with ALI/ARDS are low tidal volume (i.e. $V_T = 6 \text{ mL} \cdot \text{kg}^{-1}$ ideal body weight, plateau pressure <30 cmH$_2$O and peak pressure <35 cm H$_2$O.
- Permissive hypercapnia may be helpful to realise protective mechanical ventilation.
- Protection of the lungs may also be provided by the pump-driven veno-venous extracorporeal membrane oxygenation (ECMO) or pumpless extra corporeal lung assist (ILA).
manifestations, triggering systemic inflammatory response syndrome (SIRS), or in extremis multiple organ dysfunction syndrome (MODS).

In general the spectrum of treatment ALI/ARDS includes supportive care, ventilator support and pharmacological treatment. The first principle of treatment is to identify potential underlying causes of ALI/ARDS. Furthermore, secondary lung injury has to be avoided, such as aspiration, barotraumas, nosocomial infections and oxygen toxicity. The main aims of supportive care are maintaining oxygen delivery to end organs by avoiding anaemia and optimising cardiovascular function and body fluid balance; additionally catabolism and nutritional support have to be balanced.

With regard to mechanical ventilation, the main goal is to improve oxygenation without increasing the iatrogenic effects caused by mechanical ventilation; there are different methods available. Among the methods related to the ventilatory setting, those found really effective are to reduce tidal volume and pressures and to apply positive end-expiratory pressure (PEEP) to reduce the amount of nonaerated atelectatic lung.

Principles of protective ventilator settings for patients with ALI/ARDS are:

- Tidal volume 6 mL·kg⁻¹ ideal body weight.
- Plateau pressure, <30 cmH₂O, peak pressure <35 cmH₂O.
- This strategy of protective mechanical ventilation may be associated with permissive hypercapnia.

The “optimal” setting of PEEP is not clear, since several methods have been proposed without any clear advantages over each other.

Higher PEEP (>15 cmH₂O) might be recommended in more severe ARDS patients. Prone position might be recommended in more severe ARDS patients, according to the expertise of the clinicians. Alternative methods of ventilation include include high-frequency ventilation and airway pressure release ventilation.

Protection of the lungs may also be provided by pump-driven veno-venous extracorporeal membrane oxygenation, which improves both oxygenation and carbon dioxide removal, either by leaving the lungs “at rest” (apnoeic oxygenation) or by using low-tidal-volume low-frequency ventilation. Recently, a pumpless extracorporeal lung assist was developed using arterio-venous bypass, in which a gas exchange membrane is integrated (“interventional lung assist” (ILA)). ILA provides effective carbon dioxide elimination and a moderate improvement in oxygenation.

Concerning pharmacological treatments of ALI/ARDS, inhaled nitric oxide has not been found to be really effective and there is no clear convincing data suggesting the widespread use of corticosteroids in both early and late phases of ALI/ARDS.

Finally, based on experimental models a series of molecular mechanisms offer innovative opportunities for cell or gene therapy. These need to be elaborated in human studies, however.

References

RESPIRATORY FAILURE

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The respiratory system consists of two parts. The lung performs gas exchange, and the pump ventilates the lung. The pump consists of the chest wall, including the respiratory muscles, the respiratory controllers in the central nervous system (CNS) linked to respiratory muscles through spinal and peripheral nerves.

When respiratory failure (RF) ensues, the respiratory system fails in one or both of its gas exchange functions, i.e. oxygenation of mixed venous blood and/or elimination of carbon dioxide (CO₂) (fig. 1).

The diagnosis of RF is not clinical but based on arterial gas assessment: RF is defined by an arterial oxygen tension \( (P_{a,O2}) \leq 60 \text{ mmHg} \) and/or arterial CO₂ tension \( (P_{a,CO2}) > 45 \text{ mmHg} \). These values are not rigid; they must serve as a general guide in combination with the history and clinical evaluation. RF may be acute, chronic, or acute on chronic, with clinical presentation quite different between the types.

Acute respiratory failure (ARF) may be life-threatening in clinical presentation, arterial blood gases and acid–base status; chronic respiratory failure (CRF) is clinically indolent to unapparent, due to mechanisms of compensation of respiratory acidosis.

RF due to lung diseases (e.g. pneumonia, acute lung injury, adult respiratory distress syndrome (ARDS), emphysema, interstitial lung disease) leads to hypoxaemia with normocapnia or even hypocapnia (type I RF).

Four pathophysiological mechanisms are responsible for hypoxaemic RF:

- ventilation/perfusion \( (V'/Q') \) ratio inequalities
- shunt
- diffusion impairment
- hypoventilation

Hypoxaemia with hypoventilation is characterised by normal alveolar–arterial oxygen difference, whereas disorders due to any of the other three mechanisms are characterised by a widening of the alveolar–arterial gradient.

Abnormal desaturation of systemic venous blood in the face of extensive lung disease is an important mechanism of hypoxaemia.

Several non-chronic obstructive pulmonary disease (COPD) diseases may lead to hypoxaemic ARF, which is defined as a \( P_{a,O2} \) to oxygen inspiratory fraction \( (F_{I,O2}) \) ratio \( \leq 300 \) (table 1).

Hypoxaemia is treated with an increase in \( F_{I,O2} \) (the lower the \( V'/Q' \), the less the effect), and by recruiting airspaces with assisted ventilation. Airspace derecruitment occurs when the transpulmonary pressure falls below the airspace collapsing or closing pressure, and when the transpulmonary pressure applied during inspiration fails to exceed airspace opening pressure. Accordingly, airspace opening can be facilitated by increasing the

**Key points**

- Respiratory failure is failure of one or both of the respiratory system’s gas exchange functions.
- It is diagnosed by arterial blood gas assessment.
- The clinical presentations of acute, chronic, and acute on chronic respiratory failure can differ greatly.
transpulmonary pressure applied at end expiration (continuous positive airway pressure (CPAP) or positive end-expiratory pressure (PEEP)) and at end inspiration (i.e. inspiratory positive airway pressure).

Failure of the pump (e.g. neuromuscular diseases, opiate overdose) results in alveolar hypoventilation and hypercapnia with parallel hypoxaemia (type II RF).

In some diseases (e.g. COPD, cardiogenic pulmonary oedema), both conditions may coexist, hypoxaemia usually appearing first.

Hypercapnic RF may be the result of CNS depression, functional or mechanical defect of the chest wall, imbalance of energy demands and supplies of the respiratory muscles, and/or adaptation of central controllers in order to prevent respiratory muscle injury and avoid or postpone fatigue (table 2). Hypercapnic RF may occur either acutely, insidiously, or acutely upon a chronic CO₂ retention. In all of these conditions, the pathophysiological, common mechanism is reduced alveolar ventilation for a given CO₂ production.

Acute exacerbations of COPD (AECOPD) are periods of acute worsening which greatly affect the health status of patients with an increase in hospital admission and mortality. Estimates of in-patient mortality range 4–30%, but patients admitted due to ARF experience a higher rate, in particular elderly patients with comorbidities (up to 50%) and those requiring intensive care unit admission (11–26%).

Many causes may potentially be involved in determining ARF during AECOPD, such as bronchial infections, bronchospasm, left ventricular failure, pneumonia, pneumothorax and thromboembolism. Acute on chronic RF due to AECOPD is characterised by the worsening of hypoxaemia and a variable degree of hypercapnia and respiratory acidosis. The capacity of the patient to maintain acceptable indices of gas exchange during an AECOPD or the development of ARF depends both on the severity of the precipitating cause and on the degree of physiological dysfunction during the stable state and the subsequent physiological reserve. Worsening in V’/Q’ mismatching is probably the leading mechanism in the occurrence of the hypoxaemia by the enlargement of physiological dead space and the rise of wasted ventilation. The increase in airway resistance and the need for a higher minute ventilation may result in expiratory flow limitation, dynamic hyperinflation and related intrinsic PEEP (PEEP) with subsequent increased inspiratory threshold load and dysfunction of the respiratory muscles, which may lead to their fatigue. A rapid shallow breathing pattern may ensue in attempting to maintain adequate alveolar ventilation (VA) when these additional resistive, elastic and inspiratory threshold loads are imposed on weakened respiratory muscles. Nevertheless, despite increased stimulation of the respiratory centres, and large negative intrathoracic pressure swings, CO₂ retention and acidemia may occur. Dyspnoea, right ventricular failure, and encephalopathy characterise severe AECOPD complicated by ARF. Arterial pH reflects the acute worsening of VA and, regardless of the chronic Pa,CO₂
level, it represents the best marker of the ARF severity. Figure 2 shows a schematic representation of the sequence of responsible mechanisms that lead to acute-on-chronic respiratory failure in COPD patients.

Besides medical treatment of the underlying disease, oxygen supplementation and eventually ventilator assistance is appropriate therapy for acute on chronic respiratory failure. The goals of assisted ventilation (either invasive or noninvasive) during AECOPD, is to unload the respiratory muscles and to reduce CO\textsubscript{2} by increasing VA, thereby stabilising arterial pH until the underlying problem can be reversed.

### References

OXYGEN THERAPY AND VENTILATORY SUPPORT

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Acute oxygen therapy

Oxygen therapy is prescribed to correct hypoxaemia, rather than to reduce breathlessness, and so should always be titrated to arterial saturation ($S_aO_2$) or blood gas measurements. In acutely ill patients, high-concentration oxygen therapy should be delivered to correct $S_aO_2$ to 94–98%. In those with hypercapnic respiratory failure or at risk of ventilatory decompensation (e.g. severe chronic obstructive pulmonary disease (COPD), neuromuscular disease, obesity hypoventilation syndrome, chest wall disorder), a target $S_aO_2$ of 88–92% should be the aim. If this cannot be achieved without progressive acidosis and hypercapnia, ventilatory support should be added. In emergency situations, oxygen therapy can be delivered by a high concentration reservoir mask at a flow rate of 15 L·min$^{-1}$. In hypercapnic patients, 28% and 24% Venturi masks can be used. All acute patients require regular or continuous assessment by oximetry to ensure hypoxaemia has been corrected and dose is still appropriate. Blood gas measurements are indicated if there is deterioration in $S_aO_2$, features of CO$_2$ retention, such as drowsiness or flap, metabolic conditions or low cardiac output state.

Long-term oxygen therapy (LTOT)

Chronic hypoxaemia occurs either due to ventilation-perfusion mismatch, alveolar hypoventilation or diffusion problems in chronic lung disease, and in some conditions, e.g. COPD, all factors may be present. LTOT is used to correct hypoxaemia diurnally and nocturnally in the majority of patients. It has an additional use to palliate symptoms in those with end-stage or terminal conditions. In COPD, LTOT increases survival, reduces polycythaemia and, in some patients, may improve sleep quality and/or neuropsychiatric symptoms. LTOT is prescribed for $\geq 15$ h a day, e.g. via concentrator, to correct $S_aO_2$ to $\geq 90\%$ in those listed in table 1.

Ambulatory $O_2$ therapy is added to correct hypoxaemia on exercise. In sedentary patients using LTOT, ambulatory $O_2$ is usually prescribed at the same flow rate as daytime use. In active and mobile LTOT recipients and patients who desaturate on exertion but do not fulfil criteria for LTOT, optimum flow rates can be derived from a standard 6-min or shuttle walk, again aiming to correct $S_aO_2$ to

Key points

- Oxygen therapy is prescribed to correct hypoxaemia and should thus be titrated to arterial oxygen saturation.
- Long-term oxygen therapy can also palliate symptoms in patients with end-stage or terminal disease.
- NIV is the gold standard in treating acute hypercapnic COPD exacerbations, but is not useful in all acute respiratory situations.
- Long-term NIV home care can be more useful than oxygen therapy in chest wall and neuromuscular conditions.
There is no evidence to support the use of short-burst $O_2$ therapy.

**Acute ventilatory support**

The term respiratory support embraces invasive ventilation (via endotracheal tube or tracheostomy), noninvasive positive pressure ventilation (delivered through oronasal, nasal, oral or helmet interfaces), noninvasive negative pressure ventilation using an iron lung or cuirass-type device and continuous positive airway pressure (CPAP). CPAP does not augment minute ventilation greatly, and is therefore insufficient to control arterial carbon dioxide tension ($P_{a,CO_2}$) in markedly hypercapnic patients.

On respiratory and high-dependency wards, noninvasive positive pressure ventilation (NIV) is now gold standard therapy in managing acute hypercapnic exacerbations of COPD as it has been shown to reduce mortality by about half and to decrease the need for intubation and invasive ventilation, thereby reducing pressure on intensive care unit (ICU) beds. NIV can also facilitate weaning and reduce the need for re-intubation. However, in patients with acute lung injury, more than two system failures, and moderate or severe bulbar problems, NIV is unlikely to be successful. In those with poor cough efficiency, e.g. due to neuromuscular disease, NIV can be combined with cough-assist devices such as the cough in-exsufflator.

There is no evidence that one type of noninvasive ventilator is superior, but bilevel pressure support models are most commonly used, often starting at initial settings of inspiratory positive airway pressure 10–12 cmH$_2$O and expiratory positive airway pressure 4 cmH$_2$O, increasing according to comfort and arterial blood gas control. A close-fitting, comfortable mask/interface with minimal deadspace is also important to success rates.

**Home ventilatory support**

The evidence supporting long-term home NIV is not as secure as acute NIV use in COPD exacerbations but does have a longer track record in restrictive disorders. Long-term NIV is more effective than LTOT in patients with chest wall disease, and is the treatment of choice in neuromuscular patients, e.g. those with amyotrophic lateral sclerosis (ALS)/motor neurone disease with mild-to-moderate bulbar involvement and Duchenne muscular dystrophy, where NIV use extends life expectancy. $O_2$ use in neuromuscular disease may exacerbate hypercapnia and should not be used without close monitoring. Nocturnal NIV should be initiated in patients with symptomatic nocturnal hypoventilation, or daytime hypercapnia.

Home ventilation in COPD patients is more controversial. Several randomised studies of LTOT versus LTOT plus NIV have been performed but few had the power to examine survival and, in some, quality of life impact seems variable. There is some evidence that NIV in severe COPD may reduce ICU admissions and hospital admissions in COPD patients with recurrent hospitalisations for hypercapnic exacerbations, although larger studies are required.

Tracheostomy ventilation is required in patients with severe bulbar weakness, aspiration and in those in whom ventilatory failure cannot be controlled with NIV.

**References**


**Table 1. Criteria for long-term oxygen therapy**

<table>
<thead>
<tr>
<th>$P_{a,O_2}$</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\leq$ 7.3 kPa</td>
<td>Chronic arterial oxygen tension ($P_{a,O_2}$) ≤ 7.3 kPa</td>
</tr>
<tr>
<td>7.3–8.0 kPa if additional pulmonary hypertension, secondary polycythaemia, right heart failure or nocturnal desaturation</td>
<td></td>
</tr>
</tbody>
</table>


**Weblinks**

INTENSIVE CARE AND HIGH-DEPENDENCY UNIT

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The respiratory intensive care unit (RICU), sometimes referred to as the “high dependency unit”, is intended for patients with respiratory failure who do not require full ICU care but are considered to need more care than can usually be offered in a general ward.

The main reasons for admission to RICU are: 1) acute respiratory failure requiring noninvasive mechanical ventilation (NIV); 2) weaning of patients considered ventilator-dependent, and eventually their discharge home with a long-term ventilatory programme; and 3) requirement of intensive monitoring (preferably noninvasive).

The main expectations from a RICU are the possibility to relieve congestion of ICU beds, to guarantee a high level of nursing assistance, to adequately respond to potential sudden changes in a patient’s clinical condition and, under certain conditions, to provide a multidisciplinary rehabilitative approach to patients of high complexity.

The European Respiratory Society Task Force on RICU has defined three levels of care: 1) RICU, capable of applying both NIV and invasive ventilation, with a high nurse–patient ratio (>1:3) and an attending physician 24 h·day⁻¹, 7 days·week⁻¹; 2) respiratory intermediate care unit, capable of applying both NIV and invasive ventilation, with a nurse–patient ratio of 1:3–1:4 and the availability of a physician 24 h·day⁻¹, 7 days·week⁻¹; and 3) respiratory monitoring unit with a nurse–patient ratio <1:4, a physician on call within the hospital and the possibility of applying NIV.

These facilities may be located inside or outside a so-called “acute care hospital”. It should be borne in mind, however, that access to these different environments may differ internationally or even regionally within the same country.

Concerning the admission criteria, these are pretty well established for those patients who

Key points

- The main reasons for admission to RICU are use of “acute” NIV, weaning from mechanical ventilation and requirement of intensive monitoring.
- RICUs have three levels of care: 1) RICU, 2) respiratory intermediate care unit, and 3) respiratory monitoring unit.
- The approach to the patients admitted to a RICU is usually multidisciplinary.
- All the diagnostic (e.g., CT scans, NMR imaging) and therapeutic (e.g., major surgery) options should be readily available.
- RICUs should provide a fair amount of physical and pulmonary rehabilitation.
require “acute” application of NIV. As opposed to NIV application in the ward, the closely monitored setting permits safe application of NIV also in tenuous patients. Noninvasive management of such patients, including those with severe acute respiratory acidosis (i.e. pH <7.30) secondary to exacerbation of chronic obstructive pulmonary disease and those with hypoxaemia (i.e. arterial oxygen tension to inspiratory oxygen fraction ratio <200) requires a skilled, experienced staff and preparedness to promptly intubate the patient who deteriorates despite NIV. Delays in intubation and application of invasive ventilation may harm the patient. Theoretically, the worse the derangement in arterial blood gases, the higher the level of care should be (i.e. RICU versus respiratory monitoring unit).

There is still disagreement about the definition of a ventilator-dependent patient, in whom the transfer from the ICU to RICU may be useful in an attempt to ameliorate the chances of weaning. Various authors have used times limits as short as 48–72 h and as long as 30 days. Realistically, ~20% of patients in an ICU require mechanical ventilation for more than a week, and about half are successfully weaned over the following few days. Therefore, a limit of 2 weeks has been chosen by most authors to define the threshold for “ventilator-dependency”.

A definition, however, based only on time does not consider that for a particular patient to be regarded as ventilator-dependent (and, therefore, eligible for transfer to a RICU), the precipitating cause of the respiratory failure must have been reversed.

Some patients affected by an acute respiratory disorder may not fit the criteria of enrolment for mechanical ventilation when admitted to the hospital. However, their fragility and, very often, the high number of comorbidities do not allow the clinicians to make any firm statement about the immediate prognosis and risk of progression towards overt respiratory failure. These patients are likely to benefit from closer monitoring in a specialised environment, to avoid a delay in applying the appropriate treatment in case of worsening. Furthermore, in a subset of patients discharged from the ICU without the need for mechanical ventilation, but still having a tracheotomic tube in place, an associated increased mortality has been shown. An “intermediate step” in a protected environment after ICU discharge may be useful in these patients, primarily to allow better management of artificial airways.

The approach to the patients admitted to a RICU is usually multidisciplinary, in all cases involving physicians, respiratory therapists and nurses, and, in some cases, also involving dieticians, psychologists, physical and speech therapists, and social workers, as needed.

All the diagnostic (e.g. computed tomography (CT) scans, nuclear magnetic resonance (NMR) imaging) and therapeutic (e.g. major surgery) options should be readily available. Because most of the units are located within an acute care hospital, this is a problem in most cases. Furthermore, these units should be able to allow a reasonable level of privacy, to favour rest and permit, compared with ICUs, longer visiting hours for relatives and friends. Last but not least, these units should provide a fair amount of physical and pulmonary rehabilitation, which has been shown to help in freeing patients from mechanical ventilation and restoring them to an acceptable level of autonomy.

References
Pre-operative assessment of pulmonary risk is important in order to identify patients at risk for peri-operative morbidity and mortality, to determine possible pre-operative interventions that are beneficial for the outcome and to identify patients where surgery may be prohibitive.

Pre-operative evaluation for lung resection evaluates to which extent lung tissue can be resected without unacceptably increasing post-operative morbidity and mortality.

A careful history and physical examination are the most important tools for assessment of risk for post-operative pulmonary complications. Symptoms suggesting occult underlying lung disease (exercise intolerance, unexplained dyspnoea and cough) and the following risk factors for increased post-operative pulmonary complications need to be assessed.

**Surgery-specific risk factors** include: upper abdominal procedures; aortic, thoracic, and head and neck surgery, including neurosurgery; surgery lasting >3 h; and emergency procedures.

**Definite risk factors** include: chronic obstructive pulmonary disease (COPD); congestive heart failure; diminished general health status (American Society of Anesthesiologists (ASA) class >2 (table 1); malnutrition (serum albumin <35 mg·L⁻¹); and use of pancuronium as a neuromuscular blocker.

**Probable risk factors** include: obstructive sleep apnoea; general anaesthesia (when compared with spinal or epidural anaesthesia); abnormal chest radiograph; cigarette use within previous 8 weeks; and current upper respiratory tract infection.

It is noteworthy that pulmonary function tests are not part of routine pre-operative assessment unless patients are being evaluated for lung resection (see “Pulmonary resection”) or have unexplained dyspnoea or exercise intolerance. Clinical evaluation cannot determine whether airflow obstruction has been optimally reduced in patients with previously diagnosed COPD or asthma. Well-controlled asthma (free of wheezing, peak flows >80% predicted, or personal best) has been shown not to carry any added risk. Age and blood gases have no definitive role in the risk assessment when confounding issues such as comorbidities have been considered.

Patients with high risk (surgery-specific risk factor + one or more definite risk factors) will...
benefit from strategies to reduce pulmonary complications.

**Pre-operative interventions:** smoking cessation for 8 weeks; inhaled ipratropium or tiotropium for patients with clinically significant COPD; inhaled β-agonists for symptomatic COPD and asthma patients; pre-operative systemic glucocorticoids for COPD and asthma patients who are not optimised on inhalative treatment; delay elective surgery if respiratory infection present; antibiotics for patients with purulent sputum or change in sputum character; and inspiratory muscle training.

**Intraoperative interventions:** choose alternative procedure lasting <3 h when possible (video-assisted thoracoscopic and laparoscopic procedures have ~1/10th the pulmonary complication rates of open procedures); minimise duration of anaesthesia; delay elective surgery if respiratory infection present; antibiotics for patients with purulent sputum or change in sputum character; and inspiratory muscle training.

**Post-operative interventions:** deep-breathing exercises or incentive spirometry; and epidural analgesia instead of parenteral opioids.

**Cardiac evaluation:** history, physical examination and resting ECG are frequently required for the initial estimate of the perioperative cardiac risk. The definitive assessment of cardiac risk should respect current guidelines for cardiologists.

**Pulmonary resection**

Pulmonary resection is a high-risk procedure with a mortality of 2–3% for lobectomy and 4–6% for pneumonectomy in experienced centres. The clinical evaluation should focus on respiratory and cardiovascular pathology. Air flow limitation should be optimised before further evaluation and cardiac disease identified and managed either medically or surgically. Initial pulmonary function evaluation should include at least forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and transfer capacity of the lung for carbon monoxide (TLCO). Values >80% pred for FEV1 and TLCO are associated with an uncomplicated surgical course for resection up to a pneumonectomy. All other candidates should undergo a formal exercise test. Patients with a peak oxygen uptake ($V'\text{O}_2$) >20 mL·kg$^{-1}$·min$^{-1}$ (or >75% pred) tolerate pulmonary resection up to a

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**Table 1. American Society of Anesthesiologists (ASA) classification of pre-operative risk**

<table>
<thead>
<tr>
<th>ASA class</th>
<th>Systemic disturbance</th>
<th>PPC %</th>
<th>Mortality %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Healthy patient with no disease outside of the surgical process</td>
<td>1.2</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>2</td>
<td>Mild-to-moderate systemic disease caused by the surgical condition or by other pathological processes, medically well-controlled</td>
<td>5.4</td>
<td>0.2</td>
</tr>
<tr>
<td>3</td>
<td>Severe disease process that limits activity but is not incapacitating</td>
<td>11.4</td>
<td>1.2</td>
</tr>
<tr>
<td>4</td>
<td>Severe incapacitating disease process that is constant threat to life</td>
<td>10.9</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>Moribund patient not expected to survive 24 h with or without an operation</td>
<td>NA</td>
<td>34</td>
</tr>
<tr>
<td>E</td>
<td>Suffix to indicate emergency surgery for any class</td>
<td>Increased</td>
<td>Increased</td>
</tr>
</tbody>
</table>

PPC: post-operative pulmonary complications; NA: not applicable.
pneumonectomy, and values
>15 mL·kg⁻¹·min⁻¹ are sufficient for
lobectomy. Values <10 mL·kg⁻¹·min⁻¹ are
predictive of major post-operative
complications and disability. Further
evaluation according to a validated algorithm
(fig. 1) necessitates the estimation of the
relative contribution of the tissue earmarked
for resection by means of the predicted post-
operative (ppo) values for FEV₁, TL,CO and V'\textsubscript{O}_2
(“split function”). The ppo values of these
parameters are equal to their pre-operative
values × (1 – fractional contribution of the
tissue earmarked for resection). There are
three acceptable ways of estimating the
relative functional contribution or split lung
function: anatomical calculation; quantitative
computed tomography (CT) scanning; or split
perfusion scanning. Anatomical calculations
are by far the simplest: the number of patent
(or functional) segments that are due for
resection is subtracted from the total number
of segments (19) and this value is divided by
19 to give a fraction. The FEV₁-ppo is
estimated to be equal to the pre-operative
FEV₁ × \((19 – \text{patent segments removed})/19\).
Anatomical calculations have been
shown to overestimate the functional loss so
that patients who are deemed operable by
anatomical calculations will generally not
require radiological calculations.

Calculated ppo values on the basis of lung
perfusion scans (with technetium 99m-
labelled macroaggregates) have been shown
to correlate best with actual post-operative
values. Densitometric calculations on the
basis of CT scans are marginally less accurate
than perfusion scans. The advantage of this
method is the availability of the information
since most lung resection candidates
invariably have a pre-operative chest CT scan
and modern software simplifies the three-
dimensional reconstruction for the calculation
of the relative volume of lung to be resected.

The recent revival of simple stair climbing as a
low-cost alternative to assess exercise capacity
and operative risk is still under investigation.
One large study showed a significant
correlation between the ability to climb to a

20.6-m elevation and an uncomplicated
surgical course.

Lung volume reduction surgery for end-stage
emphysema has partly redefined the limits of
lung resection. Many patients with pre-
operative FEV₁ and TL,CO between 20–40%
pred have benefited from targeted removal of
the most emphysematous lung regions.

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MICROBIOLOGY TESTING AND INTERPRETATION

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In primary care, microbiological work-up in respiratory infections is primarily meant as an epidemiological investigation in order to guide future empiric antimicrobial policies. Hardly any study has shown that initial microbiological studies in primary care affect the outcome of respiratory infections. Nevertheless an aetiologic diagnosis, of both bacteria and viruses and mixtures of these in community-acquired pneumonia (CAP) or lower respiratory tract infections (LRTI) may be helpful in guiding treatment, particularly in the more severely ill patients. Diagnostic testing should not lead to delays in initiation of therapy, however. Even with extensive diagnostic testing, a specific aetiology is usually identified in only half of all patients, generally at least 1–2 days after the clinical diagnosis is made. With the advent of recently developed rapid techniques such as immunochromatographic tests, urinary antigen tests and particularly nucleic acid amplification tests (NAATs) that produce results within 30 min or 4–5 h, microbiological information is becoming clinically useful (table 1).

Key points
For the aetiologic diagnosis of lower respiratory tract infections (LRTIs):

- Gram stain and culture of a good quality sputum can be valuable for the microbiological diagnosis of LRTI caused by Streptococcus pneumoniae or Haemophilus influenzae.
- Urinary antigen detection is a very helpful and rapid test for the diagnosis of pneumococcal or Legionella infections.
- Serology is rarely helpful in the management of the individual patient with LRTI.
- Molecular tests for the detection of respiratory viruses and atypical pathogens in specific patient populations are desirable.

Conventional culture techniques

Blood culture For the diagnosis of pneumonia, blood cultures have a very high specificity but are positive in only about 10–20% of untreated cases. In some studies, a direct correlation has been found between the severity (based on the Fine Severity Index) of pneumonia and blood culture positivity rate. Two blood cultures should be obtained as early as possible in the disease and before any antibiotic treatment is started. Blood cultures are more sensitive for the detection of Streptococcus pneumoniae than for the detection of Haemophilus influenzae. Despite their low sensitivity, blood cultures in CAP are considered the gold standard because the organisms are recovered from a normally sterile source. Results may be available after 24–48 h.

Sputum Gram stain and culture The most frequently submitted specimen in cases of...
LRTI and more specifically in pneumonia is sputum. To be of value for microbial diagnosis and early guidance to therapy, sputum specimens must be representative of lower respiratory secretions, and must be interpreted according to strict criteria by an experienced observer. The most widely used method to assess acceptability in this regard is based on cytological criteria. The specimen should therefore be screened by microscopic examination for the relative number of polymorphonuclear cells and squamous epithelial cells in a lower power (10×) field. Invalid specimens (≥ 10 squamous epithelial cells and ≤ 25 polymorphonuclear cells/field) should not be examined further. It may be difficult to obtain good-quality, purulent sputum. Many LRTI or pneumonia patients,

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Specimen</th>
<th>Rapid tests</th>
<th>Conventional tests</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. pneumoniae</em></td>
<td>Blood</td>
<td>Blood culture</td>
<td>Culture</td>
<td>Positive in 10–20% of cases when collected within 4 days</td>
</tr>
<tr>
<td></td>
<td>Sputum</td>
<td>Gram stain</td>
<td>Culture</td>
<td>Only purulent samples acceptable. Obtained in 35–40% of patients; informative if &gt;90% Gram-positive, diplococci most relevant if Gram stain informative</td>
</tr>
<tr>
<td></td>
<td>Pleural exudates</td>
<td>Gram stain</td>
<td>Culture</td>
<td>Specific, only considered if less invasive methods nondiagnostic</td>
</tr>
<tr>
<td></td>
<td>Urine</td>
<td>Antigen test</td>
<td></td>
<td>Sensitivity 50–80% of bacteraemic cases, lacks specificity in children, more evaluation necessary</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>Blood</td>
<td>Blood culture</td>
<td>Culture</td>
<td>Less frequently positive than for <em>S. pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td>Respiratory specimens</td>
<td>Gram stain</td>
<td>Culture</td>
<td></td>
</tr>
<tr>
<td><em>Legionella spp.</em></td>
<td>Urine</td>
<td>Antigen test</td>
<td>Culture</td>
<td>Sensitivity 66–95%</td>
</tr>
<tr>
<td></td>
<td>Respiratory specimens</td>
<td>NAAT</td>
<td>Culture</td>
<td>Culture: on appropriate media, late results, less sensitive than NAAT</td>
</tr>
<tr>
<td></td>
<td>Serum</td>
<td>IgM and IgG serology</td>
<td></td>
<td>Acute and convalescent specimens. Retrospective diagnosis</td>
</tr>
<tr>
<td><em>C. pneumoniae</em> <em>M. pneumoniae</em></td>
<td>Respiratory specimens</td>
<td>NAAT</td>
<td>Culture</td>
<td>Culture: on appropriate medium; low sensitivity compared to NAAT</td>
</tr>
<tr>
<td></td>
<td>Serum</td>
<td>IgM and IgG serology</td>
<td></td>
<td>Acute and convalescent specimens. Lack of sensitivity, specificity, not appropriate for individual patient management. Retrospective results</td>
</tr>
<tr>
<td>Respiratory viruses</td>
<td>Respiratory specimens</td>
<td>Direct antigen tests, NAAT</td>
<td>Virus isolation</td>
<td>Requirement for appropriate infrastructure. Isolation less sensitive than NAAT</td>
</tr>
</tbody>
</table>

*S. pneumoniae*: *Streptococcus pneumoniae*; *H. influenzae*: *Haemophilus influenzae*; *C. pneumoniae*: *Chlamydia pneumoniae*; *M. pneumoniae*: *Mycoplasma pneumoniae*; BAL: bronchoalveolar lavage; PSB: protected specimen brush; NAAT: nucleic acid amplification test; Ig: immunoglobulin
particularly older ones, do not produce sputum. Satisfactory sputum specimens can be obtained in 32–55% of patients.

Large studies on the diagnostic value of Gram staining in primary care patients are lacking, but some hospital-based studies show that in good-quality Gram-stained sputum, the presence of a single or a preponderant morphotype of bacteria (± 90%) may be diagnostic. This is based on correspondence with the organisms recovered from blood cultures obtained in parallel, and which are the gold standard. The sensitivity and specificity for the detection of *S. pneumoniae* are 35–79% and 96%, respectively, and 42% and 99% respectively for *H. influenzae*. Sputum with a mixed flora in the Gram stain has no diagnostic value. The sputum Gram stain is therefore valuable in guiding the processing and interpretation of sputum cultures.

The sensitivity and specificity of sputum cultures are reduced by contamination with flora colonising the upper respiratory tract. The value of sputum cultures in establishing a bacterial cause of LRTI depends on how the specimens are collected and processed. The reported yield of sputum cultures has varied widely, from <20% for outpatients to >90% for hospitalised patients. The sputum Gram stain is valuable in guiding the processing and interpretation of sputum cultures. Sputum culture results are most convincing when the organism(s) isolated in culture are compatible with the morphology of the organisms present in the Gram stain. In the absence of an informative Gram stain, the predictive value of sputum culture is very low.

**Rapid antigen tests**

**Urinary antigen tests** The *S. pneumoniae* urinary antigen test in adult CAP has been shown to have a sensitivity of 65–100% and a specificity of >90%; however, weak positive results should be interpreted with caution. There is a relation between the degree of *S. pneumoniae* urinary antigen test positivity and the pneumonia severity index. Therefore, the test could be reserved for high-risk patients for whom demonstrative results of a sputum Gram stain are unavailable.

The urinary antigen test may also be applied on pleural fluid with a high sensitivity and specificity, and on serum samples with a sensitivity of 50% in bacteraemic patients and 40% in nonbacteraemic patients. Vaccination does not result in a positive urinary antigen test. The immunochromatographic urinary antigen test for *S. pneumoniae* is therefore useful for the aetologic diagnosis of severe CAP, especially for patients without demonstrative results of a sputum Gram stain.

Urinary antigen detection is currently the most helpful rapid test for the diagnosis of a *Legionella* infection. Several test formats have been developed, the enzyme immunoassay (EIA) format being more suited to test a larger number of specimens and taking a few hours to complete. The immunochromatographic format is better suited for single specimens, and produces a result within minutes. These tests are particularly useful since culture of *Legionella* spp. is slow and takes 3–4 days. *Legionella* urinary antigen detection is frequently the first positive laboratory test in this infection. The sensitivity of the tests varies between 65–70% in unconcentrated urine and increases significantly after concentration of the specimen. In *Legionella* infection, there is also a relationship between the degree of positivity of the urinary antigen test and the severity of disease: for patients with mild Legionnaires’ disease, test sensitivities range from only 40–50%, whereas for patients with severe Legionnaires’ disease who need immediate special medical care, sensitivities reach 88–100%.

**Antigen tests on pharyngeal specimens** A variety of antigen tests have been evaluated on respiratory specimens. For respiratory infections due to viruses, the optimal specimen is the nasopharyngeal aspirate. During recent years, a considerable number of previously unknown respiratory viral agents have been discovered whose in
vitro culture is very slow or even unrealised: the human metapneumovirus, the novel coronaviruses NL 63, HKU1 and human bocavirus. Antigens of the many common respiratory viruses, influenza virus, respiratory syncytial virus (RSV), adenovirus and parainfluenza viruses, can be detected by direct immunofluorescence (DIF) or by commercially available EIAs. The sensitivities of these tests vary from 50–90% depending on the virus and the patient population studied. For the detection of influenza virus infections, the sensitivity of immunofluorescence can be increased by inoculation of the clinical sample on appropriate cells, followed by immunofluorescence after 48 h. Several common respiratory viruses can be detected simultaneously by the use of pooled monoclonal antibodies. The sensitivity of the DIF test is lower in adults and older people than in children. Rapid methods for the detection of influenza virus infections are of particular interest because of the availability of antiviral agents that must be given within 48 h after onset of symptoms.

Serology

Efforts have been made to diagnose infections caused by slowly growing or difficult to grow organisms by serology. This holds particularly for Mycoplasma pneumoniae, Chlamyphila pneumoniae, Legionella infections and respiratory viruses. It should be remembered that the most reliable serologic evidence of an ongoing infection is based on a fourfold increase in titre of immunoglobulin (Ig)G (or IgG+IgM) antibodies during the evolution of the disease episode based on two serum samples collected at an interval of 14–21 days or longer, and/or the appearance of IgM antibodies during the evolution of the disease. IgM tests are usually less sensitive and specific than fourfold changes in antibody titres between paired specimens separated by several weeks. Solitary high IgG titers have no diagnostic meaning for an acute infection since the moment of the seroconversion is unknown and necessarily took place some time before the illness under observation started.

The sensitivity and specificity of serologic tests are related to the antigen used. For M. pneumoniae and C. pneumoniae, a great number of antigen preparations have been proposed: whole organisms, protein fractions, glycoprotein fractions and recombinant antigens. Several studies illustrate a lack of standardisation of antigens of M. pneumoniae.

For a number of respiratory agents, a variety of tests are available commercially. Some assays lack both sensitivity and specificity, emphasising the need for more validation and quality control.

IgM antibodies against M. pneumoniae require up to 1 week to reach diagnostic titres, and sometimes much longer. Anti-M. pneumoniae IgM antibodies can be detected in 7–25% (depending on the test applied) of acute sera and IgG antibodies in 41–63% of convalescent sera depending on the timing of the second sample illustrating the low incidence of IgM antibodies in the acute-phase serum specimens and importance of the delay between the two serum samples. Legionella antibody tests also have a sensitivity of only 61–64% depending on the assay applied and also do not substantially improve the diagnosis of legionellosis. The acute antibody test for Legionella in Legionnaires’ disease is usually negative or demonstrates very low titres. As for other aetiologies, high titres of IgG and/or IgM, above a certain threshold, present early during the disease, have been interpreted as diagnostic but at least one study showed that this titre had a very low positive predictive value.

For respiratory viral infections such as for influenza and RSV, a significant or fourfold IgG antibody increase is detected by EIA in ~80–90% of patients at only 20–30 days after the onset of disease.

The serologic measurement of specific antibody responses can mostly not offer an early diagnosis and therefore has limited
application for an aetiologic diagnosis and for the routine management of the individual patient with LRTI. Consequently, it is rather an epidemiological than a diagnostic tool.

**Nucleic acid amplification tests**

The newest approach in the diagnosis of respiratory tract infections is the detection of microbial nucleic acids by NAATs. Culture procedures for viruses and fastidious bacteria, *M. pneumoniae*, *C. pneumoniae*, *Legionella pneumophila*, *Bordetella pertussis*, which normally do not colonise the human respiratory tract, are too insensitive and too slow to be therapeutically relevant and these pathogens therefore should be detected using NAATs, whose sensitivity is almost always superior to that of the traditional procedures.

A multitude of reports has appeared on the epidemiology of LRTIs but most are restricted to a few viruses (influenza, sometimes together with RSV, to rhino-, metapneumo- or coronaviruses) and/or to some population groups, *e.g.* children, adults or the elderly. Great variations occur in function of time, place and the age-groups studied. Although the role of some new viruses is becoming more clear in specific patient populations, more studies are needed to identify the clinical relevance of some others, such as the bocavirus. All these studies were done with the traditional NAATs that require at least 1–2 days, producing *a posteriori* results that were unavailable to the clinician in time to have an impact on patient management. Real-time multiplex NAATs offer the solution. To cover the wide spectrum of aetiologic respiratory agents, a number of uni- and/or multiplex reactions are performed simultaneously. Both in-house and commercially available multiplex NAATs for the simultaneous detection of two, three or up to 22 different respiratory pathogens, including the “atypical” *M. pneumoniae*, *C. pneumoniae* and *L. pneumophila*, and respiratory viruses, with a mixture of primers have been developed.

The combined use of single target assays or of multiplex assays has increased the diagnostic yield in respiratory infections by 30–50%: combined with traditional bacteriological techniques to diagnose *S. pneumoniae* infections, >50% – and in some studies of CAP up to 70% – of aetiologic agents can be detected.

The wider application of multiplex reactions during recent years has resulted in the detection of numerous simultaneous viral infections with widely varying incidences: from 3% to even 23% or 35%, depending on whether bacterial agents are also included. The divergent incidences may result from the variety of diagnostic panels applied. Combined viral and viral–bacterial infections are diagnosed but no preferential combinations have been found. The clinical significance of combined infections remains to be further clarified. Respiratory viruses have also been increasingly recognised as causes of severe LRTIs in immunocompromised hosts. Respiratory infections are more common in solid organ recipients, particularly in lung transplant recipients. Infections are especially dangerous prior to engraftment and during 3 months after transplantation, in the setting of graft versus host disease. The origin of the infections is community-acquired as well as nosocomial.

As more epidemiological information on the role of a panel of respiratory viral pathogens becomes available, it is clear that screening for these viruses in specific patient populations such as transplant patients, very young children or the elderly is desirable and preventive and therapeutic recommendations may take this information into account.

NAATs are, however, not required for every purpose. For cohorting RSV-infected paediatric patients, the DIF tests can be as sensitive as an RT-PCR with results available within 60 min (and at lower cost than with NAATs). Very rapid chromatographic tests are also available for RSV, which can be done in the laboratory outside virology laboratory operating hours. These tests lack sensitivity, however, when applied to respiratory samples of adult patients.
Conclusion

In recent years significant progress has been made in the microbiological diagnosis of respiratory infections. A straightforward interpretation of a good-quality, Gram-stained sputum sample has been established, and has been shown to be important for rapid diagnosis of pneumonia and the interpretation of culture results in severely ill patients.

The number of possible aetiologic agents, viruses and fastidious bacteria has been extended and their epidemiology has been clarified. Sensitive and rapid methods for their detection have been developed and are increasingly validated in clinical settings.

Amplification techniques are at present more expensive than conventional approaches. However, improvements in standardisation and automation for sample preparation and technical advances will lead to increased use of amplification methods and cost reductions to rates competitive with conventional methods. Several studies have tended to show cost efficiency of rapid diagnosis of acute respiratory infections resulting from reduced antibiotic use and complementary laboratory investigations but most significantly from shorter hospitalisation and reduced isolation periods. Serologic diagnosis of those cases that remain undetected by the NAA Ts is of no clinical use since it is available only after many days or even weeks.

References

Upper respiratory tract infections (URTIs) are the most common infectious illness in the general population. They are the leading cause for people missing work or school.

**Prevalence**

URTIs usually occur during the cold months, mainly due to overcrowding inside buildings. The mean frequency is 2–4 episodes annually for adults. In children it is higher. Antigenic variation of 100s of respiratory viruses allows repeated circulation in the community.

**Spectrum**

The upper respiratory tract consists of the nose, paranasal sinuses, pharynx, larynx, trachea and bronchi. The most prevalent illness is the common cold (rhino-sinusitis), followed by sinusitis, pharyngitis/tonsillitis, laryngitis and sometimes tracheobronchitis (table 1).

Onset of symptoms usually begins after 1–3 days after exposure to a microbial pathogen. The duration of the symptoms is typically 7–10 days but may persist longer.

**Transmission and predisposition**

Transmission of pathogens happens by aerosol, droplet, or direct hand-to-hand contact. The pathogens invade the respiratory epithelium of the corresponding area. Sinusitis and acute bronchitis are often preceded by a common cold. There are predisposing conditions as allergic rhinoconjunctivitis, nasal septum deviation, immunodeficiency, or cocaine abuse. Smoking or exposure to second-hand smoke and travel are additional risk factors.

**Key points**

- URTIs are the most common infectious illness in the general population, and are the leading cause of missed work and school.
- Most URTIs are viral in origin, and typical agents are rhinoviruses, coronaviruses, adenoviruses, coxsackieviruses, influenza- and parainfluenzaviruses, human metapneumovirus, and respiratory syncytial virus.
- URTIs rarely cause permanent sequelae or death, but can progress to otitis media, bronchitis, bronchiolitis, pneumonia, sepsis, meningitis, intracranial abscess, and other infections.
- Diagnosis is usually purely clinical; diagnostic investigations should only be performed in special circumstances, such as influenza, group A streptococcal pharyngitis, infectious mononucleosis and pneumonia.
- Infection will often be self-limiting, with no specific treatment necessary; the only indications for antibiotic treatment are group A streptococcal pharyngitis, bacterial sinusitis and pertussis.
Pathogens

Most URTIs are viral in origin. More than 200 different viruses are known to cause the common cold. Typical viral agents that cause URTIs are rhinoviruses, coronaviruses, adenoviruses, coxsackieviruses, influenza- and parainfluenzaviruses, human metapneumovirus, respiratory syncytial virus and others.

Group A, but also group C and G Streptococci can cause pharyngitis (10–20% of cases), as well as other bacteria like Neisseria gonorrhoeae, Corynebacterium diphtheriae, and atypical bacteria (Chlamydia, Mycoplasma). Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis can be the bacterial cause of rhinosinusitis or tracheobronchitis. Bordetella pertussis or Bordetella parapertussis are the cause of whooping cough associated with laryngotracheitis.

Complications

URTIs rarely cause permanent sequelae or death. However they can progress to otitis media, bronchitis, bronchiolitis, pneumonia, sepsis, meningitis, intracranial abscess, and other infections. Specific complications can occur with untreated group A streptococcal pharyngitis resulting in acute rheumatic fever (ARF), acute glomerulonephritis, peritonsillar abscess, and toxic shock syndrome. Sinusitis can extend into surrounding deep tissue leading to orbital cellulitis, subperiosteal abscess, orbital abscess, frontal and maxillary osteomyelitis, subdural abscess, meningitis, and brain abscess. Epiglottitis, a presentation of laryngitis caused by H. influenzae type B, poses a risk of death due to sudden airway obstruction and other complications, including septic arthritis, meningitis, empyema and mediastinitis.

Diagnosis

In most cases, the diagnosis is purely clinical. History, inspection, palpation, percussion and auscultation (see table 1) are sufficient. Additional diagnostic investigations should only be performed in special circumstances. These include suspicion of:

<table>
<thead>
<tr>
<th>Upper respiratory tract infection</th>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common cold</td>
<td>Nasal congestion, mucopurulent nasal discharge, sneezing, sore throat, halitosis</td>
<td>Low-grade fever, nasal vocal tone, inflamed nasal mucosa</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>Unilateral facial pain, maxillary toothache, headache, purulent nasal discharge</td>
<td>Swelling, redness, tenderness to palpation or percussion overlying the affected sinuses, abnormal transillumination</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>Sore throat, odynophagia, or dysphagia, fever, absence of cough, halitosis</td>
<td>Pharyngeal erythema and exudate, palatal petechiae (doughnut lesions), tender anterior cervical lymphadenopathy, scalartiniiform rash, pharyngeal or palatal vesicles and ulcers (herpangina), tonsillar hypertrophy</td>
</tr>
<tr>
<td>Laryngitis</td>
<td>Hoarseness, voicelessness, dry cough, odynophagia, or dysphagia, halitosis</td>
<td>Low-grade fever, cervical lymphadenopathy, inspiratory stridor, tachypnoea</td>
</tr>
<tr>
<td>Tracheo-bronchitis</td>
<td>Dry or productive cough, dyspnoea</td>
<td>Low-grade fever, anterior cervical lymphadenopathy, tachypnoea, rhonchi</td>
</tr>
</tbody>
</table>

Upper respiratory tract infections
Influenza (perform pharyngeal swab for PCR).

Group A streptococcal pharyngitis (perform pharyngeal swab for rapid antigen detection test).

Infectious mononucleosis (there are usually additional symptoms such as hepatosplenomegaly and lymphocytosis; perform mononucleosis spot test in blood).

Pneumonia (perform C-reactive protein and chest radiography).

**Differential diagnosis**

Influenza viruses can cause mild URTIs but also systemic disease. The definition of influenza-like illness is fever $\geq 38.5^\circ C$ and one of the following: cough, sore throat, headache and muscle ache.

Allergic rhinoconjunctivitis is characterised by oedema of the conjunctiva, itching and increased lacrimation additional to symptoms of rhinitis. It shows seasonal variation related to allergen exposure.

Acute thyroiditis can present as sore throat, a common symptom in URTIs. Investigation of thyroid hormones, thyroid-specific autoantibodies, ultrasound and radioactive iodine uptake can help with diagnosis.

Gastro-oesophageal reflux disease (GORD) can clinically present as laryngopharyngitis and/or tracheobronchitis. History and oesophagastroduodenoscopy in more severe cases should be performed.

Wegener’s granulomatosis should be considered in patients with sinusitis not responding to therapy. Classic antineutrophil cytoplasmic antibodies and biopsy are key to diagnosis.

Asthma should be considered in patients with a nonresolving cough for $>3$ weeks.

**Treatment**

The vast majority of URTIs are viral in origin. In most cases the infection will be self-limiting and no specific treatment is necessary. Sufficient fluid intake should be advocated. The effect of zinc and vitamin C is still debated. Echinacea seems to be effective in prevention and treatment of the common cold. Nonsteroidal anti-inflammatory drugs relieve fever, headache and malaise. In general, there is no role for antibiotic therapy in the management of common cold or any mild URTI. The only indications for antibiotic treatment are group A streptococcal pharyngitis (oral penicillin or macrolide), bacterial sinusitis (aminopenicilline + β-lactamase inhibitor, cephalosporin 2nd/3rd generation) and pertussis (erythromycin or trimethoprim-sulfamethoxazole). Nasal decongestants decrease symptoms in rhinitis and sinusitis, topical nasal steroids improve sinusitis. Confirmed cases of influenza can be considered for a therapy with neuraminidase inhibitors according to Centers for Disease Control and Prevention guidelines (www.cdc.gov/flu). New treatment options for the most prevalent respiratory pathogens, human rhinoviruses, are under development.

**Prevention**

Direct hand-to-hand contact is an important mechanism of pathogen transmission. Hence, frequent hand washing or disinfection in healthcare can limit spread of infection significantly. Influenza vaccination has been shown to be very beneficial and has to be advocated. In children, the routine administration of *H. influenzae* type B (Hib) vaccination has practically eradicated Hib as a cause of URTI. A herd effect could be demonstrated, as the introduction of the pneumococcal vaccine in children with significant reduction in invasive pneumococcal disease in adults.

**References**


**Weblinks**


- [www.cdc.gov/flu](http://www.cdc.gov/flu).
INFECTIVE EXACERBATI ONS
OF COPD

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A recent American Thoracic Society (ATS)/European Respiratory Society (ERS) task force has defined the exacerbation of chronic obstructive pulmonary disease (COPD) as: “an increase in respiratory symptoms over baseline that usually requires medical intervention”. In fact, the chronic and progressive course of COPD is often aggravated by short periods of increasing symptoms, particularly increasing cough, dyspnoea and production of sputum, which can become purulent. Patients with moderate-to-severe COPD present a mean of between one and two of these episodes or exacerbations per year, but this number is dependent on the degree of functional impairment at baseline. Patients with more advanced disease may suffer from an increasing number of exacerbations.

Outcomes of exacerbations: risk factors for failure

The failure rate of ambulatory treatment of exacerbations of COPD ranges 12-26%, and failure may lead to hospital admission. The mortality of patients admitted to hospital with COPD exacerbation is ~10-14% and the mortality of those admitted to an intensive care unit (ICU) may be as high as 24%. Hospitalisation has an important impact on COPD patients, and after the first admission to hospital the mean survival time has been estimated to be 5.7 yrs. Frequent exacerbations have been demonstrated to have a negative impact on health-related quality of life in patients with COPD and survival is significantly related to the frequency and severity of exacerbations.

Identification of risk factors for failure of ambulatory treatment may allow the implementation of more aggressive broad-spectrum treatment and closer follow-up (table 1).

Aetiology of exacerbations

A variety of causes may deteriorate the clinical stability of patients with COPD: cold temperature, air pollution, lack of compliance with respiratory medication, worsening of comorbidities, and pulmonary embolism, among others. However, up to three-quarters of exacerbations can be infectious in origin, with bacteria being responsible for three quarters of these exacerbations. In addition, co-infection with respiratory viruses may be frequent in patients with severe COPD. The most frequent microorganisms causing exacerbations are presented in table 2.

Key points

- Up to 75% of COPD exacerbations are of infective aetiology.
- Haemophilus influenzae is the most frequent pathogen causing exacerbations.
- The relapse rate may be as high as 20%.
- Risk factors and bacterial resistance to antibiotics are the criteria used for the selection of antibiotics.
The role of bacteria in exacerbations has been a matter of controversy since the respiratory secretions of some patients with stable COPD carry significant concentrations of bacteria. Therefore, the isolation of such microorganisms during exacerbations should not always be interpreted as a definite demonstration of their pathogenic role. However, studies performed with specific invasive techniques have shown that both the number of patients with pathogenic bacteria in respiratory secretions and their concentrations in bronchial secretions increase during exacerbations. The change in the colonising strain of bacteria is an important mechanism originating exacerbations. The host does not have protective specific antibodies against the new strain of bacteria and the microorganism can thereby proliferate and cause the exacerbation.

**Diagnosis of infective exacerbations**

The combination of symptoms described by **Antonisen et al.**, i.e. increased dyspnoea and increased production or purulence of sputum, have been widely used to identify exacerbations that require treatment with antibiotics. However, new studies have demonstrated that the presence of green (purulent) sputum as opposed to white (mucoid) is one of the best and easiest methods to predict the bacterial aetiology and the need for antibiotic therapy. Unfortunately, no signs or symptoms can help the clinician to differentiate bacterial from viral exacerbations. Both viral and bacterial agents may co-infect a patient with COPD, and mixed infection is associated with higher inflammation, more severe symptoms and prolonged recovery time.

The degree of airflow impairment in COPD patients indicates the presence of different microorganisms during the course of exacerbations. Individuals with severe pulmonary function impairment, manifested by FEV1 <50% predicted, are at a sixfold

<table>
<thead>
<tr>
<th>Risk factors for failure after ambulatory treatment of exacerbations of COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coexisting cardiopulmonary disease</td>
</tr>
<tr>
<td>Increasing number of visits to the GP for respiratory problems (&gt;3·yr⁻¹)</td>
</tr>
<tr>
<td>Increasing number of previous exacerbations (&gt;3·yr⁻¹)</td>
</tr>
<tr>
<td>Increasing baseline dyspnoea</td>
</tr>
<tr>
<td>Severity of FEV1 impairment (FEV1 &lt;35% predicted)</td>
</tr>
<tr>
<td>Use of home oxygen</td>
</tr>
<tr>
<td>Inadequate antibiotic therapy</td>
</tr>
</tbody>
</table>

*GP: general practitioner; FEV1: forced expiratory volume in 1 s.*

**Table 2. Aetiology of exacerbations of COPD**

<table>
<thead>
<tr>
<th>Infectious exacerbations (~60–80% of all exacerbations)</th>
<th>Noninfectious exacerbations (20–40% of all exacerbations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent (70–85% of infectious exacerbations)</td>
<td>Heart failure</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Nonpulmonary infections</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Viruses (influenza/parainfluenza, rhinoviruses, coronaviruses)</td>
<td>Infrequent (15–30% of infectious exacerbations)</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td><em>Chlamydia pneumoniae</em></td>
</tr>
<tr>
<td>Opportunistic Gram-negative</td>
<td><em>Mycoplasma pneumoniae</em></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
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</tr>
</tbody>
</table>

*Infective exacerbations of COPD*
higher risk of developing acute exacerbations caused by *Haemophilus influenzae* or *Pseudomonas aeruginosa* than patients presenting FEV₁ >50% pred. Those with FEV₁ <30% pred have an even higher risk for *P. aeruginosa*.

However, the clinical presentation of exacerbation is not characteristic of any particular microorganism and no microbiological diagnostic test is available for differential diagnosis in primary care. The use of biomarkers such as procalcitonin to identify bacterial exacerbations is promising, but more studies are required.

**Antibiotic treatment of exacerbations**

Antibiotics have been shown to be superior to placebo in the treatment of exacerbations when all of the Anthonisen criteria are present; i.e. increased dyspnoea, increased production and purulence of sputum. The purulence of sputum has recently been demonstrated to be very sensitive and specific for the diagnosis of bacterial exacerbation and indicates the need for antibiotic therapy. Therefore, most guidelines also recommend antibiotic therapy in patients with two of the three aforementioned criteria if one of them is increased in purulence of sputum.

The antibiotic of choice may vary from country to country based on the prevalence of different bacteria and, more importantly, the differences in susceptibility of the causative bacteria to antibiotics. As an example, in 2000, the prevalence of macrolide-resistant *Streptococcus pneumoniae* in the UK was 12.2%, but in France it was 58.1%, while the production of β-lactamase by *H. influenzae* was 13.9% in the UK and 33.1% in France.

Guidelines recommend the use of so-called first-line antibiotics, such as amoxicillin or tetracyclin, in low-risk patients in countries with a low prevalence of antibiotic resistance, such as the Netherlands, UK and other North European countries. However, in countries with a high percentage of resistant strains or in patients with risk factors for treatment failure, the choice of an antibiotic must consider amoxycillin/clavulanate, the new fluoroquinolones (moxifloxacin, levofloxacin) or cephalosporins (cefditoren, cefuroxime).

Table 3 describes the antibiotic alternatives according to the severity of COPD.

**Nonantibiotic treatment of exacerbations**

Acute exacerbations of COPD present with increasing dyspnoea in most cases. Both infectious and noninfectious exacerbations are the result of an ongoing inflammatory reaction in the bronchial mucosa making anti-inflammatory and bronchodilator therapy mandatory.

A short course of oral corticosteroids has been demonstrated to accelerate recovery from exacerbations and reduce the rate of relapse in patients with moderate-to-severe COPD. Patients can be treated with 0.5 mg kg⁻¹·day⁻¹ of methylprednisolone or equivalent in a single morning dose for 7–14 days. Treatment for >14 days has not been demonstrated to be more beneficial and increases the likelihood of adverse side-effects. Inhaled bronchodilators, particularly short-acting inhaled β₂-agonists, must be given at increased doses during exacerbations. The short-acting bronchodilators may be prescribed with a chamber of inhalation or by nebulisation. In acute phase, repeated doses every 30–60 min can be administered with close monitoring of clinical signs and arterial gas exchange with a pulse oximeter. If a prompt response to these drugs does not occur, the addition of an anticholinergic is recommended.

Oxygen therapy should be provided in cases of hypoxaemia. Adequate levels of oxygenation are arterial oxygen tension >8.0 kPa or 60 mmHg, or arterial oxygen saturation >90%. These levels are easy to achieve in uncomplicated exacerbations. When oxygen is started, arterial blood gases should be checked 30–60 min later to ensure satisfactory oxygenation without CO₂ retention or acidosis.

The clinical and gasometric evolution of the patients will guide the decision to step down the treatment and discharge the patient from
the emergency department or hospital. Family
and home support is crucial in the first days
after discharge.

In mild and moderate ambulatory
exacerbations, clinical evaluation is required
48–72 h after initiation of therapy. In mild
cases, this evaluation can be performed by
telephone contact.

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  management of adult lower respiratory tract

<p>| Table 3. Risk classification and suggested antimicrobial therapy |
|---------------------------------|---------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th>FEV1 % pred</th>
<th>Most frequent microorganisms</th>
<th>Suggested treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-to-moderate COPD without risk factors</td>
<td>&gt;50</td>
<td><em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Moraxella catarrhalis</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Streptococcus pneumoniae</em></td>
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<tr>
<td></td>
<td></td>
<td><em>Chlamyphila pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Mycoplasma pneumoniae</em></td>
</tr>
<tr>
<td>Mild-to-moderate COPD with risk factors</td>
<td>&gt;50</td>
<td><em>H. influenzae</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. catarrhalis</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PRSP</td>
</tr>
<tr>
<td>Severe COPD</td>
<td>30–50</td>
<td><em>H. influenzae</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. catarrhalis</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PRSP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enteric Gram-negative</td>
</tr>
<tr>
<td>Very severe COPD</td>
<td>&lt;30</td>
<td><em>H. influenzae</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PRSP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enteric Gram-negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FEV1: forced expiratory volume in 1 s; PRSP: penicillin-resistant *S. pneumoniae*. #: risk factors are explained in table 1. *: in the case of intravenous therapy, other antibiotics can be used, such as piperacillin-tazobactam, imipenem or cefepime.
PNEUMONIA

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Background and definitions

Pneumonia is a condition caused by microbial infection within the lung parenchyma. This infection, together with the associated host inflammatory response, impairs normal alveolar function (i.e. gas exchange), which, together with the systemic effects of the infection, causes the clinical features of pneumonia. The gold standard for recognition of pneumonia is the presence of new lung shadowing on the chest radiograph in the setting of a compatible clinical illness.

Pneumonia is classified according to the origin of the infection as community-acquired (CAP) or hospital-acquired (nosocomial (NP)). Additional pneumonia types are in the immunocompromised and aspiration pneumonia. In each group, the causative pathogens and hence the management are different.

CAP is that which occurs in the absence of immunocompromise or prior hospital admission within the previous 7 days.

Epidemiology

CAP occurs in between one and 10 per 1,000 of the adult population each year. It is more common in children aged <5 yrs and becomes progressively more common from age 40 yrs onwards with a peak in the very elderly. It is more common in those with comorbidity, e.g. chronic obstructive pulmonary disease (COPD), bronchiectasis, chronic cardiac and renal disease. It occurs throughout the year with a peak during the winter months.

NP can occur in anyone resident in hospital for ≥7 days. It is especially common on the intensive care unit after endotracheal intubation (ventilator-associated pneumonia (VAP)) with risk being proportional to duration of intubation.

Two types of immune dysfunction predispose to pneumonia: humoral immune dysfunction, e.g. immunoglobulin deficiencies; and cell-mediated immune function in e.g. cancer chemotherapy, solid organ transplantation and bone marrow transplantation.

Aspiration pneumonia occurs especially in those with swallowing impairment and neurological impairment.

Most cases of CAP are managed in the community with a variable, but significant, proportion requiring hospital admission. Of those admitted, 5-10% may die and of those reaching the intensive care unit, 30-50% may die. Mortality is generally higher in NP and pneumonia in the immunocompromised.

Key points

- Pneumonia is very common and has a significant mortality.
- Severity assessment, aided by a severity assessment score, is a key management step.
- A variety of different pathogens can cause pneumonia.
- Antibiotic management is initially empirical and based on guidelines and knowledge of local microbial patterns and resistance rates.
Clinical features

The duration of illness before presentation is usually short. Classically there is an abrupt onset with fever, shivers and pleuritic chest pain. A slower onset over a few days may also occur. Other common symptoms include cough, sputum production, which may be purulent or blood-stained, breathlessness, muscle aches, headaches and anorexia. Nausea and diarrhoea are less common. In elderly patients, symptoms of cerebral dysfunction, such as confusion, incontinence or falls, may be the presenting feature.

Abnormalities on clinical examination include focal signs on chest examination, most commonly crackles, but occasionally the classical features of lung consolidation – dullness to percussion, bronchial breathing and enhanced vocal resonance. In addition, raised temperature, raised heart and respiratory rates, low blood pressure and mental confusion may be found.

Clinical features are not helpful in predicting the causative organism.

Investigations including radiology

Investigations are unnecessary outside hospital but in those admitted are performed to aid precise diagnosis, assess illness severity and identify the microbial cause.

The chest radiograph is essential to confirm new lung shadowing in those admitted. Classically such shadowing conforms to a lobar pattern and is associated with air bronchograms. Shadowing may occupy less than a whole lobe and may also be patchy, multilobar and bilateral. Additional features may include pleural effusion and less commonly cavitation and pneumothorax. The lower lobes are most commonly affected.

Of routine blood tests, peripheral blood white cell count may be raised, especially in bacterial infection, but C-reactive protein and procalcitonin are probably more specific. Blood urea and creatinine are helpful in severity assessment and the assessment of renal impairment, and liver function tests may be abnormal. Measures of gas exchange such as oxygen saturation and/or arterial blood gases also aid assessment of illness severity and guide management.

In routine practice, tests to identify a microbial cause are positive in only about 15% of cases of CAP and hence seldom influence management. They are probably not indicated unless the patient is severely ill. In such cases blood culture, sputum Gram stain and culture, and urine for pneumococcal and legionella antigen are indicated. Blood antibody levels or nose/throat secretion PCR-based tests for microbe-specific nucleic acids can be used for the detection of viruses and less common bacteria such as Legionella, Mycoplasma and Coxiella.

In NP, and especially in VAP, lower respiratory secretions should be sampled either by tracheal aspirate or from bronchoscopic specimens. The latter may be of value also in the immunocompromised.

Differential diagnosis

This includes acute bronchitis, COPD exacerbation, left ventricular failure, pulmonary embolism, exacerbation of pulmonary fibrosis and rare lung disorders, e.g. pulmonary eosinophilia.

Microbial aetiology and resistance

Some 10 pathogens commonly cause CAP, with Streptococcus pneumoniae being the most common overall and the most important cause of severe illness and death. Mycoplasma pneumoniae is also a common cause of mild illness, especially in young adults. Severe illness is most likely to be associated with S. pneumoniae, legionella, staphylococcal or Gram-negative bacterial infection. Legionella infection may occur in outbreaks associated with a water aerosol source such as showers or decorative fountains. Staphylococcal infection is especially common following influenza virus infection. Influenza occurs in seasonal outbreaks during the winter months and occasional pandemics. It is the commonest viral cause of CAP.
Clinically significant resistance to penicillins in *S. pneumoniae* is rare, but clinically significant macrolide resistance is more common, especially in Southern Europe (see www.earss.rivm.nl). This varies in frequency between countries.

NP is most commonly caused by Gram-negative enterobacteria or *Staphylococcus aureus*. *Pseudomonas aeruginosa* and multiresistant bacteria (*e.g.* methicillin-resistant *S. aureus* (MRSA)) are important causes of VAP.

Humoral immune deficiency is associated with bacterial infection and cell-mediated immune defects with viral and fungal infections such as *Pneumocystis jirovecii*.

Anaerobic bacteria may be important in aspiration pneumonia.

**Severity assessment**

Severity assessment is the key to deciding place of care and should also guide diagnostic tests and antimicrobial therapy. This should be done through clinical judgement guided by objective severity scores. There are many of these, but the best validated for CAP are the CURB65 (and its derivative CRB65) and the pneumonia severity index (PSI). The latter is based on a score from 20 variables and is often not practical in routine practice. The former is simpler and based on the number of severity variables present (table 1). The Clinical Pulmonary Infection Score (CPIS) may be useful in NP.

**Management**

Correction of gas exchange and fluid balance abnormalities and the provision of appropriate antimicrobial therapy are the cornerstones of management. Outside hospital rest, oral fluids and an oral antibiotic may all that is required. In hospital, oxygen at a concentration to maintain arterial oxygen saturation (>92%) should be delivered. If this cannot be achieved continuous positive airway pressure may be helpful. If there is an unacceptable rise in arterial carbon dioxide tension then assisted respiration may be required.

### Table 1. CURB65 (or CRB65) score

<table>
<thead>
<tr>
<th>Score 1 for each of:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C</strong> = mental confusion</td>
<td></td>
</tr>
<tr>
<td><strong>U</strong> = blood urea &gt;7 mmol-L⁻¹</td>
<td></td>
</tr>
<tr>
<td><strong>R</strong> = respiratory rate ≥30-min⁻¹</td>
<td></td>
</tr>
<tr>
<td><strong>B</strong> = systolic blood pressure &lt;90 mmHg or diastolic blood pressure ≤60 mmHg</td>
<td></td>
</tr>
<tr>
<td><strong>65</strong> = age ≥65 yrs</td>
<td></td>
</tr>
</tbody>
</table>

Score: mild 0-1 (mortality 1.5%), moderate 2 (9%), severe 3-5 (22%)

### Table 2. European Respiratory Society antibiotic guidelines for CAP

<table>
<thead>
<tr>
<th>CAP severity</th>
<th>Preferred</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsevere</td>
<td>Aminopenicillin ± macrolide or co-amoxiclav ± macrolide or penicillin G ± macrolide or third-generation cephalosporin ± macrolide</td>
<td>Levofloxacin or moxifloxacin</td>
</tr>
<tr>
<td>Severe</td>
<td>Third-generation cephalosporin + macrolide</td>
<td>Third-generation cephalosporin + (levofloxacin or moxifloxacin)</td>
</tr>
<tr>
<td>Severe + risk factors for <em>Pseudomonas aeruginosa</em></td>
<td>Autopseudomonal cephalosporin + ciprofloxacin</td>
<td>Piperacillin/tazobactam + (ciprofloxacin or levofloxacin) or carbapenem + (ciprofloxacin or levofloxacin)</td>
</tr>
</tbody>
</table>
ventilation should be considered. A place for noninvasive ventilation in pneumonia management has yet to be proven. Initial antibiotic therapy must be empirical and directed by illness severity according to national or international guidelines (table 2). A single antibiotic for nonsevere CAP and dual therapy for severe CAP is usual. Treatment for NP should be guided by knowledge of local microbial causes and that for pneumonia in the immunocompromised by the type of immune suppression and likely pathogens. Duration of therapy is usually 7 days in the uncomplicated, but may need to be prolonged in severe illness. Failure to respond should prompt a re-evaluation of the correct diagnosis and a more detailed search for microbial cause, for example by bronchoscopy, as long as gas exchange function will allow.

Prevention

The main preventable risk for pneumonia is tobacco smoking. In those with comorbid disease and in the elderly, influenza and pneumococcal vaccination is indicated. Recent evidence suggests that conjugate pneumococcal vaccination in children not only reduces invasive pneumococcal infection in this group, but also in adults.

References

HOSPITAL-ACQUIRED PNEUMONIA

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The currently proposed classification of hospital-acquired pneumonias includes hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP) and healthcare-associated pneumonia (HCAP) (table 1).

However, a recent statement issued by the European Respiratory Society/European Society of Clinical Microbiology and Infectious Diseases/European Society of Intensive Care Medicine calls for a redefinition of HCAP, particularly in terms of risk factors and microbial aetiology.

Epidemiology

The incidence of HAP is ~0.5–2.0% among all hospitalised patients and it is the second most common nosocomial infection, yet the first in terms of mortality (ranging 30–70%). The incidence in different hospitals and different wards of the same hospital varies considerably. The main risk factors are age, type of hospital and type of ward. Patients aged <35 yrs are less prone to develop HAP than elderly patients; the incidence of HAP may vary between 5–15 episodes per 1,000 discharges. In large teaching hospitals, the incidence is higher than in district hospitals, possibly relating to differences in patient complexity. HAP is quite uncommon in paediatric and obstetric wards, and clearly most common in surgical wards and intensive care units (ICUs), particularly in ventilated patients in whom the incidence may be >35 episodes per 1,000 patient-days.

Pathogenesis and risk factors

The understanding of the pathogenesis of HAPs is a fundamental step for the comprehension of risk factors involved. The main sources of HAP pathogens include healthcare devices, the environment, the transfer of microorganisms

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Table 1. Definitions of hospital-acquired pneumonias

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAP</td>
<td>Pneumonia that occurs ≥48 h after admission, which was not incubating at the time of admission</td>
</tr>
<tr>
<td>VAP</td>
<td>Pneumonia that arises &gt;48-72 h after endotracheal intubation</td>
</tr>
<tr>
<td>HCAP</td>
<td>Pneumonia that occurs in any patient who was hospitalised in an acute care hospital for ≥2 days within 90 days of the infection; resided in a nursing home or long-term care facility; received intravenous antibiotic therapy, chemotherapy, or wound care within the 30 days prior to the current infection; or attended hospital or haemodialysis clinic</td>
</tr>
</tbody>
</table>

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Key points

- Incidence of hospital-acquired pneumonias is ~0.5–2%, with risk factors including age, type of hospital and type of ward.
- Mortality is high (30–70%).
- Diagnosis can be difficult, and requires a combined clinical and bacteriological approach.
- Antimicrobial therapy must be both prompt and appropriate, and should be modified as culture results become available.
between the patient and staff or other patients, and oropharyngeal and gastric colonisation, with subsequent aspiration of their contents into the lungs in patients with impaired mechanical, cellular and humoral defences. Risk factors for the development of HAP can be differentiated into modifiable and non-modifiable conditions (table 2).

**Microbiology**

Gram-negative pathogens are the main cause of HAP. *Pseudomonas aeruginosa, Acinetobacter baumannii*, microorganisms belonging to the family Enterobacteriaceae (*Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., etc.) and, under certain conditions, microorganisms such as *Haemophilus influenzae* are involved in HAP aetiology. Among Gram-positive pathogens, *Staphylococcus aureus, Streptococcus* spp. and *Streptococcus pneumoniae* are the most common agents, accounting for 35–39% of all cases. Nonbacterial pathogens such as *Aspergillus* spp. and viruses (cytomegalovirus) have been described.

In general, there are significant geographical differences in the rates of resistance between some European areas and even within countries, from one hospital to another.

Taking into account the time course of pneumonia development, the expected pathogens in early-onset pneumonia (onset in ≤ 4 days of hospital admission) include *S. aureus, S. pneumoniae* and *H. influenzae*, as well as nondrug-resistant Gram-negative enteric bacteria (GNEB), and in late-onset pneumonia (onset >4 days of hospital admission) include methicillin-resistant *S. aureus*, drug-resistant

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**Table 2. Main recommendations for the management of modifiable risk factors for HAP and VAP**

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Host related</td>
<td>Adequate nutrition, enteral feeding via orogastric tubes</td>
</tr>
<tr>
<td></td>
<td>Reduction/discontinuation of immunosuppressive treatments</td>
</tr>
<tr>
<td></td>
<td>Prevent unplanned extubation (restraints, sedation)</td>
</tr>
<tr>
<td></td>
<td>Kinetic beds</td>
</tr>
<tr>
<td></td>
<td>Incentive spirometry, deep breathing and pain control</td>
</tr>
<tr>
<td>Device/treatment related</td>
<td>Minimise use of sedatives and paralytics</td>
</tr>
<tr>
<td></td>
<td>Avoid gastric overdistention</td>
</tr>
<tr>
<td></td>
<td>Avoid intubation and reintubation</td>
</tr>
<tr>
<td></td>
<td>Expeditious removal of endotracheal and nasogastric tubes</td>
</tr>
<tr>
<td></td>
<td>Semirecumbent positioning</td>
</tr>
<tr>
<td></td>
<td>Drain condensate from ventilator circuits</td>
</tr>
<tr>
<td></td>
<td>Endotracheal tube cuff pressure (&gt;20 cmH₂O prevents leakage of bacterial pathogens around the cuff into lower respiratory tract)</td>
</tr>
<tr>
<td></td>
<td>Continuous aspiration of subglottic secretions</td>
</tr>
<tr>
<td></td>
<td>Use of heat moisture exchangers (reduces ventilator circuit colonisation but not VAP incidence)</td>
</tr>
<tr>
<td>Environment related</td>
<td>Attention to infection-control procedures, <em>i.e.</em> staff education, hand washing, patient isolation</td>
</tr>
<tr>
<td></td>
<td>Microbiological surveillance programme</td>
</tr>
</tbody>
</table>

**Table 3. Major points for HAP diagnosis**

- Medical history and physical examination
- Chest radiograph (posteroanterior and lateral)
- Blood gas analysis
- Blood cultures
- Thoracentesis if pleural effusion
- Endotracheal aspirate, bronchoalveolar lavage or protected brush sample for culture before antibiotic (negative results do not rule out viral or Legionella infections)
- Extrapulmonary site of infection should be investigated
GNEB, *P. aeruginosa* and *A. baumannii* among other potentially drug-resistant microorganisms.

**Diagnostic strategy**

The clinical diagnosis of HAP is often difficult to establish. The American Thoracic Society/Infectious Diseases Society of America guidelines suggest the use of a combined clinical and bacteriological strategy. Table 3 summarises the major points and recommendations of the guidelines.

In case of doubt or relevant disagreement between the clinical presentation and the radiological findings, it is recommended to perform a computed tomographic scan. The presence of new chest radiographic infiltrates plus one of the three clinical variables (fever >38°C, leukocytosis or leukopenia and purulent secretions) is sufficient to start antimicrobial treatment.

**Treatment**

Prompt administration of appropriate antimicrobial treatment is crucial in order to achieve an optimal outcome, and inappropriate antimicrobial treatment is associated with an excess mortality from pneumonia. Antibiotic selection for empirical therapy of HAP should be based primarily on the risk of multidrug-resistant pathogen infection. Table 4 shows the proposed empirical treatment approach.

Once the results of respiratory tract and blood cultures become available, therapy should be focused or narrowed, based on the identity of specific pathogens and their susceptibility to specific antimicrobials. An 8-day antibiotic course can be appropriate provided that the patient has a good clinical response and difficult-to-treat pathogens are not involved as an aetiological agent.

**References**


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**Table 4. Antimicrobial treatment of nosocomial pneumonia**

<table>
<thead>
<tr>
<th>Recommended treatment options</th>
<th>Recommended dosages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early-onset pneumonia without any additional risk factors</strong></td>
<td><strong>Aminopenicillin plus β-lactamase-inhibitor</strong> or Second/third generation cephalosporin or Respiratory fluoroquinolone</td>
</tr>
<tr>
<td><strong>Late-onset or risk factors for multidrug-resistant pathogens</strong></td>
<td><strong>Anti-<em>Pseudomonas</em> β-lactams</strong> or <strong>Carbenapens PLUS</strong> Fluoroquinolone Addition of coverage for MRSA if suspected</td>
</tr>
<tr>
<td></td>
<td><strong>Imipenem 3 x 1 g</strong>; meropenem 3 x 1 g</td>
</tr>
</tbody>
</table>

MRSA: methicillin-resistant *Staphylococcus aureus*. #: Ertapenem has been suggested; however, its use on a regular basis would lead to a considerable risk of overtreatment.
PNEUMONIA IN THE IMMUNOCOMPROMISED HOST

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In contrast to community- and hospital-acquired pneumonia, pneumonia in the immunocompromised host is not defined by the setting of pneumonia acquisition but by the immune status of the host. In this context, immune suppression is best defined as a relevant risk for so-called opportunistic pathogens such as fungi, viruses, mycobacteria and parasites.

The expected pathogen patterns differ according to the type of immune suppression (table 1). Overall, there are five main types of immunosuppression:

- iatrogenic (through steroidal and nonsteroidal agents)
- neutropenia (usually through antineoplastic chemotherapy)
- haematopoetic stem-cell transplantation (HSCT)
- solid organ transplantation
- HIV infection

Each immunosuppressive condition confers characteristic risk profiles for pulmonary infections according to the type of immune failure. Some conditions additionally show time- or extent-dependent risk profiles.

Pulmonary infections in the immunocompromised host usually consistute an emergency. Thus, immediate appropriate antimicrobial treatment is mandatory. Since the spectrum of potential pathogens is far more diverse than in immunocompetent hosts, a systematic approach to the management of these patients is required. This approach should include a comprehensive diagnostic evaluation, indications for empirical initial antimicrobial treatment, also in the absence of definite pathogen identification, and for salvage management in case of treatment failure.

The basic diagnostic evaluation should include history, physical examination and chest radiography as well as a basic microbiological workup (sputum, blood cultures). A computed tomography (CT) scan of the lung (multi-slice scan and high-resolution (HR)CT) is usually indicated in patients in whom a straightforward diagnosis cannot be made. It can be particularly valuable in patients at risk of fungi (Pneumocystis and Aspergillus). Bronchoscopy is usually indicated in patients with bilateral infiltrates, unusual clinical and radiographical

Key points

- Different types of immunosuppression confer vulnerability to different respiratory pathogens, which may be bacterial, viral, mycobacterial or fungal.
- The approach to treatment should include comprehensive diagnostic evaluation, indications for empirical antimicrobial treatment and a plan in case of treatment failure.
presentations and those with treatment failure. When performing bronchoscopy, particular care has to be taken to comply with the methodology of retrieving uncontaminated samples of the lower respiratory tract, and a comprehensive evaluation of the samples retrieved. Bronchoalveolar lavage (BAL) is the most important sample, and stains and cultures should be investigated for all relevant pathogens. Occasionally, transbronchial biopsies and/or transbronchial needle aspiration may be rewarding.

In the following, typical pneumonias in the immunosuppressed host are described in more detail.

**Pneumocystis jirovecii pneumonia (PJP)**

PJP in HIV-infected patients presents with at least one of the following symptoms: fever, cough and dyspnoea on exertion. Chest radiograph typically discloses bilateral interstitial infiltrates in a perihilar distribution but may also be normal in the early course. In the latter case, HRCT may reveal ground glass opacities in a patchy or geographical distribution. Atypical cystic presentations may occur. Blood gas analysis shows wide alveolar–arterial gradients. The typical laboratory finding is an elevated lactate dehydrogenase. Specific diagnosis is required and may be established by examination of induced sputum or BAL. The treatment of choice (also for prophylaxis) is trimethoprim-sulfamethoxazole. Second-line options include pentamidine and clindamycin/primaquin. Adjunctive steroids are indicated in patients with acute respiratory failure.

**Table 1. Types of immunosuppression and typical infectious complications**

<table>
<thead>
<tr>
<th>Type of complication</th>
<th>Main immune disorder</th>
<th>Typical Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iatrogenic (steroids)</td>
<td>Macrophages, T-cells</td>
<td>Bacteria, fungi (Aspergillus spp.), Mycobacterium tuberculosis</td>
</tr>
<tr>
<td>Iatrogenic (anti-TNF-α)</td>
<td>TNF-α</td>
<td>M. tuberculosis</td>
</tr>
<tr>
<td>Neutropenia, stem cell transplantation</td>
<td>Neutrophils</td>
<td>Bacteria</td>
</tr>
<tr>
<td></td>
<td>Short duration (&lt;10 days)</td>
<td>Additionally: fungi (Aspergillus spp.)</td>
</tr>
<tr>
<td></td>
<td>Long duration (&gt;10 days)</td>
<td></td>
</tr>
<tr>
<td>Solid organ transplantation</td>
<td>Early (month 1): neutrophils</td>
<td>Bacteria</td>
</tr>
<tr>
<td></td>
<td>Intermediate (months 2-6): macrophages, T-cells</td>
<td>Fungi, viruses, parasites</td>
</tr>
<tr>
<td></td>
<td>Late (months &gt;6): depends on extent of immune suppression</td>
<td>Variable</td>
</tr>
<tr>
<td>HIV infection</td>
<td>T-cells (CD-4)</td>
<td>No risk</td>
</tr>
<tr>
<td></td>
<td>CD4 &gt;500·μL⁻¹</td>
<td>Bacteria, M. tuberculosis</td>
</tr>
<tr>
<td></td>
<td>CD4 200-500·μL⁻¹</td>
<td>Additionally: Pneumocystis jirovecii</td>
</tr>
<tr>
<td></td>
<td>CD4 &lt;200·μL⁻¹</td>
<td>Additionally: Aspergillus spp., atypical mycobacteria</td>
</tr>
<tr>
<td></td>
<td>CD4 &lt;50·μL⁻¹</td>
<td></td>
</tr>
</tbody>
</table>

TNF: tumour necrosis factor.

TNF: tumour necrosis factor.
**Cytomegalovirus pneumonia (CMVP)**

CMVP is defined as pulmonary signs and symptoms and the detection of CMV in pulmonary samples. Nevertheless, patients may shed CMV in the absence of CMVP. Co-infections with other opportunistic pathogens are frequently encountered. After introduction of CMV prophylaxis, the incidence in allogeneic HSCT is 10–30%, with the highest risk in seropositive recipients, while it is rare in autologous HSCT (< 10%). Also, the onset is shifted to >100 days. Clinical presentation is unspecific. Radiologically, there is typically an interstitial pattern with tiny pulmonary nodules and patchy areas of consolidation. HRCT is more sensitive. Diagnosis is made by demonstration of inclusion bodies within epithelial cells of the lower respiratory tract (sensitivity 90%, specificity 98%). Culture of BAL fluid lacks specificity. The value of CMV pp65 antigen and PCR is controversial. The treatment of choice is ganciclovir and valganciclovir, combined with CMV immune globulin. Second-line agents are foscarnet and cidofovir. Antiviral prophylaxis and monitoring are the main preventive strategies.

**Tuberculosis (TB)**

Patients with lowered CD-4 cell counts as well as on chronic steroid and anti-tumour necrosis factor (TNF)-α treatment are at increased risk of TB. Co-infection with TB and HIV alters the natural history of both diseases. TB in HIV-infected patients presents like primary infection (patchy infiltrates, mediastinal lymph node enlargement, pleural effusion and bacteraemia). Concurrent treatment of TB and HIV is challenging due to the many complex interactions of anti-TB drugs and antiretroviral agents. Patients who are candidates for chronic steroid or anti-TNF-α treatment should be evaluated for TB infection and, in case of positive skin testing or interferon-γ release assay, receive prophylaxis.

**Aspergillus pneumonia (AP)**

Definite diagnosis of AP in neutropenic patients requires tissue biopsy and can only rarely be established. Therefore, probable and possible diagnosis is based on a set of clinical, microbiological and radiographic criteria. HRCT is the method of choice to detect AP early in its course. Typical, albeit not specific signs of AP include the “halo” sign, as well as nodular and peripheral patchy densities near to vessels. The “air crescent” sign, representing cavitation, is a late marker of AP. The galactomannan antigen test in serum and BAL has a sensitivity of ~70% and a specificity of 90%. Bronchoscopy is usually indicated. Early initiation of treatment is crucial. The treatment of choice for definite AP is voriconazole, or alternatively liposomal amphotericin B. Second-line options include caspofungin and posaconazole. Mortality reaches ~50-60%.

**References**

PLEURAL INFECTION AND LUNG ABSCESS

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Pleural infection

Pleural infection occurs when microorganisms, most commonly bacteria, enter the pleural space. It can be confirmed when pleural fluid has a positive Gram stain or culture, is frankly purulent or, in the context of sepsis, has an acidic pH. Pleural infection is a common and serious medical problem. It is associated with a mortality rate of 15–20%.

Epidemiology

- Greatest incidence in the elderly and children but can occur at any age.
- Twice as common in males.
- 20% of adults with pleural infection have diabetes mellitus.
- Other important risk factors include aspiration, immunosuppression, poor dentition, pleural procedures, thoracic surgery and penetrating chest trauma.

Pathophysiology

Pleural infection most frequently follows community-acquired pneumonia (CAP) with bacterial migration from the lung parenchyma into a parapneumonic effusion. It may also follow hospital-acquired and aspiration pneumonia with effusion, traumatic or iatrogenic pleural penetration or be a primary phenomenon. Primary pleural infection is probably the consequence of bacteraemia, the origin of which has not been fully elucidated. Microbiological data has suggested the oropharynx as one possible source.

Bacteriology

Bacteria are ultimately cultured from either pleural fluid or blood in 60–70% of cases of pleural infection. The microbiology of community-acquired pleural infection is different from that of hospital-acquired pleural infection and CAP such that these should be considered three distinct diseases requiring different empirical antibiotic regimes.

In community-acquired pleural infection, Streptococcus species (largely Streptococcus milleri and Streptococcus pneumoniae) account for 50% of positive cultures with Staphylococcus species, anaerobic and Gram-negative organisms making up the other half. Anaerobic organisms commonly co-exist with aerobes, particularly the Streptococcus milleri group. Atypical pneumonia organisms such as Legionella and Mycoplasma species are extremely unusual causes of pleural infection.

Key points

- Pleural infection is common and serious, with a mortality rate of 15–20%.
- Blood, in addition to pleural fluid, should always be cultured.
- Initial management is with broad spectrum antibiotics and prompt chest drainage.
- Lung abscess has a 10% mortality rate.
- Invasive procedures are only required when lung abscess does not respond to prolonged empirical antibiotics or underlying neoplasm is suspected.
In nosocomial pleural infection, *Staphylococcus* species (including MRSA) and Gram-negative organisms are responsible for most positive cultures.

**Investigations**

- When a patient presents with sepsis and clinical and chest radiographic signs of a pleural effusion, a diagnostic pleural aspiration should always be performed to establish the presence of pleural infection.

- Pleural fluid should always be sent for culture and cytological examination. The pH of nonpurulent pleural fluid should be measured using a heparinised arterial blood gas syringe and blood gas machine, and fluid should also be sent for protein and lactate dehydrogenase.

- In the correct clinical context, a pleural fluid pH of $\leq 7.2$, positive pleural fluid culture or Gram stain, purulent pleural fluid and loculation on thoracic ultrasound differentiate pleural infection from simple parapneumonic effusion and indicate the need for chest tube drainage.

- Blood cultures should be sent (along with standard baseline blood tests) as they may achieve a microbiological diagnosis when there is no growth from pleural fluid.

**Radiology**

- Chest radiography often demonstrates a pleural effusion and consolidation. When pleural fluid has entered the organising phase there may be a lentiform pleural opacity (fig. 1).

- Ultrasound may demonstrate an anechoic, complex septated, complex nonseptated or homogenously echogenic (reflecting pus in empyema) appearance in pleural infection and is important in guiding aspiration and drain site.

- Contrast-enhanced computed tomography (CT) scans demonstrate brightly enhancing pleural thickening in the organising phase of pleural infection. CT is only required when initial drainage of fluid is incomplete for the planning of further drains or thoracic surgical intervention or if other pathology such as pulmonary abscess, neoplastic lesions or oesophageal rupture is suspected.

**Management**

**Immediate treatment** The following steps should be implemented.

- Broad-spectrum intravenous antibiotics.
- Chest tube drainage.

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**Table 1: Clinical classification of pleural infection.**

<table>
<thead>
<tr>
<th>Pleural fluid appearance</th>
<th>Simple parapneumonic effusion</th>
<th>Complicated parapneumonic effusion</th>
<th>Empyema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural fluid pH ≥ 7.2</td>
<td>Straw-coloured, bloody or turbid</td>
<td>Straw-coloured, bloody or turbid</td>
<td>Frank pus</td>
</tr>
<tr>
<td>Pleural fluid Gram stain</td>
<td>Negative</td>
<td>Usually ≤ 7.2</td>
<td>Should not be measured</td>
</tr>
<tr>
<td>Pleural fluid culture</td>
<td>Negative</td>
<td>May be positive</td>
<td>May be positive</td>
</tr>
<tr>
<td>Thoracic ultrasound appearance</td>
<td>Usually anechoic but septation can occur. No pleural thickening</td>
<td>May be positive</td>
<td>Homogenously echogenic. Usually evidence of pleural thickening</td>
</tr>
<tr>
<td>Immediate management</td>
<td>Antibiotics for pneumonia. This does not represent pleural infection</td>
<td>Intravenous antibiotics and chest tube drainage</td>
<td>Intravenous antibiotics and chest tube drainage</td>
</tr>
</tbody>
</table>

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Pleural infection and lung abscess
Nutritional supplementation (oral or nasogastric).
Thromboprophylaxis.
Vigilant monitoring for evidence of worsening sepsis indicating need for early thoracic surgery.

It is not possible to reliably identify, by presenting radiological, pleural fluid or clinical features, for which patients’ primary medical management will not achieve resolution of sepsis, necessitating thoracic surgery.

Antibiotics

Examples of suitable empirical antibiotic regimes with broad-spectrum coverage and good penetration to the pleural space include penicillin-clavulanic acid combinations in community-acquired infection and carbopenems with vancomycin in nosocomial infection. When cultures are available, antibiotics should be modified accordingly. As anaerobes can be difficult to culture, their presence should be assumed and cover continued (unless Streptococcus pneumoniae, which is not known to co-exist with anaerobes, is isolated). Conventionally, \( \geq 5 \) days’ i.v. antibiotics is followed by 2–4 weeks of oral treatment.

Chest tube drainage

Small-bore (12–14 f) chest tubes are now generally preferred to large-bore tubes as they can be placed via a seldinger technique and are more comfortable for patients. There is no evidence that large-bore tubes achieve superior fluid drainage (although this is still the subject of significant debate). Regular saline flushes (20 mL 6-hourly) may help to maintain tube patency and large-volume 0.9% saline irrigation of the pleural space has been adopted by some European centres with reports of improved primary treatment success rates (not yet supported by published evidence).

The viscosity and degree of septation of pleural fluid may impair tube drainage but routine use of intrapleural fibrinolytics has not been shown to be of benefit.

Thoracic surgery

The most compelling indication for referral for surgical intervention is failure of sepsis to improve despite appropriate antibiotics and tube drainage. This assessment is usually made after 5 days’ medical treatment. While surgical and anaesthetic complications are more common in the elderly and frail, the vast majority of deaths as a result of pleural infection are in patients aged \( > 65 \) yrs, and this group in particular should be considered at an early stage for limited surgical drainage procedures.

Available surgical approaches include:

- video-assisted thoracoscopic surgery (VATS).
- open thoracotomy and decortication.
- rib resection and open drainage (often performed under local anaesthetic).
- mini-thoracotomy (usually VATS-assisted)

Outcome

- Patients should be followed up for \( \geq 3 \) months to allow the early detection of recurrent sepsis or persistent breathlessness.
20–30% of patients ultimately require surgical intervention.

Pleural infection in the elderly and hospital-acquired disease have a particularly poor outcome.

Mean mortality rates of 15–20% have been reported in recent series.

**Lung abscess**

In contrast to pleural infection, the incidence and mortality rate of lung abscess have steadily declined since the advent of penicillin.

Risk factors include:

- more common in males (2:1).
- immunocompromised states.
- aspiration of any cause.
- pneumonia (particularly *Staphylococcus aureus* and *Klebsiella pneumoniae*).
- bronchial obstruction (e.g. endobronchial neoplasm in 10–20% cases).
- haematogenous spread of infection.

**Diagnosis**

Symptoms may be acute or insidious in onset and commonly include cough, fever, chest pain, night sweats, weight loss and purulent or bloodstained sputum. There may be no specific examination findings or chest auscultation may mimic pneumonia. Anaemia is common in patients with a chronic lung abscess.

**Radiology**

- Plain chest radiography classically demonstrates a well circumscribed opacity within the lung field. Rightsided abscesses are twice as common as left. Dependent segments are most commonly affected when the abscess follows aspiration.
- CT is often required to distinguish a parenchymal abscess from empyema and may assist in the detection of neoplastic lesions.
- On CT, abscesses have an irregular wall and an indistinct outer margin that makes an acute angle with the chest wall. In contrast, an empyema is lenticular, well defined and causes compression of the underlying lung with vascular crowding (fig. 2).

Conditions with a similar radiological presentation to lung abscess:

- Neoplastic lesions
- Pulmonary vasculitis
- Pulmonary infarction
- Bullae and cysts
- Rheumatoid nodules
- Pneumoconiosis

**Bacteriology and obtaining cultures**

The microbiology of lung abscesses has changed over recent decades due to immunocompromise and immunosupression being at least as aetiologically important as aspiration.

- Polymicrobial in $\geq 50\%$.
- Anaerobes (e.g. *Fusobacterium*, *Prevotella* sp., *Peptostreptococcus* sp.) present in 30–50%.
- Aerobic bacteria now appear to be cultured more commonly than anaerobes (particularly *Klebsiella pneumoniae* and *Staphylococcus aureus*).
- Fungi, *Nocardia*, mycobacteria, *Amoeba*, *Actinomycosis* and *Echinococcus* are more unusual causes of a parenchymal abcess.

Most patients are treated effectively with broad-spectrum antibiotics in the absence of a microbiological diagnosis. Blood cultures should be sent and sputum cultured if available.

- Bronchoscopy should be employed when there is particular suspicion of an underlying endobronchial neoplasm or inhaled foreign body. Culture of bronchial
washings is of relatively low accuracy and often fails to focus antibiotic selection beyond empirical choices.

- Image-guided (CT, ultrasound or fluoroscopic) percutaneous aspiration is associated with a 14% risk of pneumothorax but obtains a microbiological diagnosis in 80–90% of cases and changes antibiotic choice in up to 47%. It is usually reserved for cases that do not respond to empirical broad-spectrum antibiotics.

Management

A prolonged course (4–6 weeks depending on clinical and radiological response) of antibiotics is the foundation of treatment. β-lactam/β-lactamase-inhibitor combinations cover the majority of causative bacteria and are a good empirical choice. Local antibiotic policies differ.

Fever and infective symptoms usually settle within a week of appropriate antibiotics. Sustained resolution of sepsis is the most important marker of successful conservative management (radiological resolution can take >3 months).

The elderly, immunocompromised and patients with very large abscesses (>6 cm) or bronchial obstruction are most likely to require invasive intervention.

Drainage When appropriate antibiotic therapy fails, image guided percutaneous drainage is preferred to surgery. Successful drainage and avoidance of surgery has been reported in 84% of cases. It can be achieved with CT, ultrasound or fluoroscopic guidance. Complications, such as bronchopleural fistulae, haemothorax and empyema, are infrequent.

Percutaneous drainage should be considered if signs of systemic sepsis persist after 2 weeks of broad-spectrum antibiotic therapy.

Surgery Surgical excision can be avoided in >90% of patients. It should only be considered at an early stage when there evidence of localised obstructing malignancy or life-threatening complications such as intractible haemoptysis, bronchopleural fistula or empyema.

Perioperative mortality rates of up to 16% have been reported following surgery for lung abscess.

Prognosis Lung abscesses are associated with a 10% mortality rate.

The elderly or immunocompromised and those with large abscesses (>6 cm), underlying malignancy, malnutrition or delay in diagnosis and treatment have a particularly poor outcome.

References

INFLUENZA, PANDEMICS AND SARS

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Seasonal and pandemic influenza

Virology Influenza viruses are RNA orthomyxoviruses with three main types, A, B and C. Viral surface proteins include haemagglutinin (H) and neuraminidase (N) which are involved in viral attachment and release respectively. There are 16 haemagglutinin (H1 to H16) and 9 neuraminidase types (N1 to N9). Influenza viruses are described in a standardised manner according to their type/location of first isolate/laboratory strain number/year of isolate/H and N subtypes. For example: influenza A/Hong Kong/1/68/H3N2 (the cause of the 1968 “Hong Kong” pandemic).

The natural reservoir hosts of all influenza A virus subtypes are water birds. The host specificity of the various influenza A virus subtypes is partially determined by the binding affinity of hemagglutinin to sialic acid residues on the host cell.

A notable feature of influenza A viruses is their propensity to undergo antigenic variation. The appearance of a novel antigenic type demonstrating efficient human-to-human transmission is a prerequisite for a pandemic. Only influenza A viruses have been associated with pandemics.

Seasonal influenza Influenza is mostly a self-limiting viral upper respiratory tract infection that is managed in the community. Pneumonia is the most frequent serious complication of influenza.

The neuraminidase inhibitors, oseltamivir and zanamivir, are effective in the prophylaxis and treatment of influenza A infection.

The 2009 influenza A(H1N1) pandemic was of low severity compared to the 1918 pandemic.

SARS coronavirus (SARS-CoV) is the causative agent of SARS. Wild mammals, such as the palm civet cat, were most likely the pre-epidemic source of SARS-CoV. Bats are most likely the natural reservoir for coronaviruses.

The management of SARS is chiefly supportive. Basic infection control measures are the cornerstone of containment of any future outbreak.

Key points

- Influenza is mostly a self-limiting viral upper respiratory tract infection that is managed in the community. Pneumonia is the most frequent serious complication of influenza.
- The neuraminidase inhibitors, oseltamivir and zanamivir, are effective in the prophylaxis and treatment of influenza A infection.
- The 2009 influenza A(H1N1) pandemic was of low severity compared to the 1918 pandemic.
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A notable feature of influenza A viruses is their propensity to undergo antigenic variation. The appearance of a novel antigenic type demonstrating efficient human-to-human transmission is a prerequisite for a pandemic. Only influenza A viruses have been associated with pandemics.
The mean incubation period is 2–4 days with a range up to 7 days. An abrupt onset of high fever (up to 41°C) is the main presenting feature. The fever peaks within the first 24 h of illness and usually lasts for 3 days. Cough is the next commonest symptom (85%) which may be associated with sputum production in up to 40% of cases. Malaise (80%), chills (70%), headaches (65%) and myalgia (50%) may be prominent. Coryza and sore throat are reported in about half of patients. In addition, children may present with vomiting, diarrhoea and abdominal pain but these symptoms are uncommon in adults. The mean duration of symptoms is 4 days.

Two main classes of drug are active against influenza. The M2 ion channel inhibitors, amantadine and rimantadine, are effective against influenza A. However, their use is hindered by the rapid emergence of resistance to these drugs together with a high incidence of side-effects. The neuraminidase inhibitors, oseltamivir and zanamivir, are effective against influenza A and B. Fortunately, although resistance to oseltamivir has been reported, this is not widespread in seasonal influenza A(H3N2). Oseltamivir is often preferred over zanamivir because of ease of administration (oral versus inhaled/intravenous). Other neuraminidase inhibitors are also being developed, such as peramivir (intravenous). A Cochrane meta-analysis of randomised controlled trials of neuraminidase inhibitors in the treatment of influenza reported that the efficacy of oral oseltamivir at 75 mg daily was 61% (risk ratio 0.39, 95% CI 0.18–0.85) and of inhaled zanamivir at 10 mg daily was 62% (risk ratio 0.38, 95% CI 0.17–0.85). In clinical terms, this benefit translates to a shortening of the illness by 0.5–1 day. The review found the published evidence insufficient to answer the question whether neuraminidase inhibitors are effective in reducing the complications of lower respiratory tract infection, antibiotic use, or admissions to hospital. Oseltamivir use was associated with nausea (odds ratio 1.79, 95% CI 1.10–2.93).

**Chemoprophylaxis and vaccination** Both oseltamivir and zanamivir taken as prophylactic agents reduce the chance of symptomatic laboratory-confirmed influenza (risk ratio 0.38, 95% CI 0.17–0.85 for zanamivir 10 mg daily; risk ratio 0.39, 95% CI 0.18–0.85 for oseltamivir 75 mg daily). However, the effect of neuraminidase inhibitors on the prophylaxis of influenza-like illness, which includes infections other than influenza, is uncertain. Oseltamivir has also been demonstrated to be 58–84% efficacious as post-exposure prophylaxis.

Immunisation is the backbone of influenza prevention. The relative protective efficacy in children and young healthy adults is 70–90%. Efficacy is lower (~40%) in the elderly.

**Oseltamivir resistance** In 1977, influenza A(H1N1) re-emerged and co-circulated with influenza A(H3N2), with the latter remaining the dominant seasonal human influenza virus (fig. 1). During the 2007/2008 influenza season, oseltamivir-resistant seasonal influenza A(H1N1) viruses emerged suddenly and spread globally. These viruses carried a histidine-to-tyrosine mutation at residue 275 of the neuraminidase protein (H275Y). Laboratory and limited epidemiological data indicated that the viral fitness and virulence of these oseltamivir-resistant influenza A(H1N1) viruses were no different from oseltamivir-susceptible strains.

In Europe, over the 2008/2009 influenza season, influenza A(H3N2) continued to predominate but almost all co-circulating seasonal influenza A(H1N1) viruses were oseltamivir-resistant. In contrast, in the USA, oseltamivir-resistant influenza A(H1N1) viruses predominated in the 2008/2009 season, prompting the USA to issue guidelines recommending the use of zanamivir or a combination of oseltamivir and rimantadine when seasonal influenza A(H1N1) virus infection was suspected.

H275Y mutations in 2009 pandemic influenza A(H1N1) viruses have also been identified. Fortunately, such oseltamivir-resistant isolates have been infrequent and...
sporadic. They have been found mainly in immunosuppressed patients being treated with oseltamivir.

Complications of influenza Although influenza is mostly a self-limiting illness even without specific treatment, some patient groups experience significant morbidity and mortality. Persons at risk of complications from influenza include pregnant women, the frail elderly, those who are immunosuppressed and those with chronic medical conditions such as heart disease, chronic respiratory disease (mostly asthma and chronic obstructive pulmonary disease (COPD)), cancer, diabetes, renal disease, rheumatologic disease, dementia and stroke. Rates of hospitalisation and death are increased in all these patient groups.

Pneumonia is the most frequent serious complication of influenza. Two main clinical patterns are described: primary viral pneumonia and secondary bacterial pneumonia.

Patients with primary viral pneumonia typically become breathless within the first few days of onset of fever. This may be associated with tachypnoea, cyanosis and bilateral lung crackles on chest examination. A leukocytosis is usual. The commonest chest radiographic abnormality is of diffuse bilateral interstitial infiltrates similar to pulmonary congestion. Progression to respiratory failure is well recognised. Mortality rates of 6–40% have been reported. In severe cases, pathological findings are similar to those seen in acute respiratory distress syndrome.

Patients with secondary bacterial pneumonia complicating influenza typically experience an amelioration of the initial symptoms of viral infection. However, 4–10 days later, a recurrence of fever together with breathlessness and a productive cough ensues. Clinical features at this point are indistinguishable from community-acquired bacterial pneumonia. The three commonest pathogens implicated are *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae*.

In children, the commonest respiratory complication, though not the most serious, is otitis media.

In addition to the specific complications listed in table 1, patients with influenza may also experience a worsening of a pre-existing medical illness such as COPD or cardiac failure.

Management of the complications of influenza should follow the same principles for each specific condition regardless of influenza. In the case of influenza A primary viral pneumonia, higher doses of neuraminidase inhibitors (oseltamivir 150 mg b.i.d.) have been advocated based on experience with human cases of viral pneumonia resulting from avian influenza A H5N1 infection. There are no randomised trials of therapy in primary viral pneumonia.

Pandemic influenza In the 20th century, pandemics occurred in 1918 (H1N1), 1957 (H2N2) and 1968 (H3N2) (fig. 1). Each of these pandemics had a different impact and tempo. The 1918 pandemic was the most deadly, claiming the lives of an estimated 40–100 million people globally. In contrast, the subsequent two pandemics were much less severe, accounting for an estimated 1–2 million deaths each.

![Figure 1. Influenza pandemics and subtypes, 1918–2009. #: re-emergence of H1N1, possibly from accidental laboratory release – strain closely related to 1950 strain. ¶: new reassortment of six gene segments from triple reassortant North American swine influenza virus lineages and two gene segments from Eurasian swine influenza virus lineages.](image-url)
In early April 2009, the first cases of the most recent influenza pandemic were identified in Mexico. The 2009 pandemic influenza A(H1N1) virus is a triple-reassortant virus containing genes from human, swine and avian influenza viruses. It caused an infection that was clinically similar to seasonal influenza. Gastrointestinal symptoms amongst adults were commoner than in seasonal influenza. Mainly children and young adults were affected and most illnesses were self-limiting. In persons aged ≥60 yrs, it is likely that pre-existing cross-reactive antibodies due to previous exposure to antigenically related influenza viruses provided protection against infection.

Compared to the 1918 pandemic, hospitalisation and mortality rates were low. In Canada, the risk of hospital admission amongst laboratory-confirmed cases was ~4.5% and the case-fatality rate was 0.3%. In the UK, the overall estimated case-fatality rate was 26 per 100,000; lowest for children aged 5–14 yrs (11 per 100,000) and highest for those aged ≥65 yrs (980 per 100,000). Hospitalisation rates varied between countries. Of those hospitalised, 9–31% required intensive care support, predominantly because of diffuse viral pneumonitis. Mortality of ICU admitted patients was 14–46%.

Patients at risk of complications from seasonal influenza were similarly at risk from 2009 H1N1 virus infection. In addition, pregnant women, especially in the third trimester and with HIV co-infection, were at higher risk of severe infection. Some non-trial data suggested that early treatment of 2009 influenza A(H1N1) virus infection with neuraminidase inhibitors reduced the duration of hospitalisation and the risk of progression to severe disease. Many critically ill patients received increased doses of antivirals for extended durations during the pandemic (e.g. oseltamivir 150 mg b.i.d. for 10 days in adults). This practice was not based on evidence from randomised controlled trials.

Severe acute respiratory syndrome (SARS)

Epidemiology The global outbreak of severe acute respiratory syndrome (SARS) in 2002/2003 affected 8,096 individuals in 26 countries, 774 of whom died. The three most severely affected regions were mainland China, Hong Kong and Taiwan with 5,327, 1,755 and 674 cases, respectively.

The first human case was identified in the city of Foshan, Guangdong Province, China on November 16, 2002 and the last known case of the initial outbreak experienced the onset of symptoms on June 16, 2003 in Taiwan.

A novel coronavirus, the SARS coronavirus (SARS-CoV), was identified as the causative

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence</th>
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<tr>
<td>Otitis media</td>
<td>Common</td>
</tr>
<tr>
<td>Secondary bacterial pneumonia</td>
<td>Common</td>
</tr>
<tr>
<td>Primary viral pneumonia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Myositis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Rare</td>
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<td>Encephalitis/encephalopathy</td>
<td>Rare</td>
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<tr>
<td>Reye's syndrome</td>
<td></td>
</tr>
<tr>
<td>Febrile convulsions</td>
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</table>

Table 1. Complications of influenza in adults and children.
agent of SARS in April 2003. Close human–animal contact associated with many of the early cases in China supported the concept of SARS as a zoonotic infection. The palm civet cat *Paguma larvata* has been identified as the likely main pre-epidemic animal source. Bats are most probably the natural reservoir for coronaviruses. Coronaviruses sharing 87–92% genome nucleotide identity with SARS-CoV have been found in horseshoe bats *Rhinolophus* sp. Accordingly, one hypothesis is that coronaviruses were transmitted from horseshoe bats to civet cats and then to humans (fig. 2).

Infections later in the course of the outbreak were due mainly to human-to-human transmission. Molecular evolutionary changes of the SARS-CoV have been described that might explain the shift in mode of transmission. Nosocomial transmission was particularly high, with attack rates amongst healthcare workers in some centres ranging from 10–60%. In contrast, community transmission rates were much lower with typically <10% of contacts infected.

The mean incubation period of SARS is estimated at 4–6 days with a maximum incubation period of 10 days. Overall, SARS may be considered to be low to moderately transmissible. A few remarkable “super-spreading events” (SSEs) were associated with SARS in which single individuals were responsible for infecting many more individuals than average. In one SSE at the Prince of Wales Hospital, Hong Kong, a single patient infected 143 people.

**Clinical features** The clinical presenting features of SARS infection are nonspecific. Fever (93%), chills (61%), malaise (46%), cough (41%) and rigors (38%) were the predominant symptoms recorded in the Hong Kong-wide clinical database of SARS patients. High-volume, watery, nonbloody diarrhoea is present in a sizeable minority of patients (~20%) in the early stages of disease and increases in frequency (up to 70%) by the second week of illness. It is usually self-limiting. Similarly, respiratory symptoms of cough, breathlessness and sputum production are less frequently (<50%) encountered in the first 4 days of illness, but increase to a peak (70%) by day 9–10 of illness. Typically, a dry cough is the first respiratory symptom. This is followed by breathlessness, which worsens at the start of the second week.

Radiological changes of airspace consolidation are usually unilateral and localised in the first week. The infiltrates are commoner in the lower lobes (70%) and the periphery (75%). Cavitation, lymphadenopathy and pleural effusions are not described in association with SARS infection. The extent of radiological abnormality correlates with severity of illness and prognosis.

Figure 2. Possible origin of SARS, based on phylogenetic studies.
Laboratory test abnormalities include lymphopenia, neutropenia, thrombocytopenia and raised levels of lactate dehydrogenase (LDH), alanine aminotransferase, creatinine kinase, and activated partial thromboplastin time.

Respiratory failure occurs in 20–25% of patients, mainly adults. Unusually, the incidence of barotrauma (manifest as a pneumothorax or pneumomediastinum) was observed to be higher in severely ill patients with SARS than might be expected despite the use of low-volume, low-pressure mechanical ventilation strategies. The reason for this is unclear. Patients with SARS requiring critical care support have a mortality of ~25%. Features associated with a poor prognosis include advanced age, male sex, presence of comorbid illness, high serum LDH and neutrophilia at presentation, and an initial radiograph with more than one zone of involvement. Overall, adults suffer a more severe disease than children.

**Virology** SARS-CoV is detectable by RT-PCR and by culture from respiratory tract, faecal and urine samples. Virus RNA is also detectable in serum, plasma and cerebrospinal fluid thus indicating multisystem infection. Diagnostic yields are better with nasopharyngeal aspirates and faeces compared to throat swabs. A retrospective diagnosis of SARS is possible using serological tests.

**Clinical management** The management of SARS is chiefly supportive. Chemical compounds that have reported activity against SARS-CoV include glycyrrhizin, baicalin, reserpine, noclosamide, ribavirin, protease inhibitors (lopinavir, nelfinavir), interferon (IFN)-α and IFN-β. A comparative study using IFN alfacon-1 (n=22), and another using a lopinavir/ritonavir combination (n=41), suggested clinical benefit. However, there are no randomised controlled trials of treatment.

Corticosteroids were used during the SARS outbreak as an immunomodulatory agent with the intention of limiting damage that might be caused by the host immune response. In reported series, there were large variations in type, dose, route and duration of corticosteroids used. Unsurprisingly, different conclusions about the efficacies of corticosteroids were drawn.

Basic infection control measures are the cornerstone of containment of any future outbreak. As subclinical infection with SARS has not been described and the peak in viral load occurs late (second week), effective infection control measures can often be instituted prior to widespread transmission.

**Practice points regarding the clinical diagnosis of influenza or SARS**

The early symptoms in both influenza and SARS are nonspecific, comprising primarily a fever in association with respiratory symptoms such as cough and systemic symptoms such as malaise or chills. A clinical diagnosis of influenza or SARS is therefore crucially dependent on epidemiological features. In the case of influenza, an influenza-like illness (ILI) in the setting of local or community circulation of influenza viruses (e.g. during an influenza season, or during a pandemic) greatly increases the likelihood that the illness is due to influenza virus infection – the positive predictive value of an ILI for laboratory-confirmed influenza can range from 20–70%. Alternative pathogens to consider in instances of an ILI include parainfluenza virus, adenovirus, rhinovirus, *Mycoplasma pneumoniae* and even *S. pneumoniae*. Similarly, a clinical diagnosis of SARS requires the establishment of an epidemiological link with another patient with SARS, or exposure to likely animal sources of SARS-CoV. Virological testing is necessary to make a definitive diagnosis in both influenza and SARS.

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- Jefferson T, *et al.* Neuraminidase inhibitors for preventing and treating influenza in healthy


PULMONARY TUBERCULOSIS

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The World Health Organization (WHO) has declared tuberculosis (TB) a global emergency due to its burden in terms of cases and deaths. Among the factors contributing to maintenance of the TB pandemic are: the large number of patients co-infected with HIV; bacterial multidrug resistance (MDR) to anti-TB drugs (i.e. strains resistant to at least isoniazid and rifampicin); migration from high-incidence countries; and the social determinants of the disease (poverty, drug abuse and homelessness).

TB can affect virtually every organ, most importantly the lungs (pulmonary TB), and is typically associated with granuloma formation.

Aetiology

TB is an infectious disease caused by slightly bent, thin, aerobic, non-motile, non-spore-forming beaded rods belonging to the family Mycobacteriaceae and to the order Actinomycetales. Of the pathogenic species belonging to the Mycobacterium tuberculosis complex, the most frequent and important agent of human disease is M. tuberculosis. Mycobacteria are 2–4 μm long and 0.2–5 μm wide. They are defined as acid-fast bacilli (AFB) due to the cell wall structure, crucial to their survival and characterised by a significant content of mycolic acid attached to the underlying peptidoglycan-bound polysaccharide arabinogalactan. Another important carbohydrate structural antigen of the cell wall is lipoarabinomannan, which facilitates the survival of mycobacteria within macrophages. The peptidoglycan network, located just outside the cell membrane, confers cell wall rigidity.

This structure provides a barrier that is responsible for many of the medically challenging characteristics of TB, including resistance to antibacterial agents and to host defence mechanisms. It has been clearly demonstrated that the quality and quantity of the cell wall components affect mycobacterial virulence, pathogenicity and growth rate.
**Pathogenesis**

Mycobacteria are spread through air droplets expelled when those with infectious pulmonary TB cough, sneeze or speak. Close contacts (those with prolonged, frequent or intense contact with pulmonary TB sufferers) are at highest risk of becoming infected. Bacteria are carried on droplet nuclei in the air and can enter the body through the airways. The majority of the bacilli are trapped in the upper parts of the airways where the mucus-secreting goblet cells are located. The mucus catches antigens, and the cilia on the surface of the cells constantly beat the mucus and its entrapped particles upward for removal. This system provides humans with an initial physical first-line defence that prevents infection in most contacts of pulmonary TB patients.

Bacteria in small droplets that can bypass the mucociliary system and reach the alveoli are quickly surrounded and engulfed by alveolar macrophages, which are part of the innate immune system and are the most abundant phagocytic cells located in the alveolar spaces; they are readily available without requiring previous exposure. Numerous bacterial and host mechanisms are involved in the uptake of the mycobacteria, such as mycobacterial lipoarabinomannans, ligands for macrophages’ receptors or the complement proteins C2a and C3b that bind to the cell wall and enhance recognition of the mycobacteria by effector macrophages. The subsequent phagocytosis starts a cascade of events that results in successful control of the infection, followed by latent TB infection (LTBI) in the majority of cases; rarely, infection progresses to active disease, called primary progressive pulmonary TB (common among children aged ≤4 yrs). The outcome is essentially determined by the balance that occurs between host defences and the invading mycobacteria.

During the initial phase (2–12 weeks) of pulmonary TB, the bacteria continue to multiply slowly (a cell division every 25–35 h) and T-lymphocytes are attracted by cytokines released by macrophages. In the immunocompetent, the next defensive stage is formation of granuloma around mycobacteria, which limits bacterial replication and spread to other pulmonary sites. This condition establishes latency of the infection. Lesions in those with an adequate immune system generally undergo fibrosis and calcification, while in immunocompromised subjects, they progress to primary progressive pulmonary TB.

The majority of infected individuals who ultimately develop pulmonary TB do so within the first year or two after infection; dormant bacilli, however, may persist for years before being reactivated to produce secondary pulmonary TB, which is often infectious. Overall, it is estimated that lifetime risk of developing TB is 10% in those who are immunocompetent and ≤50% in HIV-positive individuals. Age is an important determinant of the risk of disease after infection. Among infected subjects, the incidence is highest in childhood up to the age of 8 yrs, with a second peak during adolescence and early adulthood. The risk may increase in the elderly, possibly because of waning immunity and comorbidities (*i.e.* diabetes).

**Epidemiology**

WHO estimates that 9.27 million new cases of TB occurred in 2007 compared with 9.24 million in 2006. Of them, an estimated 44% or 4.1 million were infectious (new pulmonary sputum smear-positive cases). India, China, Indonesia, Nigeria and South Africa have the highest numbers of incident cases. Asia (South-East Asia and the Western Pacific region) accounts for 55% of global cases and Africa for 31%; the other three regions (the Americas, Europe and the Eastern Mediterranean region) account for small fractions of global cases. Among the 15 countries with the highest estimated TB incidence rates, 13 are in Africa, a phenomenon linked to high rates of HIV co-infection. In both the African and European regions, prevalence rates increased substantially during the 1990s.
There were an estimated 13.7 million prevalent cases of TB in 2007, a slight decrease from 13.9 million in 2006. Of these cases, an estimated 5% were HIV positive. Of the 511,000 incident cases of MDR-TB in 2007, 68% were sputum smear-positive.

Overall, 1.77 million TB deaths occurred in 2007. An estimated 456,000 were of people who were HIV-positive. Deaths from TB among HIV-positive individuals accounted for 23% of the estimated 2 million HIV deaths that occurred in 2007.

The World Health Assembly outcome targets (i.e., to achieve a case-detection rate of \( \geq 70\% \) for new smear-positive cases and a treatment success rate of \( \geq 85\% \) for such cases) provide a quantitative indication of the effectiveness of national TB programmes in finding, diagnosing and successfully treating those with TB.

The 2.6 million new smear-positive cases in 2007 represent 64% of the 4.1 million estimated cases. This is a small increase from 63% in 2006, following a slow increase from 35 to 43% between 1995 and 2001, and a more rapid increase from 43 to 60% between 2001 and 2005. Africa had the lowest case-detection rate (47%). Globally, the rate of treatment success was 85% in 2006; the target for treatment success was reached because of the high treatment success rates reported from South-East Asia and the Western Pacific region (87 and 92%, respectively).

**Clinical features**

Before the recognition of HIV infection, \( \geq 75\sim 80\% \) of all TB cases were limited to the lungs. In recent decades, increases have been seen in extrapulmonary cases alone, and in pulmonary and extrapulmonary cases.

**Primary pulmonary TB** Pulmonary mycobacterial entry is often asymptomatic. Associated paratracheal lymphadenopathy may occur because the bacilli spread from the lungs through the lymphatic system.

In the majority of cases, the lesion heals spontaneously and may later be evident as a small calcified nodule (Ghon lesion). If the primary lesion enlarges, mainly seen in children and in individuals with impaired immunity, pleural effusion is a typical finding. This effusion develops because the bacilli infiltrate the pleural space from an adjacent subpleural focus. The effusion may remain small, resolving spontaneously, or it may become large enough to induce clinical symptoms such as fever, pain and dyspnoea.

**Secondary pulmonary TB** Secondary pulmonary TB results from endogenous reactivation of LTBI and is frequently localised to pulmonary segments, where the high oxygen concentration favours mycobacterial replication (upper lobes).

Early signs and symptoms are often nonspecific and insidious, consisting mainly of fatigue (decreased muscle mass), general malaise, weakness, weight loss (lack of appetite and altered metabolism associated with systemic inflammatory response to mycobacteria), and a low-grade fever accompanied by chills and night sweats. Cough eventually develops in the majority of patients; it could be initially non-productive, but subsequently it may be accompanied by the production of purulent sputum often streaked with blood. Haemoptysis may be due to: the destruction of a vessel located in a pulmonary cavity; the rupture of a dilated vessel in a cavity (Rasmussen’s aneurysm); or the formation of an aspergilloma in an old cavity. In some patients, the presence of inflamed subpleural parenchyma may cause pleuritic pain. Extensive disease may lead to dyspnoea or orthopnoea. Although numerous individuals with pulmonary TB have no physical characteristics, rales may be detected over involved areas during inspiration, particularly after coughing. Haematologic examinations might reveal mild or moderate anaemia, strictly related to the weakness, and leukocytosis. Chronic cough (e.g. cough lasting for 2–3 weeks) has to be considered the main clinical symptom.
Diagnosis

At ≥100 yrs old, sputum smear microscopy is still the most widely used technique for the diagnosis of pulmonary TB. Although highly specific, the lower limit for detection of microscopy is 0.5–1 × 10^6 organisms·mL^{-1} sputum and only about half of all culture-positive cases have sputum smear-positive results. There is evidence that sensitivity may be lower among HIV-infected subjects. AFB microscopy is simple to perform but suboptimal results are described where adequate quality-assurance programmes are absent. WHO has proposed a case definition for sputum smear-negative pulmonary TB based on three negative sputum smears, radiographic abnormalities consistent with active pulmonary TB, and no response to a course of broad-spectrum antibiotics. Although smear-negative pulmonary TB cases are not considered to be infectious, their high number is causing increasing concern in high HIV-prevalence, low-income settings.

Sputum induction with hypertonic saline is a useful technique for diagnosing pulmonary TB in individuals who are either sputum smear negative or unable to produce sputum. Repeated sputum induction increases the yield of both smear and culture. It avoids invasive procedures and provides a means of diagnosis in resource-poor settings. It is worth noting that sputum induction should be carefully conducted in a well-ventilated setting, as it is a cough-inducing procedure with a high risk of transmission.

Mycobacterial culture is considered the gold standard; however, false-positive results do occur, primarily as a consequence of laboratory contamination. Moreover, several weeks are required for the performance of culture-based methods, although the use of liquid media has decreased pulmonary TB diagnosis time. Presently, in Europe, a “definite” case of TB is a culture-positive case, while all other cases (including culture negative, sputum smear positive) are “other than definite”. Drug susceptibility testing for first- and second-line drugs is also useful in order to better define the phenotype of the isolated strain in culture-confirmed cases.

Molecular techniques, based on gene amplification, offer increased sensitivity and specificity for diagnosis. The major limitation, mainly for low-income countries, is their current high cost and the risk of contamination (false-positive results).

Chest radiology (fig. 1) and computed tomography (CT) are useful tools that complement bacteriological examinations in the diagnosis of pulmonary TB. Although over- and under-reading have been described, these tools can offer important information to the clinician. Chest radiography is commonly used to screen individuals harbouring a significantly higher risk of pulmonary TB (e.g. prisoners, contacts of infectious cases, etc.) than the general population. Among the tools indirectly used to detect mycobacterial infection, the tuberculin skin test (TST) deserves to be mentioned; it must be noted, however, that it has several limitations, including poor specificity, difficult administration and the risk of anergy.

Figure 1. Pulmonary tuberculosis due to multidrug-resistant strains of *Mycobacterium tuberculosis*. A 21-yr-old female with isolated left upper lobe infiltrate.
False-negative reactions are common in immunosuppressed patients and in those with overwhelming pulmonary TB. Positive results are obtained when patients have been infected with *M. tuberculosis* but do not have active disease, and when subjects have been sensitised by nontuberculous mycobacteria or bacille Calmette-Guérin (BCG) vaccination.

Finally, interferon (IFN)-γ release assays (IGRAs) have recently been introduced into clinical practice. Their application in specimens collected from the infected organ or tissue is still under evaluation. These techniques can increase the low specificity of TST based on the immune response (release of IFN-γ) to early-secreted antigenic target protein (ESAT)-6 and culture filtrate protein (CFP)-10, which are antigens specific to *M. tuberculosis* and are not produced by *Mycobacterium bovis* BCG.

**Treatment**

Due to their higher bacillary burden, individuals with active TB and positive sputum smear test results are the main source of TB transmission in the community. The highest priority in TB control programmes is the rapid identification of new cases of sputum smear-positive pulmonary TB and effective treatment. It has been estimated that case-finding and effective treatment of smear-positive individuals could decrease the number of TB cases globally by one half within a decade.

The longer the interval between doses, the easier and less expensive the task of providing treatment to large numbers of patients, particularly in high-prevalence countries. Short-course regimens are divided into an initial or bactericidal phase and a continuation or sterilising phase. Pan-susceptible TB is defined as TB susceptible to all first-line agents.

WHO recommends treatment of new cases of pulmonary TB (both sputum smear-positive cases, belonging to Category I, and sputum smear-negative cases, belonging to Category III) with a standardised regimen of four first-line anti-TB drugs, including isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months, followed by isoniazid and rifampicin for 4 months (tables 1 and 2). Because of the higher probability of drug resistance, re-treatment cases (Category II) require a fifth drug during the continuation phase (streptomycin for 2 months). Both the intensive and the continuation phases of treatment (3 and 5 months, respectively) are longer in Category II than in Categories I and III (table 2).

MDR-TB is caused by mycobacteria that are resistant to at least isoniazid and rifampicin, the two most potent first-line anti-TB drugs. While MDR-TB has been documented for many years, a new term, extensively drug-resistant (XDR)-TB, appeared in the literature for the first time in March 2006. It describes a severe form of TB caused by strains of *M. tuberculosis* that are resistant to at least isoniazid and rifampicin (*i.e.* MDR-TB), as well as any fluoroquinolone and at least one of three injectable drugs used in anti-TB treatment: capreomycin, kanamycin and/or amikacin.

To achieve a regimen designed to treat the majority of patients with a minimum of four effective drugs as is recommended, it may be necessary to use five, six or more drugs to cover all the possible patterns of resistance when drug susceptibility testing (DST) results for second-line agents are not available (table 3). An injectable agent and a fluoroquinolone form the core of the preferred regimen.

The most recent WHO guidelines propose different treatment strategies for individuals suspected to harbour MDR-TB strains. Depending on specific country conditions, treatment protocols may recommend a standardised treatment regimen for all MDR-TB cases (*e.g.* in countries where DST is not widely available), or may alternatively recommend individualised treatment based on individual DST results. If standardised combinations of second-line drugs are chosen, representative national data on predominant resistance patterns to specific treatment
<table>
<thead>
<tr>
<th>Anti-TB drugs</th>
<th>Recommended daily dosage</th>
<th>Common adverse effects (not exclusive)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1: first-line oral agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>5 mg-kg(^{-1}) q.d.</td>
<td>Elevated transaminases; hepatitis; peripheral neuropathy; GI intolerance; CNS toxicity</td>
</tr>
<tr>
<td></td>
<td>Should not exceed 300 mg per day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Always consider co-administering vitamin B6</td>
<td></td>
</tr>
<tr>
<td>Rifampicin</td>
<td>10 mg-kg(^{-1}) q.d.</td>
<td>Elevation of liver enzymes; hepatitis; hypersensitivity; fever; gastrointestinal disorders: anorexia, nausea, vomiting, abdominal pain; discoloration (orange or brown) of urine, tears and other body fluids; thrombopenia</td>
</tr>
<tr>
<td></td>
<td>&gt;50 kg: 600 mg; &lt;50 kg: 450 mg</td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15-25 mg-kg(^{-1}) q.d.</td>
<td>Optic neuritis; hyperuricaemia; peripheral neuropathy (rare)</td>
</tr>
<tr>
<td></td>
<td>Maximum 2.0 g per day</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>30 mg-kg(^{-1}) q.d.</td>
<td>Arthralgia; hyperuricaemia; toxic hepatitis; gastrointestinal discomfort</td>
</tr>
<tr>
<td></td>
<td>Maximum 2.0 g per day</td>
<td></td>
</tr>
<tr>
<td><strong>Group 2: injectables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptomycin(#)</td>
<td>0.75-1 g q.d.</td>
<td>Auditory and vestibular nerve damage (non-reversible); renal failure (usually reversible); allergies; nausea; skin rash, neuromuscular blockade</td>
</tr>
<tr>
<td></td>
<td>&lt;50 kg: 0.75 g per day; &gt;50 kg: 1 g per day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum cumulative dose 50 g</td>
<td></td>
</tr>
<tr>
<td>Amikacin(^\star)</td>
<td>0.75-1 g q.d.</td>
<td>Auditory and vestibular nerve damage (non-reversible); renal failure (usually reversible); allergies; nausea; skin rash, neuromuscular blockade</td>
</tr>
<tr>
<td></td>
<td>&lt;50 kg: 0.75 g per day; &gt;50 kg: 1 g per day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum cumulative dose 50 g</td>
<td></td>
</tr>
<tr>
<td>Capreomycin(#)</td>
<td>0.75-1 g q.d.</td>
<td>Auditory and vestibular nerve damage (non-reversible); renal failure (usually reversible); Bartter-like syndrome; allergies; neuromuscular blockade</td>
</tr>
<tr>
<td></td>
<td>&lt;50 kg: 0.75 g per day; &gt;50 kg: 1 g per day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum cumulative dose 50 g</td>
<td></td>
</tr>
<tr>
<td>Kanamycin(^\star)</td>
<td>375-500 mg b.i.d.</td>
<td>Auditory and vestibular nerve damage (non-reversible); renal failure (usually reversible); allergies; nausea; skin rash, neuromuscular blockade</td>
</tr>
<tr>
<td></td>
<td>&lt;50 kg: 0.75 g per day; &gt;50 kg: 1 g per day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum cumulative dose 50 g</td>
<td></td>
</tr>
<tr>
<td><strong>Group 3: fluoroquinolones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levofloxacin(^\star)</td>
<td>500-1,000 mg q.d.</td>
<td>Gastrointestinal discomfort, CNS disorders, tendon rupture (rare); hypersensitivity</td>
</tr>
<tr>
<td>Ciprofloxacin(^\star)</td>
<td>500-750 mg b.i.d.</td>
<td>Gastrointestinal discomfort, CNS disorders, tendon rupture (rare); hypersensitivity</td>
</tr>
</tbody>
</table>
Table 1. Continued

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin*</td>
<td>400 mg q.d.</td>
<td>Gastrointestinal discomfort; headache; dizziness; hallucinations; increased transaminases; QT prolongation: <em>Clostridium difficile</em> colitis</td>
</tr>
</tbody>
</table>

**Group 4: second-line oral agents**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifabutin</td>
<td>150–450 mg q.d.</td>
<td>Anaemia; gastrointestinal discomfort; discoloration (orange or brown) of urine and other body fluids; uveitis; elevated liver enzymes</td>
</tr>
<tr>
<td>Ethionamid</td>
<td>0.75–1 g q.d.</td>
<td>Severe gastrointestinal intolerance; nausea; vomiting; hepatitis; CNS disorders</td>
</tr>
<tr>
<td>Prothionamide</td>
<td>0.75–1 g q.d.</td>
<td>Severe gastrointestinal intolerance; nausea; vomiting; hepatitis; CNS disorders</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>250 mg t.i.d. Maximum 1,000 mg per day</td>
<td>CNS disorders; anxiety; confusion; dizziness; psychosis; seizures; headache</td>
</tr>
<tr>
<td>Terizidone</td>
<td>250 mg t.i.d. Maximum 1,000 mg per day</td>
<td>CNS disorders; anxiety; confusion; dizziness; psychosis; seizures; headache</td>
</tr>
<tr>
<td>Para-aminosalicylic acid</td>
<td>4 g t.i.d.</td>
<td>Gastrointestinal intolerance; nausea; diarrhoea; vomiting; hypersensitivity</td>
</tr>
<tr>
<td>Thiacetazone</td>
<td>50 mg t.i.d.</td>
<td>Hypersensitivity; gastrointestinal intolerance; vertigo; hepatitis</td>
</tr>
</tbody>
</table>

**Group 5: oral reserve drugs with uncertain anti-TB activity**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linezolid</td>
<td>600 mg q.d.</td>
<td>Thrombopenia, anaemia, neuropathy</td>
</tr>
<tr>
<td>(recommended for 600 mg b.i.d. dosage for MRSA and VRE infections)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clofazimine</td>
<td>100 mg q.d.</td>
<td>Ichthyosis; gastrointestinal discomfort; nausea; vomiting; discoloration of the skin</td>
</tr>
<tr>
<td>Amoxicillin–clavunate</td>
<td>875–125 mg b.i.d. or 500–250 mg t.i.d.</td>
<td>Gastrointestinal discomfort; diarrhoea; rash</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500 mg b.i.d.</td>
<td>Gastrointestinal discomfort</td>
</tr>
</tbody>
</table>

CNS: central nervous system; MRSA: methicillin-resistant *Staphylococcus aureus*; VRE: vancomycin-resistant Enterococcus.

* intravenous/intramuscular administration only; †: intravenous administration only; +: also available for intravenous injection.

Categories are needed. An alternative approach is to design a regimen on the basis of the individual history of previous anti-TB therapy, and eventually redesign it guided by individual DST. Relevant laboratory capacity is necessary if this option is chosen, as DST on most second-line drugs must be performed.

Although an individual patient's treatment duration should be guided by sputum smear and culture conversion, in general an injectable agent should be continued for at least the first 6 months of treatment. The entire treatment should be no less than 18 months after culture conversion.
Table 2: World Health Organization (WHO)-recommended treatment categories and regimens

<table>
<thead>
<tr>
<th>Patient treatment category</th>
<th>Patient diagnostic category</th>
<th>Treatment regimens*</th>
<th>Initial phase</th>
<th>Continuation phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>New pulmonary TB cases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category I</td>
<td>New smear-positive</td>
<td>Preferred: 2 HRZE</td>
<td>Preferred: 4 HR; 4 HR3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>patients, new smear-</td>
<td>Optional: 2 HRZE</td>
<td>Optional: 6 HE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>negative patients with</td>
<td>Optional: 2 HRZE3</td>
<td>Optional: 4 HR3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>extensive parenchymal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>involvement, concomitant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HIV-related diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category III</td>
<td>New smear-negative</td>
<td>Preferred: 2 HRZE</td>
<td>Preferred: 4 HR, 4 HR3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pulmonary TB (other</td>
<td>Optional: 2 HRZE</td>
<td>Optional: 6 HE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>than in Category I)</td>
<td>Optional: 2 HRZE3</td>
<td>Optional: 4 HR3</td>
<td></td>
</tr>
<tr>
<td><strong>Re-treatment pulmonary TB cases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category II</td>
<td>Relapses, treatment</td>
<td>Preferred: 2 HRZES/1</td>
<td>Preferred: 5 HRE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>after default*</td>
<td>HRZE3</td>
<td>Optional: 5 HRE3</td>
<td></td>
</tr>
</tbody>
</table>

TB: tuberculosis; H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; S: streptomycin. *: Numbers preceding regimens indicate the length of treatment in months. Numbers following regimens indicate the frequency of administration per week. Where no number is given after the regimen, administration is daily. **: The thrice weekly treatment was less effective than daily treatment as measured by conversion rates at 2 months, with a suggestion of less favourable outcomes overall; although the difference in outcome from the 8-month daily regimen was negligible. ***: In settings with proven high prevalence of drug-resistant or multidrug-resistant TB cases, national programmes can design standardised regimens or can allow the use of individualised regimen, including second-line drugs to treat treatment failures of Category I.

Table 3: General principles for designing an empiric regimen to treat multidrug-resistant tuberculosis

<table>
<thead>
<tr>
<th>Basic principles</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use at least four drugs of known effectiveness or that are highly likely to be effective</td>
<td>Effectiveness is supported by a number of factors (the more of them that are present, the more likely it is the drug will be effective): 1) susceptibility seen upon drug susceptibility testing 2) no previous history of treatment failure with drug 3) no known close contacts with resistance to drug 4) drug resistance screening indicates resistance is rare in similar patients 5) no common use of drug in the area If at least four drugs are not certain to be effective, use from five to seven drugs, depending on the specific drugs and level of uncertainty</td>
</tr>
<tr>
<td>Do not use drugs for which resistance crosses over</td>
<td>1) Rifamycins (rifampicin, rifabutin, rifapentin, rifalazil): have high level of cross-resistance 2) Fluoroquinolones: variable cross-resistance; in vitro data show some higher-generation agents remain susceptible when lower-generation agents are resistant (clinical significance of the phenomenon still unknown) 3) Aminoglycosides and polypeptides: not all cross-resist; in general, only kanamycin and amikacin fully cross-resist</td>
</tr>
<tr>
<td>Eliminate drugs likely to be unsafe for the patient</td>
<td>1) Known severe allergy or difficult-to-manage intolerance 2) High risk of severe adverse effects, including renal failure, deafness, hepatitis, depression and/or psychosis 3) Unknown or questionable drug quality</td>
</tr>
</tbody>
</table>
Treatment with second-line anti-TB chemotherapy in MDR- and XDR-TB is frequently influenced by the occurrence of adverse drug events. Unfortunately, reliable indicators to individually guide the duration of anti-TB drug treatment are not available. For all the reasons previously listed, treatment of MDR- and XDR-TB cases should be managed in highly specialised reference centres, identified by national authorities.

Scaling-up of culture and DST capacities, and the expanded use of high-technology assays for rapid determination of resistance are necessary if better control of MDR- and XDR-TB is to be achieved. The majority of resistant cases can be treated successfully if well-designed regimens are used and surgical options are carefully considered. Nevertheless, the development of new (more effective and less toxic) drugs to treat patients is urgently needed. Adherence to internationally agreed standards of care and control practices is imperative.

References

EXTRAPULMONARY TUBERCULOSIS

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The World Health Organization (WHO) definition of extrapulmonary tuberculosis (EPTB) is: “A patient with tuberculosis of organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genito-urinary tract, skin, joints and bones, and meninges. Diagnosis should be based on one culture-positive specimen, or histological or strong clinical evidence consistent with active extrapulmonary disease, followed by a decision by a clinician to treat with a full course of anti-tuberculosis chemotherapy”.

A patient diagnosed with both pulmonary tuberculosis (PTB) and EPTB should be classified as a case of PTB.

The definition mentions neither the eyes nor the ear–nose–throat region. However, these tissues are also, but scarcely, possible localisations.

General aspects of EPTB

Only a minority of cases (<30%) suffer from EPTB. However this could be biased by the definition because in countries with a differentiated registry (PTB, EPTB, and EPTB+PTB), EPTB localisations comprise nearly 50% of all the cases.

In low-income countries, males appear to be affected by tuberculosis (TB) more often than females. However, this difference is not so clear in high-income countries; the mechanism is not clearly understood. No evidence is available to suggest that EPTB affects one of the sexes more frequently.

Immunosuppression appears to be an important cause for EPTB and is reflected by a sharp incline in reported cases of EPTB with the rise of the incidence of HIV infection. In high-income countries, and countries with a lower incidence of HIV infection, biological agents like tumour necrosis factor-α inhibitors are relatively important causes of EPTB.

“The result of tuberculous bacillaemia must be the insemination in various parts of the body of foci most of which remain latent.” Therefore, EPTB can be the result of a primary infection in severely immunocompromised hosts or can be the result of reactivation of dormant bacilli in previously infected subjects.

Sites of EPTB

The two most common localisations of EPTB are the cervical lymph nodes and the pulmonary pleura. Other sites are, in declining order, bones and joints, meninges and central nervous system (CNS), abdominal lymph nodes, peritoneum and gastrointestinal tract, genito-urinary tract and pericardium.

Key points

• EPTB localisations appear in up to 50% of TB patients.
• Obtaining culture confirmation is essential in the treatment of both PTB and EPTB.
• Treatment of EPTB does not differ from PTB in the majority of EPTB localisations.
It should be noted that gastric aspirate in children with PTB often contains mycobacteria. This is, however, not an indication of EPTB but should be considered as a local spread of mycobacteria by swallowing sputum.

In immunocompromised hosts, the presentation of EPTB is often different compared with immunocompetent hosts. Dissemination of the disease is more common and clinicians should be aware of other localisations. Dissemination is more likely because ill-formed granuloma occur more frequently in immunocompromised hosts.

The term miliary TB refers to a radiological finding of the chest radiography and should not be used in this context.

**Diagnosis**

In countries with all possible diagnostic resources on average 70% of all the TB cases are culture confirmed. One can imagine that in EPTB samples are more difficult to obtain compared with PTB. Furthermore some of the EPTB localisations contain only few mycobacteria. Culture or PCR confirmation will thus be lower in these cases. Using the Dutch TB registry PTB is culture confirmed in nearly 80% and EPTB in about 60% of the cases.

Specific staining is in low-income countries often the only available diagnostic tool and because of the relative simplicity should always be undertaken.

Some promising reports on interferon-γ release assays in the diagnosis of EPTB (pleural and meningitis TB) have been published. However, these tests are no proof of active infection, they will not provide culture results or drug susceptibility reports and can therefore only be supportive in the search for mycobacteria. However, it remains most important to obtain materials for culture and drug susceptibility tests (DST).

**Treatment**

In general, treatment for EPTB does not differ from that for PTB. Depending on local or national guidelines, the treatment consists of a full course of at least four anti-TB drugs (isoniazid, rifampicin, ethambutol and pyrazinamide) in the first 2 months and than another 4–7 months of isoniazid and rifampicin in culture confirmed cases with normal drug susceptibility [D]. In countries with a high prevalence of drug resistance for one or more of these drugs, a fifth or even sixth drug should be added awaiting culture and DST.

**Specific localisations**

**Cervical lymph nodes**  Involvement of the lymph nodes or lymphadenitis is the most common localisation of EPTB. Concomitant pulmonary infection occurs in 5–10% of the cases and therefore generalised symptoms are unusual. During medical treatment the lymph nodes can rapidly increase in size (paradox reaction) and to prevent fistula, fine-needle aspiration of its content may prove beneficial. In children, lymphadenitis is often caused by nontuberculous mycobacteria and this requires a different treatment approach. Confirmation of the causative organism is therefore crucial.

**Other lymph nodes**  Other common sites of lymph node involvement are axillary, inguinal and abdominal. Culture results (Mycobacterium tuberculosis versus nontuberculous mycobacteria) for these localisations do not differ between children and adults.

**TB of the pleura**  In general, the pleurisy is one sided and the majority of cases have a tendency toward spontaneous resolution. Therefore the diagnosis can be delayed for a prolonged period until a new effusion appears. Large amounts of pleural fluid are often observed with relatively low numbers of mycobacteria. An accompanying hypersensitivity reaction is held responsible for this phenomenon. Because of this low bacterial burden, the confirmation of TB can often be difficult. TB empyema is a rare condition compared with pleurisy and often requires surgical drainage and decortication combined with medical treatment.
TB of the meninges and CNS Meningitis is the most common presentation of involvement of the nervous system. The infection can cause hydrocephalus and through involvement of the cranial nerves paralysis of the nervus abducens. Classically the patient is not able to look outward with one eye and this eye is rotated towards the nose. Neurological deterioration is classified in three grades based on the performance on the Glasgow Coma Scale. Apart from antibiotic treatment, it is recommended to add steroids (0.5 mg·kg⁻¹) in stages II and III. Survival is positively influenced by this regimen, but neurological outcome is not better in the groups treated with steroids. Others recommend steroids independent of the stage. Antibiotic treatment should be at least 9 months. However, according to the British guidelines, treatment should be continued for 1 yr. The WHO recommends to replace ethambutol by streptomycin in TB meningitis.

TB of the pericardium This condition is sometimes difficult to diagnose because, just like pleural effusion, the bacterial load is low. Pericardial effusion and, at a later stage, constrictive pericarditis can cause severe inflow limitation resulting in serious haemodynamic problems. Steroids are recommended to reduce the effusion and to prevent thickening of the pericardium adjuvant. No data is available on the amount and duration of steroid treatment. It appears reasonable to prescribe 0.5 mg·kg⁻¹ for the first 2 months and than decrease the dose gradually to zero over a period of 4 months.

Bone and joint TB Any bone or joint can be affected, but the classical lesion is a fracture of the vertebrae resulting in a kyphotic change of the spine (Pott’s disease). In general, the larger bones and joints are more often affected compared with the smaller ones. Joint involvement presents as a mono- arthritis. Diagnosis of both bone and joint involvement is generally made by biopsy. Aspiration of synovial fluid seldom yields the diagnosis. Medical treatment is the treatment of choice and should be prolonged to 9 months. Surgery is reserved for complicated cases such as neurological involvement or instability of the spine.

References

Weblinks
The incidence of active tuberculosis (TB) is increased in patients with impaired cellular immunity, such as HIV-infected patients, solid-organ and stem cell transplant recipients, patients receiving tumour necrosis factor (TNF)-α antagonists and patients with end-stage renal failure. This emphasises the particular importance of the cellular arm of the adaptive immune response for efficient control of Mycobacterium tuberculosis. Moreover, the presence of M. tuberculosis-specific CD4 T-cell immunity is used as a surrogate marker for a previous contact. Consequently, a detailed knowledge of the pathomechanisms leading to increased incidence of TB in immunocompromised patients has also contributed to a better understanding of the principles of decreased test sensitivity in this vulnerable patient group.

Pathomechanisms of impaired TB control

The general incidence of TB in immunocompromised patients may vary depending on the geographical location and may range from <1% to up to 15% in low- and high-prevalence countries, respectively. The relative risk to develop TB and its underlying pathomechanisms may differ widely among the various groups due to differences in the cause and extent of immunodeficiency (table 1). The dramatic reduction in CD4 T-cell numbers in HIV-infected patients, in particular in those with AIDS, not only contributes to a severely impaired control of TB, but also to a high percentage of false-negative diagnoses by immune-based tests. Similarly, immunosuppressive drug-treatment after transplantation is associated with a decrease in T-cell function and may lead to a progressive decrease in M. tuberculosis specific T-cell immunity over time. This not only facilitates reactivation but also contributes to a decreased sensitivity of immune-based testing. The uraemia-associated immunodeficiency syndrome in patients with end-stage renal failure has been characterised by a defect in co-stimulatory signals to antigen-specific T-cells thereby contributing to an impaired efficiency of vaccinations and increased risk of infectious complications including TB. Finally, an increased incidence of active TB in patients receiving TNF-α antagonists is attributed to an impaired T-cell function and failure to maintain the integrity of granuloma in latently infected patients.

Key points

- TB has a higher incidence among people with impaired cellular immunity.
- Diagnosis is often delayed owing to early lack of symptoms or unusual presentation.
- Screening for latent TB infection prior to immunosuppressive treatments can be a useful preventive measure.
Clinical presentation of active TB

Active TB in immunocompromised patients can pose a number of challenges. Due to the impaired immune response, patients may be clinically oligosymptomatic in the beginning of active disease and its diagnosis is often delayed due to atypical presentations and more frequent extrapulmonary dissemination. Active TB is further aggravated by a significantly higher morbidity due to a more fatal course in the face of a weakened immune system. In addition, treatment is frequently complicated due to complex drug interactions and altered pharmacokinetics. The treatment of TB is also more difficult to manage in HIV-infected patients, as immune restoration induced by anti-retroviral therapy may be responsible for a paradoxical worsening of TB manifestations, a phenomenon defined as immune reconstitution inflammatory syndrome.

Preventative approaches

The increased risk of active TB in immunocompromised patients may result from an immunosuppression-induced reactivation of a previously acquired latent TB infection (LTBI) or new infections. While the extent of new infections is difficult to control as it largely depends on the overall prevalence of TB, the risk of progression from LTBI to active disease may be minimised by the early identification and treatment of latently infected patients. Although risk assessment in immunocompromised patients is often hampered by a low sensitivity of commonly used immune-based tests, current guidelines recommend a regular screening for evidence of LTBI and, if possible, treatment prior to conditions of immunodeficiency, i.e. screening and treatment prior to transplantation or TNF-α antagonist therapy. Until recently, LTBI screening was exclusively carried out by the use of tuberculin skin-testing, where the cut-off of positivity is defined by the extent of immunodeficiency. At present, however, novel interferon-γ release assays (IGRA) are more widely applied that are of higher specificity as compared with skin-testing. In addition, accumulating evidence suggests that IGRA may be of higher sensitivity in immunocompromised patients although large studies, in particular in highly immunocompromised patients, are still lacking.

Conclusions

TB in immunocompromised patients is more frequent as compared with the general population, and morbidity and mortality is high. Risk assessment needs integrative approaches that should consider clinical findings, the extent of immunodeficiency and the overall prevalence of TB.

References


<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative risk</th>
<th>Pathomechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection (AIDS)</td>
<td>100–170</td>
<td>Low CD4 T-cell counts</td>
</tr>
<tr>
<td>HIV infection (no AIDS)</td>
<td>50–100</td>
<td></td>
</tr>
<tr>
<td>Transplantation</td>
<td>20–74</td>
<td>Decreased T-cell function and numbers</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>10–25</td>
<td>Co-stimulation deficiency, chronic inflammation</td>
</tr>
<tr>
<td>TNF-α antagonists</td>
<td>2–9</td>
<td>Disintegration of granuloma</td>
</tr>
</tbody>
</table>

Table 1. Pathomechanisms and relative risk for TB in immunocompromised patients relative to persons without known risk factors (risk = 1)


LATENT TUBERCULOSIS

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Individuals who are in close contact with a patient with a transmissible form of tuberculosis (TB; usually smear-positive pulmonary TB) may inhale droplets containing mycobacteria, which settle in the airways and give rise to a local inflammatory reaction. The risk of infection is related to the concentration of mycobacteria in the air and the duration of contact. Some exposed individuals develop an active disease (TB) within a couple of weeks or months; others will control the incipient infection and stay for a prolonged period (up to years) in a state of equilibrium called ‘latent infection’ or ‘latent TB’ or LTBI.

LTBI and risk of TB

Individuals with latent TB have no signs or symptoms of active TB, and only immunological markers of a prior contact with mycobacteria. It is impossible to know if individuals with latent TB still harbour living mycobacteria. The only gold standard for the infection is the development of the disease, which happens in a minority of exposed individuals. Why and how the infected individuals will develop TB is unknown. Estimates are that ~10% of infected individuals may develop TB, half of them within 2 yrs after infection, and 90% will never develop the disease. Some infected individuals have a higher risk of later reactivation than others (for instance immunocompromised individuals, patients receiving immunosuppressive therapy and small children). As only a minority of contacts develop TB, there is a possibility that most contacts eradicate the mycobacteria but still retain an immunological marker of the primary contact, even in the absence of living mycobacteria.

Treatment of latent TB

As the persons in contact with a case of TB have a much higher risk of developing the disease in the future than the average population, particularly if they have a positive tuberculin reaction or a positive interferon-γ release assay (IGRA) test, the detection of latent TB among exposed contacts is important because a preventive treatment can reduce this risk. In countries or populations with a low incidence of TB, the search for latent infection among contacts and the

Key points

- The risk of latent TB infection (LTBI) depends on the intensity and duration of exposure to a source case with untreated pulmonary TB.
- Some infected contacts will develop TB at a later time-point. Timely detection of infected contacts and preventive treatment of those at highest risk of reactivation is costeffective and reduces the pool of future cases of active TB.
- Before prescribing a preventive treatment, active TB should be excluded by a chest radiograph and, if abnormal, by a bacteriological examination of sputum.
- The tests for the detection of latent infection are the tuberculin skin test and the Interferon-Gamma Release Assays (IGRAs). The latter have the advantage of a greater specificity.
prescription of preventive treatment may contribute to the control of the disease by reducing the pool of potential future cases. The currently recommended preventive treatments are 9 months of isoniazid, 4 months of rifampicin or 3 months of an association of isoniazid and rifampicin.

As the immunological reaction after the contact with mycobacteria needs several days or weeks to be complete, the proof of a recent sensitisation is usually not present before this time (the window period). Therefore, the search for latent infection is usually performed only 4–8 weeks after the last contact. In some cases, where the progression from infection to disease may be rapid (such as immunocompromised contacts or children aged <5 yrs), a first testing with a clinical examination may be performed as soon as possible after the last contact and repeated several weeks later, if the results are negative. A test performed immediately after the last contact will usually indicate a prior sensitisation and may be observed among contacts born in a region with high prevalence of TB and in elderly people, independently of recent contacts.

Tests for detection of LTBI

The tests used for the detection of latent infection are all indirect and rely on the reaction between sensitised lymphocytes and antigens from Mycobacterium tuberculosis. The traditional test is the tuberculin skin test measuring the cutaneous reaction elicited by the intradermal injection of a mixture of antigens from M. tuberculosis cultures. New tests have recently been developed and introduced on the market. The tuberculin skin test measuring the release of cytokines (interferon-γ) by lymphocytes incubated with two or three specific antigens present in M. tuberculosis but absent in Mycobacterium bovis bacille-Calmette–Guerin and in most nontuberculous mycobacteria (IGRAs). The in vitro tests are (at least) equally sensitive as the tuberculin test but have the advantage of a greater specificity, and therefore avoid in practice the false-positive skin reactions elicited by prior BCG vaccination or contact with nontuberculous mycobacteria.

Detection in low-prevalence countries

In low-prevalence countries, the search for infected individuals is usually performed among persons who recently had a contact with a patient with pulmonary TB (contact investigation), in healthcare workers potentially exposed to untreated cases of TB and in immunocompromised patients with a risk of reactivation higher than the general population. Infected contacts considered at risk of developing TB in the future are either followed clinically or offered a preventive treatment. All contacts with immunological signs of infection (positive tuberculin skin test or IGRA) should have at least a chest radiograph for detecting signs of past or recent TB. Before prescribing a preventive treatment in contacts with an abnormal chest radiograph, the presence of an active TB should be excluded by a bacteriological examination of sputum. The efficiency of the preventive treatment largely depends on the rate of treatment completion.

Detection in high-prevalence countries

In high-prevalence countries, formal contact investigations are usually not performed, as most of the contacts may already have immunological signs of prior infection, but it is currently recommended to search for the presence of secondary cases of TB among the close relatives and to consider the protection of small children with a preventive treatment if one of the parents has a form of transmissible TB.

Controversies and open questions

There are still controversies about the definition of infectiousness (only smear-positive cases or all cases with pulmonary TB), the extent of the contact investigation (only close and prolonged contacts or all contacts) and about the indications of preventive treatment (only infected contact with a high risk of reactivation or all contacts or individuals with a positive tuberculin or IGRA test).
reaction). Prospective studies on the risk of reactivation among contacts with a positive immunological reaction will help to clarify these issues.

References

Nontuberculous mycobacteria (NTM) is the term indicating those *Mycobacterium* species that are different from *Mycobacterium tuberculosis* complex (MTC) and *Mycobacterium leprae* whose detection in clinical samples is almost invariably associated with disease. The most important features distinguishing NTM from MTC include a lower pathogenicity and the lack of human-to-human transmission. In addition, *in vitro* resistance to first-line antituberculous drugs is another important distinctive issue. The majority of the >120 NTM species recognised currently has been associated with disease in man or animals.

**Epidemiology and pathogenesis**

NTM are widely distributed in both natural and man-made environments; organisms can be found in soil and water with high isolation rates. Human disease is suspected to be acquired from environmental exposure and pulmonary infection is likely to depend on the aerosol route. Although much remains to be understood about the pathogenesis of NTM infections, the following is now well established:

- In HIV-infected patients, disseminated NTM infections occur only after the CD4+ T-lymphocyte count has dropped below 500 μL⁻¹.
- In HIV-uninfected patients, NTM infections may be associated with specific mutations in interferon-γ and interleukin-12 synthesis and response pathways.

The most common clinical manifestation of NTM infection is pulmonary disease, but lymphatic, skin/soft tissue, osteoarticular and disseminated disease are also important.

**Pulmonary disease**

In immunocompetent subjects, NTM lung disease presents as one of the following clinical forms:

**Cavitary lung disease** This pattern, which closely resembles pulmonary TB, involves the upper lobes of older males usually affected by a pre-existing destructive or obstructive lung condition such as pneumoconiosis, chronic bronchitis with emphysema (frequently associated with long-lasting, heavy smoking) and bronchiectasis. Thin-walled cavities with scarce parenchymal infiltrate and a marked pleural thickening are characteristic.

**Key points**

- Important features distinguishing NTM from *M. tuberculosis* complex include lower pathogenicity and lack of human-to-human transmission.
- Diagnosis of NTM disease requires both clinical and microbiological criteria to be met.
- Treatment is disappointing and is characterised by long duration and side-effects, leading to poor compliance.
and symptoms include chronic cough with sputum production and weakness. With advanced disease, dyspnoea, fever, weight loss and haemoptysis can also occur.

**Nodular bronchiectasis** This pattern (also known as *Lady Windermere’s syndrome*) has been described in slender elderly females with structural chest abnormalities (pectus excavatum, scoliosis and mitral valve prolapse), but no evidence of pre-existing lung disease. Indolent productive cough and purulent sputum are the most common presenting symptoms, while constitutional symptoms and haemoptysis are not common unless extensive disease is present. The radiographic findings include small nodular infiltrates and cylindrical bronchiectasis, predominately located within the middle lobe and lingula.

**Hypersensivity pneumonitis (HP)** A syndrome indistinguishable from HP has been reported in subjects exposed to household water laden with *Mycobacterium avium* complex (MAC) organisms (hot tubs and medicinal baths). Full recovery usually occurs without any specific therapy (simply by avoiding further contact with contaminated solutions), but sometimes a combination therapy of steroids and antibiotics may be required.

In addition, NTM lung disease may be associated with the following conditions:

- HIV infection. Although NTM are frequently recovered from respiratory specimens of HIV-infected subjects, extrapulmonary or disseminated disease are more likely to occur. The most relevant exception to this generalisation is given by *Mycobacterium kansasii*.
- Immune reconstitution inflammatory syndrome.
- Transplantation including both solid-organ and haematopoietic stem cell transplants.
- Treatment with tumour necrosis factor-α antagonists.
- Cystic fibrosis.

**Laboratory diagnosis**

Mycobacterial culture remains the cornerstone with which to make a definitive diagnosis. Therefore, appropriate, high-quality specimens properly collected from all patients with suspected NTM disease have to be sent to a certified laboratory. Due to the ubiquitous occurrence of NTM in the environment, the recognition of disease as opposed to contamination of specimens or transient colonisation may be difficult. While smear-positive samples strongly suggest an active disease, a single positive culture (especially with small numbers of organisms) does not suffice to set such a diagnosis. In this context, the American Thoracic Society has recently updated the criteria for the diagnosis of pulmonary disease caused by NTM (table 1).

It is necessary to fulfil all the above elements to establish a correct diagnosis. Although these criteria are derived from experience with MAC, it is reasonable to believe they would work with other species provided that contamination of clinical specimens and medical devices with environmental NTM (pseudoinfection) has been excluded. Today, the combined use of automated liquid culture for detection and drug susceptibility testing (DST) plus the use of genetic probe technology for identification of mycobacteria

<table>
<thead>
<tr>
<th>Clinical criteria (both required):</th>
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<tbody>
<tr>
<td>Pulmonary symptoms, cavitary or noncavitary lung disease</td>
<td></td>
</tr>
<tr>
<td>Appropriate exclusion of other causes for the disease</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Microbiological criteria (only one required):</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive culture results from at least two separate expectorated sputum samples</td>
<td></td>
</tr>
<tr>
<td>Positive culture results from at least one bronchial wash or lavage</td>
<td></td>
</tr>
<tr>
<td>A transbronchial or lung biopsy showing granulomata and/or acid-fast bacilli (AFB) and positive culture for NTM</td>
<td></td>
</tr>
<tr>
<td>Biopsy showing granulomata and/or AFB and one or more sputa or bronchial washings that are culture-positive for NTM</td>
<td></td>
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</tbody>
</table>
is mandatory in all laboratories wishing to perform mycobacteriology.

**Treatment**

Treatment regimens for NTM disease are still largely undefined and outcome remains disappointing despite considerable upgrading in mycobacteriology and the availability of some new antimicrobials. Treatment success is impared by the long duration of regimens, their side-effects and drug interactions, which prevent patients from full compliance (table 2). In addition, although many NTM species may be susceptible in vitro to one or more antituberculous drugs, correlation between DST results and clinical outcome is poor.

**References**

- Field SK, Cowie RL. Lung disease due to the more common nontuberculous mycobacteria. Chest 2006; 129: 1653-1672.

### Table 2. Clinical and radiographic features of pulmonary infections caused by the most frequently encountered NTM

<table>
<thead>
<tr>
<th>Species</th>
<th>Pathogenicity; outcome</th>
<th>Radiographic findings</th>
<th>Treatment (time in months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycobacterium avium complex</td>
<td>+ +; poor/fair</td>
<td>Upper lobe cavitations</td>
<td>Clarithromycin, ethambutol, rifampin (18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Middle lobe bronchiectasis</td>
<td>Clarithromycin, ethambutol, rifampin (18)</td>
</tr>
<tr>
<td>Mycobacterium kansasii</td>
<td>+ + +; good</td>
<td>Upper lobe cavitations</td>
<td>Rifampin, isoniazid, ethambutol (18)</td>
</tr>
<tr>
<td>Mycobacterium malmoense</td>
<td>+ + +; fair</td>
<td>Upper lobe infiltrates</td>
<td>Rifampin, ethambutol (24)</td>
</tr>
<tr>
<td>Mycobacterium xenopi</td>
<td>+; poor</td>
<td>Upper lobe cavitations and nodules</td>
<td>Clarithromycin, rifampin, ethambutol, moxifloxacin (18)</td>
</tr>
<tr>
<td>Mycobacterium szulgai</td>
<td>+ + +; good</td>
<td>Upper lobe cavitations</td>
<td>Rifampin, isoniazid, ethambutol, pyrazinamide (18)</td>
</tr>
<tr>
<td>Mycobacterium simiae</td>
<td>+; poor</td>
<td>Upper lobe cavitations and nodules</td>
<td>Clarithromycin, moxifloxacin cotrimoxazole (18)</td>
</tr>
<tr>
<td>Mycobacterium abscessus</td>
<td>+ +; poor</td>
<td>Multilobar interstitial and nodular lesions</td>
<td>Clarithromycin, amikacin, cefoxitin (1); surgical resection</td>
</tr>
</tbody>
</table>

+ number of + indicates degree of pathogenicity. Reproduced from PERSIMONI and SCARPARO (2008), with permission from the publisher.
CHAPTER 9:

AIRWAY DISEASES

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Rhinitis is one of the commonest human diseases. Its most important features are inflammation and structural changes of the nasal mucosa. The causes are heterogeneous and, if allergy and infections are dominant, it is often difficult to find a single common aetiology in chronic rhinitis. It is important to consider that rhinitis is often associated with sinusitis and lower airway diseases such as asthma. Rhinitis is a mild disease, but it interferes with sleep quality and daily life.

Epidemiology

Rhinitis is still increasing in prevalence in most countries. In some studies, 25–30% of the population is suffering from rhinitis, often linked to immunoglobulin (Ig)E sensitisation. It may increase with age, as demonstrated in both children and adults, and there is growing evidence that emerging countries are affected by an increase in prevalence. Thus, rhinitis is an important health problem worldwide. It affects health-related quality of life in both adults and children. It is usually a mild disease, but its direct and indirect costs are substantial. Absenteeism at school or at work is often reported by subjects suffering from rhinitis. Rhinitis is often associated with other IgE-related disease and the continuum linking upper and lower airways is well represented by the association of rhinitis and asthma, which frequently coexist: asthma is present in 20–50% of patients with allergic rhinitis. Rhinitis is present in up to 80% of asthma patients. Whether allergic rhinitis precedes, triggers or precipitates asthma is something that requires supportive data. Atopic status plays a potentially prominent role in this relationship, although it is not a prerequisite. The risk factors for rhinitis need to be better known and understood in order for preventive measures to be implemented.

Definition and clinical aspects of rhinitis

Allergic rhinitis is defined as inflammation of the nasal mucosa characterised clinically by nasal discharge, blockage, sneezing and itch, with two or more symptoms occurring for >1 h on most days. It can be further classified as intermittent (symptoms occurring on <4 days out of 7 or for <4 weeks per year) or persistent (symptoms occurring on ≥4 days out of 7 or for ≥4 weeks per year). The impact of chronic rhinitis on sleep, daily activities, work or school is a major determinant of quality-of-life impairment in patients. The perception of nasal symptoms is highly variable, a fact illustrated in patients suffering from chronic obstructive pulmonary disease and other chronic respiratory conditions.
disease, where a discrepancy between nasal inflammation and symptoms has been demonstrated. From a clinical point of view, it is thus difficult to rely on patients’ reports of symptoms as the only way to assess rhinitis.

Nonallergic rhinitis is difficult to differentiate clinically from allergic rhinitis. Exacerbations are usually associated with infections but several other triggers, including drugs, may cause recurrent symptoms.

**Pathological and mechanistic aspects**

Pseudostratified epithelium and a large highly developed vasculature cover the nasal wall. Tight junctions, peptidases and a large antioxidant apparatus are key features of the anatomical barrier of the nasal epithelium. The mucosal-associated lymphoid tissue is developed in the nose. Structural abnormalities including changes of the basement membrane have been reported in rhinitis. Inflammatory cells such as eosinophils, mast cells, T-cells and macrophages infiltrate the epithelium and submucosa. Mast cell-derived inflammatory mediators are overexpressed, such as histamine, chemokines and cytokines including interleukin (IL)-5, RANTES, IL-4, IL-13, granulocyte macrophage colony-stimulating factor. Most of these molecules trigger a local eosinophilic inflammatory response.

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**Figure 1. Treatment algorithm for allergic rhinitis. Ig: immunoglobulin; CS: corticosteroids. Reproduced from the ARIA guidelines, with permission from the publisher.**
process. Allergens, microorganisms and pollutants are potential triggers that can generate acute and chronic inflammatory reactions through the epithelium. The release of various mediators is responsible for most of the clinical symptoms reported by patients. Nasal hypersecretion, sneezing and itching are related to the release of vasoactive and proinflammatory mediators such as histamine and sulphido-leukotrienes. Persistent nasal obstruction is linked to the perpetuation of inflammatory reactions mostly related, in allergic rhinitis, to eosinophilic infiltration.

**Effects of anti-inflammatory treatment**

Intranasal corticosteroids and intranasal or oral antihistamines, have been shown to have effects on different aspects of inflammation in allergic rhinitis. Additionally, intranasal anticholinergic therapy provides relief for excessive rhinorrhea, while leukotriene antagonists block the cysteinyl leukotriene receptor. Nasal obstruction improves significantly more with intranasal corticosteroids compared with most of the other pharmacological strategies. Specific immunotherapy using sublingual, oral or subcutaneous routes has been proven effective and safe in intermittent and persistent allergic rhinitis. Allergen avoidance is not effective in allergic rhinitis. Several studies have demonstrated that the effective treatment of rhinitis decreases the burden of asthma as assessed by unscheduled visits to physicians and emergency rooms due to acute exacerbations.

Treatment should be directed according to the cause: nonallergic rhinitis should be treated by nasal decongestant and anticholinergic therapy. Allergic rhinitis should be treated according to the ARIA guidelines (fig. 1).

The term rhinitis covers a heterogeneous group of diseases. Allergic rhinitis and its associated diseases have been well defined and treatment is codified. Mucosal inflammation is the hallmark of rhinitis. Its natural history and its relationship with sinusitis and lower airways diseases need to be clarified. New treatments and management strategies are required, especially in the most chronic severe forms.

**References**


**Weblink**

Asthma is a chronic inflammatory disease of the airways, characterised clinically by recurrent respiratory symptoms: dyspnoea, wheezing, chest tightness and/or cough, almost always associated with reversible airflow limitation. Other characteristics of asthma are an exaggerated responsiveness of the airways to various stimuli, and in most cases a rather specific chronic inflammation of the airways characterised by an increased number of CD4+ Th2 lymphocytes, eosinophils and methacromatic cells in the airway mucosa, and increased thickness of the reticular layer of the epithelial basement membrane.

Familial predisposition, atopy, and exposure to allergens and sensitising agents are important risk factors for asthma, even though the causes of asthma – the factors responsible for the development of asthma rather than its exacerbations – remain largely undetermined.

Asthma is a heterogeneous syndrome that, over the years, has been divided into many clinical subtypes, e.g. allergic asthma, adult-onset asthma that is usually nonallergic, occupational asthma, asthma in smokers and asthma in the obese.

Minimum requirements for the diagnosis of asthma

The diagnosis of asthma is based on clinical history and lung function tests, particularly peak expiratory flow (PEF) and spirometry, with assessment of variable and/or reversible airflow limitation. Allergy tests are also usually performed during the first assessment of a patient with suspected asthma to identify possible triggers of asthma and to guide their avoidance.

Asthma clusters in families, and its genetic determinants appear to be linked to those of other allergic immunoglobulin (Ig) E-mediated diseases. Thus, a personal or family history of asthma and/or allergic rhinitis, atopic dermatitis or eczema increases the likelihood of a diagnosis of asthma.

Symptoms and medical history

Most patients with asthma seek medical attention because of respiratory symptoms. A typical feature of asthma symptoms is their variability. One or more of the following symptoms: wheezing, chest tightness, and/or episodic shortness of breath are reported by >90% of patients with asthma. However, the presence of these symptoms is not diagnostic, because identical symptoms may be triggered
by different stimuli in nonasthmatics, e.g. by acute viral infections. In some asthmatics, wheezing and chest tightness are absent, and the only symptom the patient complains of is chronic cough (“cough-variant asthma”).

Symptoms of asthma may be triggered or worsened by several factors, such as exercise, exposure to allergens, viral infections and emotions. Recurrent exacerbations of respiratory symptoms, worsening of lung function requiring change of treatment, unscheduled requests for medical assistance and sometimes hospitalisation are also among the characteristic clinical features of asthma.

Physical activity is an important trigger of symptoms (wheezing and/or cough) for most asthma patients, particularly children. For some, it is the only cause. Exercise-induced asthma usually develops not during exercise but 5–10 min afterwards, and it resolves spontaneously within 30–45 min. Prompt relief of symptoms after the use of inhaled β₂-agonist, or prevention by pre-treatment with an inhaled β₂-agonist before exercise, supports a diagnosis of asthma. Important aspects of personal history are exposure to agents known to worsen asthma in the home (some types of heating or cooking system, house dust mites), workplace conditions, air-conditioning, pets, cockroaches, environmental tobacco smoke or even the general environment, e.g. diesel fumes in traffic.

Since the respiratory symptoms of asthma are nonspecific, the differential diagnosis is quite extensive. The main goal for the physician is to consider and exclude other possible diagnoses (table 1). This is even more important if the response to a trial of therapy (bronchodilators) has been negative.

While respiratory symptoms suggest asthma, the *sine qua non* for the objective diagnosis of asthma is the presence of reversible airflow limitation in subjects with persistent airway obstruction, and/or airway hyperresponsiveness or increased PEF variability in subjects without airway obstruction.

**Physical examination**

In mild asthma, physical examination is usually normal under stable conditions but becomes characteristically abnormal during asthma attacks and when asthma is more severe or uncontrolled. Typical physical signs of asthma attacks are wheezing on auscultation, cough, expiratory rhonchi throughout the chest and signs of acute hyperinflation (e.g. poor diaphragmatic excursion at percussion, use of accessory muscles of respiration). Some patients, particularly children, may present with a predominant nonproductive cough (cough-variant asthma). In some asthmatics, wheezing – which usually reflects airflow limitation – may be absent or detectable only on forced expiration, even in the presence of significant airflow limitation; this may be due to hyperinflation or to very marked airflow limitation. In these patients, however, the severity of asthma is mostly indicated by other signs, such as cyanosis, drowsiness, difficulty in speaking, tachycardia, hyperinflated chest, use of accessory muscles and intercostal recession.

**Lung function tests**

**Spirometry** Lung function tests play a crucial role in the diagnosis and follow-up of asthma. Spirometric measurements – FEV₁ and slow vital capacity (VC) or forced vital capacity (FVC) – are the standard means for assessing airflow limitation. Spirometry is recommended at the time of diagnosis and for the assessment of the severity of both asthma and chronic obstructive pulmonary disease (COPD). It should be repeated to monitor the disease and when there is a need for reassessment, such as during exacerbations.

Measurements of residual volume and total lung capacity may also be useful in determining the degree of hyperinflation and/or enlargement of airspaces. Lung volumes may help in the differential diagnosis with COPD, but are not necessary for the diagnosis nor for the assessment of severity of asthma. In asthma, airflow limitation is usually reversible, either spontaneously or after
treatment, except for moderate/severe asthma with fixed airway obstruction (see below).

An important tool for the diagnosis and subsequent monitoring of asthma treatment is the PEF meter. If spirometry does not reveal airflow limitation, the home monitoring of PEF for 2–4 weeks may help to detect an increased variability of airway calibre, and thus to diagnose. Daily monitoring of PEF (at least in the morning at awakening and in the evening hours, preferably after bronchodilator inhalation) is also useful to assess the severity of asthma and its response to treatment, and it can help patients to detect early signs of asthma deterioration. Diurnal variability is calculated as follows:

\[
\frac{(\text{PEF}_{\text{max}} - \text{PEF}_{\text{min}})}{(\text{PEF}_{\text{max}} + \text{PEF}_{\text{min}}) / 2} \times 100
\]

A diurnal PEF variability of >20% is diagnostic of asthma, and the magnitude of the variability is broadly proportional to disease severity. PEF monitoring may be of use not only in establishing a diagnosis of asthma and assessing its severity but also in uncovering an occupational cause for asthma. When used in this way, PEF should be measured more frequently than twice daily, and special attention should be paid to changes occurring in and out of the workplace.

**Reversibility to bronchodilators**

Reversibility to bronchodilators (i.e. a >12% reversibility response and >200 mL in FEV1 after bronchodilator) confirms the diagnosis of asthma. Poorly reversible airflow limitation is usually defined by the absolute reduction of post-bronchodilator FEV1/FVC ratios to <0.7. However, because this parameter decreases with ageing, it should be confirmed with postbronchodilator FEV1/VC values below the lower limit of normal. Reversibility is often not present at the time of examination.

Table 1. Differential diagnosis of asthma

<table>
<thead>
<tr>
<th>Localised pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled foreign body</td>
</tr>
<tr>
<td>Endobronchial tumour</td>
</tr>
<tr>
<td>Vocal cord dysfunction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diffuse airway pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Eosinophilic bronchitis</td>
</tr>
<tr>
<td>Postinfectious airway hyperresponsiveness</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>Left ventricular failure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other pathologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastro-oesophageal reflux</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Pulmonary eosinophilia syndromes</td>
</tr>
<tr>
<td>Drug-induced airway hyperresponsiveness</td>
</tr>
</tbody>
</table>

Table 2. History, symptoms and results of pulmonary function tests in the differential diagnosis between asthma and COPD

<table>
<thead>
<tr>
<th></th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Mainly in childhood</td>
<td>In mid to late adult life</td>
</tr>
<tr>
<td>Smoking</td>
<td>Usually nonsmokers</td>
<td>Almost invariably smokers</td>
</tr>
<tr>
<td>Chronic cough and sputum</td>
<td>Absent</td>
<td>Frequent (chronic bronchitis)</td>
</tr>
<tr>
<td>Dyspnoea on effort</td>
<td>Variable and reversible to treatment</td>
<td>Constant, poorly reversible and progressive</td>
</tr>
<tr>
<td>Nocturnal symptoms</td>
<td>Relatively common</td>
<td>Relatively uncommon</td>
</tr>
<tr>
<td>Airflow limitation</td>
<td>Increased diurnal variability</td>
<td>Normal diurnal variability</td>
</tr>
<tr>
<td>Response to bronchodilator</td>
<td>Good</td>
<td>Poor</td>
</tr>
<tr>
<td>Airway hyperresponsiveness</td>
<td>In most patients, with or without airflow limitation</td>
<td>In most patients with airflow limitation</td>
</tr>
</tbody>
</table>
particularly in patients on treatment, and thus the absence of reversibility does not exclude the diagnosis. However, repeated testing of reversibility of both clinical features and functional abnormalities may be useful in obtaining the best level of asthma control achievable and/or the best lung function for individual patients. Achieving and maintaining lung function at the best possible level is one of the objectives of asthma management.

**Airway hyperresponsiveness** In patients who have symptoms consistent with asthma but who have normal lung function, bronchial provocation tests with methacholine, histamine or exercise are helpful in measuring airway hyperresponsiveness and thereby confirming or excluding the diagnosis of active asthma. These measurements are very sensitive, but poorly specific for a diagnosis of asthma. This means that while a negative test can be used to exclude a diagnosis of active asthma, a positive test does not always mean that a patient has asthma. While the measurement of airway hyperresponsiveness may be useful to confirm asthma in subjects with normal baseline lung function, it is not useful in presence of nonreversible airflow limitation, and thus in the differential diagnosis between asthma and COPD.

**Arterial blood gases**

In severe asthma and, more importantly, during acute exacerbations of asthma, the measurement of arterial blood gases while the patient is breathing air and/or after oxygen administration is essential for the diagnosis of chronic and/or acute respiratory failure. This test should be performed in all patients with clinical signs of acute or chronic respiratory and/or heart failure, and anyway in patients with a PEF <50%, those who do not respond to treatment and those with an arterial oxygen saturation ≤92%.

**Allergy tests**

The presence of allergic disorders in a patient’s family history should be investigated in all patients with symptoms of asthma. A history provides important information about the patient’s lifestyle and occupation, both of which influence exposure to allergens and the time and factors possibly involved in onset and in exacerbations of asthma. Skin tests with all relevant allergens present in the geographic area in which the patient lives are the primary diagnostic tool in determining allergic status. Measurement of specific IgE is not usually more informative than a skin test, and is more expensive. Measurement of total IgE in serum has no value as a diagnostic test

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### Table 3. Ancillary tests in the differential diagnosis between stable asthma and COPD

<table>
<thead>
<tr>
<th>Ancillary test</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversibility to bronchodilator and/or glucocorticosteroids</td>
<td>Usually present</td>
<td>Usually absent</td>
</tr>
<tr>
<td>Lung volumes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual volume, total lung capacity</td>
<td>Usually normal or, if increased, reversible</td>
<td>Usually irreversibly increased</td>
</tr>
<tr>
<td>Diffusing capacity</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Airway hyperresponsiveness</td>
<td>Increased</td>
<td>Might be increased but usually not measurable due to airflow limitation</td>
</tr>
<tr>
<td>Allergy tests</td>
<td>Often positive</td>
<td>Often negative</td>
</tr>
<tr>
<td>Imaging of the chest</td>
<td>Usually normal</td>
<td>Usually abnormal in advanced stages</td>
</tr>
<tr>
<td>Sputum</td>
<td>Eosinophilia</td>
<td>Neutrophilia</td>
</tr>
<tr>
<td>Exhaled nitric oxide</td>
<td>Increased</td>
<td>Usually normal</td>
</tr>
</tbody>
</table>
for atopy. The main limitation of methods to assess allergic status is that a positive test does not necessarily mean that the disease is allergic in nature or that it is causing asthma, as some individuals have specific IgE antibodies without any symptoms and it may not be causally involved. The relevant exposure and its relation to symptoms must be confirmed by patient history.

**Additional tests**

While the diagnosis and assessment of severity of asthma and COPD can be fully established on the basis of clinical history and lung function tests (including arterial blood gases – see below), additional tests might be helpful to better characterise individual patients.

**Imaging** While chest radiography may be useful to exclude diseases that may mimic asthma, it is not required in the confirmation of the diagnosis and management of asthma. The utility of chest radiography is to exclude other conditions that may imitate or complicate asthma, particularly acute asthma. Examples include pneumonia, cardiogenic pulmonary oedema, pulmonary thromboembolism, tumours (especially those that result in airway obstruction with resulting peripheral atelectasis) and pneumothorax.

**Assessment of airway inflammation**

While airway biopsies and bronchoalveolar lavage may provide useful information in research protocols, they are considered too invasive for the diagnosis or staging of asthma. By contrast, noninvasive markers of airway inflammation have been increasingly used in research protocols, particularly to
differentiate asthma from COPD and measure response to treatment.

**Exhaled nitric oxide** Exhaled nitric oxide (NO) is increased in atopic asthma, but less so in nonatopic asthma. It is reduced by glucocorticosteroids, but not by bronchodilators. Measurement of airway inflammation is not required for the diagnosis, assessment of severity and/or treatment of asthma in clinical practice.

**Differential diagnosis between asthma and COPD**

In most patients, the clinical presentation and particularly the history provide the strongest diagnostic criteria to distinguish asthma from COPD (table 2). Pulmonary function tests, particularly spirometry, that show a nearly complete reversibility of airflow limitation may help to confirm a diagnosis of asthma, and those that show poorly reversible airflow limitation may help to confirm the diagnosis of COPD (table 2). Differential diagnosis between asthma and COPD becomes more difficult in elderly patients, in whom some features may overlap, such as smoking and atopy and, more importantly, when the patient develops poorly reversible airflow limitation that responds only partially to treatment. In these cases, symptoms, lung function, airway responsiveness, imaging and even pathological findings may overlap and thus may not provide solid information for the differential diagnosis. Because the differential diagnosis mainly aims to provide better treatment, it is important in these cases to undertake an individual approach and to perform additional tests. Reversibility to corticosteroids alone or in combination with long-acting bronchodilators, measurements of lung volumes and diffusing capacity, analysis of sputum and exhaled NO, and imaging of the chest may demonstrate whether asthma or COPD is the predominant cause of airflow limitation (table 3). In contrast, reversibility to bronchodilator and assessment of airway hyperresponsiveness or skin testing may not be useful in these patients.

**Comorbidities of asthma**

The coexistence of chronic rhinitis, nasal polyposis and sinusitis may contribute to the severity of asthma: There is broad evidence to show that adequate treatment of these upper airway diseases is beneficial to asthma by

---

**Table 4. Levels of asthma control**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controlled (all of the following)</th>
<th>Partly controlled (any measure present in any week)</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime symptoms</td>
<td>None (twice or less per week)</td>
<td>More than twice per week</td>
<td>Three or more features of partly controlled asthma present in any week</td>
</tr>
<tr>
<td>Limitations of activities</td>
<td>None</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>Nocturnal symptoms/awakening</td>
<td>None</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>Need for reliever/rescue treatment</td>
<td>None (twice or less per week)</td>
<td>More than twice per week</td>
<td></td>
</tr>
<tr>
<td>Lung function (PEF or FEV1)</td>
<td>Normal</td>
<td>&lt;80% predicted or personal best (if known)</td>
<td></td>
</tr>
<tr>
<td>Exacerbations</td>
<td>None</td>
<td>≥1 per year</td>
<td>One in any week</td>
</tr>
</tbody>
</table>

PEF: peak expiratory flow; FEV1: forced expiratory volume in 1 s. " Lung function is not a reliable test for children aged ≤5 yrs; 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 asthma week. Reproduced from the Global Strategy for Asthma Management and Prevention, with permission.
Figure 2. Management of asthma exacerbations in the acute care setting. PEF: peak expiratory flow; FEV1: forced expiratory volume in 1 s; PaCO₂: arterial carbon dioxide tension; PaO₂: arterial oxygen tension. Reproduced from the Global Strategy for Asthma Management and Prevention, with permission.
mechanisms not clearly understood. The "one airway" concept developed by the World Health Organization ARIA Group has drawn attention to the importance of treating the whole respiratory tract when managing asthma. Gastro-oesophageal reflux is also occasionally associated with asthma, both in adults and in children, but treatment of reflux usually has little overall effect on mild-to-moderate asthma. A frequent and quite important comorbidity of asthma in adults is COPD, most probably due to smoking, which is quite common in asthmatics. Smoking modifies the airway pathology of asthmatics to a COPD-like pattern and reduces the response to treatment. Comorbidities may become important in severe asthma, whereas they play a much less important role overall in the clinical manifestations of mild-to-moderate asthma.

Management

Considering its chronic nature and lifelong duration, asthma can be effectively managed only by developing a partnership between the patient and his or her doctor or health professional, that may provide the tools for a guided self-management (possibly written) plan including self-monitoring, and periodic review of treatment and level of asthma control. Education plays a major role in this partnership.

Long-term pharmacological treatment

The main goal of pharmacological asthma treatment is to achieve and maintain control of symptoms and prevention of exacerbations (table 4) using the safest treatment algorithm. While the initial treatment should be started according to the level of severity at the first visit, subsequently treatment should be adjusted according to the level of control achieved (fig. 1). Usually regular treatment is lowered only after a significant period of acceptable control, e.g. not <3 months. This means that monitoring of asthma is essential to maintain control and to establish the lowest step and dose of treatment. Step-up and step-down of treatment is not standardised, and thus should be tailored to the individual patient to achieve and maintain control with the minimum amount of medication.

Medications to treat asthma can be classified as controllers or relievers. Medications are preferably administered by inhalation, as it is more efficacious and has fewer side-effects. Controllers (inhaled glucocorticosteroids alone or in combination with long-acting β2-agonists) are medications to be taken daily, over the long term, to keep asthma under clinical control. In asthma, long-acting β2-agonists should be used only in combination with inhaled corticosteroids when the latter are insufficient to achieve control, and should be discontinued only when control is maintained for a sufficiently long time (e.g. ≥ 3 months).

Only in patients not controlled by full doses of inhaled glucocorticosteroids combined with long acting β2-agonists may other secondary agents be considered (anti-leukotrienes, theophylline, systemic steroids, monoclonal anti-IgE antibodies in very specific cases).

Relievers (rapid-acting β2-agonists alone or in combination in combination with inhaled steroids) are medications used on an as-needed basis that act quickly to reverse bronchoconstriction and relieve its symptoms. Ideally, if patients are adequately controlled, they should not need rescue medications.

Allergen immunotherapy may be considered in patients with asthma caused by specific allergens for which there are standardised extracts. Only patients with single or two similar allergen sensitivities whose role is confirmed by the history and who have preserved lung function are candidates for this treatment (which, however, has limited efficacy and is long and relatively expensive). Specific immunotherapy should be considered only after strict environmental avoidance and pharmacological interventions, including inhaled glucocorticosteroids, have failed to control the disease. Smoking asthmatics are resistant to anti-asthma medications and should be primarily treated for smoking addiction. Smokers with asthma may develop features of COPD.

Treatment of exacerbations

Shortness of breath, cough, wheezing, and/or chest tightness may develop or worsen.
recurrently in subjects with asthma even when they are under regular treatment. Milder exacerbations are usually managed by the patient with an increased as-needed use of rapid acting β₂-agonists alone or in combination with inhaled steroids. More severe exacerbations or exacerbations that do not respond to the increased use of rescue medications require repetitive administration of rescue medication and systemic, preferably oral, glucocorticosteroids, associated in the very severe cases with oxygen supplementation (fig. 2). Severe exacerbations require medical attention or even hospital admission.

**Special considerations**

Special considerations are required for patients with specific conditions and/or comorbidities, e.g. rhino/sinusitis and/or nasal polyps, aspirin-induced asthma particularly if associated with episodes of anaphylaxis, occupational asthma or obesity.

Additionally, patients with asthma should be informed that they may require specific medical attention in case of smoking addiction, pregnancy, surgery or infections (e.g. influenza epidemics).

**References**

Vocal cord dysfunction (VCD) is characterised by paradoxical vocal cord adduction during inspiration and/or expiration, leading to symptoms of breathlessness and wheeze. It is a poorly understood condition that often co-exists with asthma and chronic cough and shares common triggers such as psychological factors, gastro-oesophageal reflux and rhinosinus disease. The management of VCD focuses on establishing the correct diagnosis, identification and treatment of underlying triggers, and speech therapy. Further research is required to define VCD, establish its natural history and develop evidence-based therapies.

**Terminology**

Numerous terms have been used to describe VCD. These include hysterical croup, Munchausen’s stridor, pseudo-asthma, factitious asthma, upper airway dysfunction, functional upper airway obstruction, irritable larynx syndrome, emotional laryngeal wheeze, laryngeal hyper-responsiveness, and paradoxical vocal cord movement. Indeed, there is disagreement of what constitutes VCD, with some limiting it to an early description by Christopher et al. (1983) of a conversion disorder meeting a strict definition of inspiratory adduction and posterior chinking of vocal cords, to those who use all encompassing VCD definition of all cases demonstrating paradoxical vocal cord movement (PVCM).

**Epidemiology**

While the true prevalence of VCD in the general population is unknown, it is more common in females, athletes, army recruits, and patients with asthma or chronic cough (table 1).

**Pathogenesis**

VCD was seen largely as a conversion disorder of psychogenic origin. The larynx is innervated by a complex neurological network, and the association between stress and comorbid psychology and VCD attacks strengthened this view. More recently it became apparent that PVCM “VCD” exists outside the conversion disorder prototype. Laryngeal closure is a normal physiological reaction to exposure to irritants (e.g. aspiration), but this reaction normally only lasts for few seconds. Acute (e.g. toxic fume inhalation) or recurrent irritation (e.g. repeated extreme cold air exposure) may lead to laryngeal hypersensitivity manifesting as vocal cord adduction and airflow limitation. Laryngeal hypersensitivity may form part of unified allergic airway syndrome with asthma and rhinitis. The association of laryngeal hypersensitivity with altered autonomic balance status maintained by central brain activity has been postulated to underlie development of VCD.

**Clinical presentation**

VCD presentation varies from cases with predominant throat symptoms, usually

**Key points**

- VCD is not well understood, and there is as yet no consensus definition.
- Classically, symptoms appear abruptly, resolve quickly and do not respond well to asthma medication.
- Long-term treatment is based around speech therapy and psychotherapy.
referred to ear, nose and throat (ENT) specialists, to asthma presenting to respiratory clinic, or angio-oedema presenting in an immunology clinic. Often the diagnosis of VCD is made after treatment for asthma has not been successful.

Patients may report rapid onset attacks of dyspnoea which may be preceded by intense coughing, sensation of strangulation or breathing through a straw, throat or upper chest tightness, dysphonia, or stridor. Classical VCD symptoms are of abrupt onset, resolve quickly and respond poorly to asthma medication.

Elucidation of triggers of VCD attacks is important for diagnostic and therapeutic purposes. Commonly associated triggers include exposure to cold air, exercise, inhalation of strong smells such as perfumes or chemical cleaning agents, smoke, cough, reflux, viral infections, allergens and emotional stress. Psychological morbidity and sexual abuse are experienced in some VCD sufferers. The physical examination of patients with VCD is usually unremarkable outside symptomatic attacks. During symptoms, examination may reveal stridor or wheeze originating at laryngeal level with clear chest auscultation. The severity of respiratory distress varies from mild to severe with tachypnoea, but oxygen saturation level is often normal. Extreme forms of VCD can lead to collapse and loss of consciousness usually leading to resolution of the attack or intubation. If intubated, the airway inflation pressure is characteristically normal.

**Diagnosis**

Flow-volume loops may show inspiratory loop truncation representing extra-thoracic airflow obstruction. The maximal inspiratory flow at 50% of the forced vital capacity (FVC)/maximal expiratory flow at 50% of the FVC ratio can be reduced due to predominant inspiratory flow limitation. An abnormally high forced inspiratory flow at 25% of the FVC/forced inspiratory flow at 75% of the FVC ratio would indicate an initially normal flow followed by rapid flow decline reflecting paradoxical vocal cord movement during inspiration. However, various studies reported the insensitivity of spirometry to diagnose VCD. Sensitivity of spirometry may be enhanced by histamine or other forms of airway challenge.

Impulse oscillometry can discriminate between central versus peripheral airway obstruction, and may be more sensitive than spirometry. Airway fluoroscopy and colour Doppler ultrasound imaging of vocal cords movement are other noninvasive tools that have not been standardised against laryngoscopy.

**Laryngoscopy**

VCD diagnosis is established by laryngoscopical demonstration of paradoxical vocal cord movement whilst the patient experiences spontaneous or induced symptoms. Agreed laryngoscopy standards have not been developed, with some advocating pre-procedure sedation and analgesia, whilst others recommend avoiding these measures. Following short periods of quiet breathing, specific manoeuvres such as repeating low and high pitched sounds, and forceful inspiration and expiration are conducted to induce an attack. Vocal cord movements are timed against respiratory cycle phases by putting a hand on the patient’s chest. In VCD, the vocal cords adduct anteriorly leaving an open posterior glottic.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Prevalence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory asthma</td>
<td>5-10</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>2.8</td>
</tr>
<tr>
<td>Army recruits with stress-induced asthma</td>
<td>15</td>
</tr>
<tr>
<td>Olympic athletes</td>
<td>5</td>
</tr>
<tr>
<td>Childhood acute asthma*</td>
<td>14</td>
</tr>
</tbody>
</table>

* Presenting to emergency department. The reported mean age at VCD diagnosis is 14.5 yrs in children and 33 yrs in adults.
chink (Fig. 1). The adduction occurs during inspiration or throughout the respiratory cycle. False-negative PVCM can be secondary to gag reflex or coughing. The larynx should also be inspected for signs of laryngo-pharyngeal reflux. VCD should be distinguished from vocal cord immobility due to paralysis, amyotrophic lateral sclerosis, cricoarytenoid joint dysfunction and Reinke’s oedema. Laryngeal electromyography may help in differentiation. Normal laryngoscopy in the absence of symptoms does not exclude VCD. The presence of atypical features of asthma and/or VCD should prompt further investigations, such as CT of head-neck-thorax and bronchoscopy.

Differential diagnosis

- Laryngeal oedema (angio-oedema).
- Allergic laryngitis.
- Subglottic stenosis.
- Laryngomalacia, tracheomalacia.
- Vocal cord paralysis.
- Systemic disease affecting larynx/upper airways (e.g. relapsing chondritis, Wegener’s granulomatosis).

Investigations of causes of VCD

A careful history is essential to guide investigations. The presence of concomitant rhinitis/asthma or allergic airway disease needs to be assessed by lung function, skin allergy testing, blood/sputum eosinophils and exhaled nitric oxide. Gastro-oesophageal reflux disease symptoms or laryngeal reflexive changes on laryngoscopy should prompt further testing (e.g. oesophageal manometry and pH studies). Underlying psychological issues should be assessed.

Treatment

The diagnosis and treatment is best conducted in a multidisciplinary team setting comprised of respiratory physician, speech therapist, ENT specialist and psychologist. The diagnosis is explained to the patient, preferably with support of imaging or illustration. The patient’s good understanding of VCD is prerequisite to effective treatment. A management plan should be formulated that bear in mind co-existing asthma. Due to VCD under-recognition, patients should carry an alert card listing medication and treatment strategy.

Treatment of acute attacks

The treating physician should adopt a calm reassuring manner and ask patient to focus on expiration with an “S” sound that helps in diverting attention. A panting manoeuvre can abort acute attacks by inducing vocal cord abduction. Where hypoxaemia and hypercapnia has been excluded, sedation with benzodiazepines may help patient relaxation. Heliox gas mixture (e.g. 72% helium and 28% oxygen) can alleviate symptoms by enhancing upper airway laminar air flow. Intubation or tracheostomy should be avoided. In extreme cases presenting with an apparent life-threatening attack, the clinical decision will remain with the treating physician. If intubation is contemplated, prior inspection and documentation of the status of vocal cords is recommended.
Long-term treatment

Speech therapy forms the mainstay of VCD treatment with the primary aim of teaching patients to relax upper airways and control laryngeal area. It is conducted in four to six successive sessions to enable the patient to practice breathing techniques to abort or treat acute attacks. Patients are taught to exhale gently and avoid forceful inspiration in a rhythmic manner, followed by introduction of expiratory resistance by asking patient to produce sounds such as “S”. The role of speech therapist extends to making diagnosis, identification and treatment of triggers and relaxation therapy.

Psychotherapy should form an integral part of VCD management, given the VCD link to adverse psychology. Psychotherapy can include relaxation therapy, management of stress and anxiety, and the development of coping strategies.

Other unproven therapies for VCD include inhaled anticholinergic drugs to abort exercise-induced VCD attacks, enhancing inspiratory resistance by a face mask device, continuous positive airway pressure, and injection of vocal cords by botulinum toxin A (botox). Tracheostomy has been used as a last resort in intractable cases.

Prognosis

The long-term outcome of VCD is unknown. VCD prognosis will probably depend on initial disease severity and associated morbidities. One study reported complete resolution of VCD within a 5-yr time frame, with symptoms disappearing within 6 months in many who had good response to speech therapy. However, intractable forms of the disease did not seem to improve over a 10-yr observation period.

Conclusion

VCD is a relatively uncommon condition that mimics and co-exists with asthma, and presents episodically thus making its diagnosis challenging and often delayed. Patients can become frequent healthcare users with substantial morbidity as result of erroneous diagnosis and toxic medication use. Establishing proper diagnosis and treatment can be effective and rewarding to both the patient and healthcare professionals.

References

BRONCHITIS

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Definition
Transient airway inflammation localised to the respiratory mucosa of the central airways and clinically characterised by cough and sputum production. Fever and dyspnoea can occur.

Symptoms
Cough is the cardinal symptom and is observed in 100% of cases. It usually persists for up to 2 weeks but in 26% it can stay for up to 8 weeks. Other symptoms include sputum production (90%), dyspnoea, wheezing (62%), rhonchi, chest pain, fever, hoarseness and malaise.

Epidemiology
Acute bronchitis is one of the most frequent human diseases worldwide, with children being most often affected. On average children contract bronchitis 2-6 times per year, and adults 2-3 times per year. The prevalence in UK is 44 cases per 1,000 adults per year. 82% of episodes occur during the cold months.

Aetiology/risk factors
Respiratory infections are the main trigger of acute bronchitis. However, in only 55% of cases can pathogens be detected. Respiratory viruses are the most frequent pathogens. Rhino-, adeno-, echo-, influenza-, parainfluenza-, entero- and coronaviruses, Coxsackie virus and respiratory syncytial viruses (RSV) represent the usual spectrum. Parainfluenza, entero- and rhinoviruses infect mainly in the autumn, while influenza, RSV and coronaviruses infect mainly in winter and early spring. Typical bacteria are Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis. Atypical bacteria (e.g. Mycoplasma pneumoniae, Chlamydia pneumoniae) and Bordetella pertussis also play a role.

Specific risk factors are not identified and it is currently not clear whether cigarette smoking increases the risk of acute bronchitis. There are epidemiological data showing that the frequency of bronchitis is increased after school holidays, which indicates that crowding facilitates dissemination of respiratory infections.

Prognosis
Acute bronchitis is usually a self-limiting disease. However, there are only sparse data on prognosis and rate of complications. In a study investigating 653 previously healthy adulty with lower respiratory tract symptoms, 20% of patients had persistent symptoms. In 40% of these patients, there was reversible airway obstruction. In another study, a third of

Key points
- Respiratory viral infection is the most common cause of acute bronchitis.
- Acute bronchitis is usually a self-limiting disease.
- The diagnosis of acute bronchitis is purely clinical and in most cases symptomatic treatment is sufficient.
- Chronic bronchitis is defined clinically as productive cough for 3 months in each of 2 successive years.
patients developed asthma or chronic bronchitis symptoms.

**Diagnosis**

Diagnosis is purely clinical. Cough, sputum production optionally accompanied by dyspnoea and/or wheezing are suggestive. Tachycardia and tachypnoea are usually absent, and vital signs are normal. Complicated cases show fever; however, in these cases differential diagnosis like pneumonia or systemic influenza should be considered. Clinical signs of pneumonia (rales, egophony, dullness on percussion) should be absent. Acute bronchitis should be differentiated from asthma, which typically presents as progressive cough accompanied by wheezing, tachypnoea, respiratory distress and hypoxaemia. It should also be distinguished from bronchiectasis, a distinct phenomenon associated with permanent dilatation of bronchi and chronic cough. Laboratory investigations are not necessary. In more severe cases, sputum culture can be considered to guide antibiotic therapy.

**Therapy**

Therapeutic goals are reduction of symptoms and prevention of complications with as few side-effects as possible. Antibiotic therapy cannot be recommended generally, but in patients with fever and/or comorbidities, aminopenicillins or cephalosporins (second generation) can be administered. Dextromethorphan has been shown to reduce cough efficiently. In patients with dyspnoea and/or wheezing, short-acting bronchodilators can be beneficial.

**Chronic bronchitis**

Chronic bronchitis is defined clinically as chronic productive cough for 3 months in each of two successive years in a patient in whom other causes of productive chronic cough have been excluded. Cigarette smoking is by far the most important and preventable risk factor. Chronic bronchitis is a major component of chronic obstructive pulmonary disease.

**References**

GASTRO-OESOPHAGEAL REFUX

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Gastro-oesophageal reflux disease (GORD) is an increasingly prevalent condition that affects up to 20% of the Western population. Transient lower oesophageal sphincter relaxations (TLOSRs) are now recognised as a major factor in the pathophysiology of GORD. Although GORD often causes typical symptoms such as heartburn or regurgitation, it may also present with atypical or extra-oesophageal symptoms, including respiratory and ear, nose and throat symptoms and disorders. Respiratory manifestations of GORD represent one of the most prevalent and challenging of these extra-oesophageal syndromes. The relationship between reflux and respiratory symptoms is frequently difficult to establish with a high degree of certainty and diagnostic, as well as therapeutic, management remains largely empirical. In contrast to oesophageal GORD manifestations, efficacy of acid-suppressive therapy in extra-oesophageal GORD symptoms has not been well established.

Pathophysiology

There are a number of potential mechanisms whereby GORD may aggravate or trigger respiratory disease. Direct aspiration of gastric refluxate into the airway occurs as a consequence of failure of the normal protective mechanisms to foreign material, i.e. reflex contraction of the upper oesophageal sphincter and closure of glottis and vocal cords is likely to be relevant in cystic fibrosis (CF) and rejection after lung transplantation. A vagally mediated oesophageal tracheobronchial reflex has been postulated to account for the association between acid reflux and cough or asthma. Oesophageal sensory stimulation can release tachykinins into the airways and may increase the bronchomotor responsiveness to airway stimuli bronchospasms. It has also been postulated that chronic exposure of the oesophageal mucosa to gastric juices can produce long-lasting hypersensitivity to a variety of stimuli that can cause the symptom

Key points

- GORD is a common disorder caused by the reflux of gastric contents into the oesophagus because of impaired function of the lower oesophageal sphincter and may result in oesophageal and extra-oesophageal symptoms.
- The relationship between reflux and respiratory symptoms or disorders is frequently difficult to establish with a high degree of certainty.
- Diagnostic, as well as therapeutic, management remains largely empirical.
- Treatment with PPI has been shown to improve cough in patients with acid GOR-induced cough but the effect of PPI remains disappointing when treating GOR in other respiratory diseases.
- Antireflux surgery was associated with improved allograft function after lung transplantation.
even in the absence of increased oesophageal acid exposure or oesophagitis.

**GOR in asthma and COPD**

GORD is a common condition among patients with obstructive pulmonary diseases. Probably one-third of asthmatics present with GORD (prevalence range 10–84%) and some 50–60% of chronic obstructive pulmonary disease (COPD) patients have abnormally high oesophageal acid exposure times, which is more than the general population. There is no clear understanding of why this is true but it may be due to the fact that airway obstruction, diaphragmatic flattening, β2-agonists and theophylline are able to promote oesophageal reflux. Often COPD or asthmatic patients with GORD do not have classic symptoms of GORD.

Recent randomised controlled data suggest that it is not a useful practice for mild-to-moderate asthmatic patients to treat asymptomatic GORD with proton pump inhibitors (PPIs) as it will not improve asthma control. Asthma outcome may only improve to some extent with PPI management among patients who present with severe difficult-to-control asthma and symptomatic GORD.

Reflux symptoms in COPD patients were associated with an increased number of COPD exacerbations and oxygen desaturation coincided with episodes of increased oesophageal acidity in 40% of patients with severe COPD and GORD. Uncontrolled data suggest that PPI treatment may decrease the number of COPD exacerbations.

**GOR-induced cough**

Studies have determined GOR to be a cause for chronic cough in up to 43% of patients referred for specialist evaluation. According to published guidelines GORD investigations are indicated in patients with chronic cough. Only a minority of patients with chronic cough and GORD have typical digestive symptoms and/or clear evidence of oesophagitis. The treatment of cough-associated reflux has been evaluated in many uncontrolled and a few controlled trials of drug therapy and antireflux surgery. A recent Cochrane systematic review retrieved 13 randomised, controlled trials of GORD treatment for cough in children and adults. Meta-analysis of the studies comparing PPI treatment (2 or 3 months) with placebo showed no difference between placebo and PPI (odds ratio 0.46, 95% CI 0.19–1.15) in the resolution of cough, although sensitivity analyses showed significant changes in cough scores in those receiving PPI in cross-over trials. Further randomised, parallel-design, placebo-controlled, double-blind trials are needed.

Based on these data two different management strategies of patients with suspected reflux-related cough can be proposed. The empirical strategy with PPI (usually double dose) given for at least 3 months is probably the most popular one but it should be underlined that this strategy is not supported by strong evidence. Appropriate initial selection of potential responders to GORD treatment could be done on the basis of the presence of typical reflux symptoms.

The second strategy consists of investigations, which should ideally detect both acidic and nonacidic reflux. Patients who failed to respond to empirical therapy should be investigated. In well-selected patients, antireflux surgery may be indicated for long-term control. This may also be the case for patients with refractory acidic or nonacidic reflux and a well-documented correlation between reflux episodes and cough.

**GOR in advanced lung disease**

The prevalence of increased GOR in CF is estimated to be between 35% and 81%. Acid GOR is most common, but weakly acidic GOR may also occur. Patients with CF have a high risk for gastric aspiration, as demonstrated by increased bile acids in saliva, sputum or in bronchoalveolar lavage fluid. Half of the CF patients with increased GOR or gastric aspiration do not present oesophageal symptoms like heartburn or regurgitation. The characteristics of GOR and material aspirated depend on the genotype with bile acids.
aspiration being more important in DF508 homozygotes. The causal relationship between GOR, aspiration and respiratory symptoms is not completely elucidated. Recent results suggest that patients with increased oesophageal acid exposure have more cough and a positive association between GOR and cough is associated with poorer lung function. Bile acid levels in sputum are correlated with elastase levels in sputum and forced expiratory volume in 1 s.

GOR may play a role in the pathogenesis and/or progression of idiopathic pulmonary fibrosis (specifically in acute exacerbation) as a recurrent inflammatory stimulus. Studies have found a high prevalence of reflux (36–87%) among patients with idiopathic pulmonary fibrosis. Pre-transplant patients with idiopathic pulmonary fibrosis undergoing antireflux surgery had reduced supplementary oxygen dependence compared with other pre-transplant patients with idiopathic pulmonary fibrosis. In addition, there are anecdotal cases of idiopathic pulmonary fibrosis disease stability following treatment for reflux. While it cannot be proven that disease stability was caused by control of reflux, they suggest that a subset of patients with idiopathic pulmonary fibrosis may benefit from antireflux therapy.

GOR and gastric aspiration have also been implicated as a potential nonalloimmune cause of lung allograft rejection (bronchiolitis obliterans syndrome (BOS)) after lung transplantation. Standard oesophageal pH recordings indicated an increased oesophageal acid exposure in >70% of lung transplant patients. Luminal gastric components such as pepsin and bile acids have been demonstrated in bronchial material of lung transplant recipients and were more prevalent in the lungs of patients with BOS. Aspiration of bile acids was related to weakly acidic reflux events and especially those occurring during the night were also associated with reduced concentration of pulmonary surfactant collectin proteins and reduced freedom from BOS. Aspiration even in the absence of an increased number of GOR events might therefore feature as a potential risk factor for the development of BOS after lung transplantation. Antireflux surgery was associated with improved allograft function.

Management of GORD

In general practice, most cases of GORD are diagnosed on the basis of typical symptoms and the response to inhibition of gastric acid secretion. Endoscopy, oesophageal manometry or acid instillation in the oesophagus (Bernstein test) have limited sensitivity and specificity for the diagnosis of GORD. 24-h oesophageal pH monitoring can provide useful information, in particular through assessment of the temporal association between symptoms and reflux events. The addition of impedance monitoring to pH monitoring further improves GOR diagnosis as it also detects nonacid (weakly acidic) reflux events and allows testing whilst the patient is on a PPI. Investigations of the routine diagnostic value of the measurement of pepsin and bile acid concentrations in saliva, sputum or BALF are in progress.

Medications interfering with acid production, especially the PPIs, are the cornerstone of GORD treatment. Acid-suppressive therapy is highly effective in the healing and maintenance of oesophagitis, but seems to be poorly effective when GORD is presumed to underlie extra-oesophageal symptoms. Symptoms that persist during standard acid suppressive therapy regimens have also been related to nonacid or weakly acidic reflux. There is little evidence that further intensification of acid suppression beyond high-dose PPI twice daily is of any benefit for these patients. Several attempts to improve symptoms in these patients through the addition of gastroprokinetic drugs have thus far not been successful. At present, the only alternative for these patients is a surgical fundoplication, but not all patients are eligible for surgery, the intervention is not without complications, and poor responders to PPI therapy are also less certain to experience symptom relief from surgery. Two classes of drugs, the γ-aminobutyric acid (GABA)-B agonists and the metabotropic glutamate
receptor-5 antagonists are currently under evaluation for their ability to reduce TLOSRs and improve (weakly acidic) reflux and symptoms that are refractory to PPI therapy. Other pathways that are under investigation include mucosal protective agents, inhibitors of acid-sensitive ion channels, and endoscopic antireflux procedures.

References

COPD AND EMPHYSEMA

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Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to its severity in individual patients. Its pulmonary component is characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. Cigarette smoking is by far the most common risk factor for the disease. COPD is a major cause of morbidity and mortality worldwide. It affects ~10% of the general population but its prevalence among smokers may reach 50%. According to an American Thoracic Society/European Respiratory Society Task Force, COPD is a preventable and treatable disease characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences. The cardinal symptoms of COPD – dyspnoea, cough and sputum production – are chronic and progressive.

COPD comprises pathological changes in four different compartments of the lungs (central airways, peripheral airways, lung parenchyma and pulmonary vasculature), which are variably present in people with the disease. Airflow limitation in COPD is caused by the presence of an abnormal inflammatory cellular infiltrate in the small airways, remodelling and thickening of the airway wall. The destruction of alveoli and enlargement of airspaces, which are anatomical hallmarks of emphysema, contribute to the loss of elastic recoil and the loss of outward traction on the small airways, leading to their collapse on expiration. This results in airflow obstruction, air trapping and hyperinflation. In general, the inflammatory and structural changes in the airways increase with disease severity and persist even after smoking cessation.

Chronic obstructive bronchitis and/or emphysema
COPD is a heterogeneous disease. Two main phenotypes are recognised: chronic bronchitis and emphysema.

Chronic bronchitis is characterised by cough and sputum production for at least 3 months in each of two consecutive years. The symptoms may precede the development of COPD. A strong genetic component, in conjunction with environmental insult, probably accounts for the development of COPD. Smoking cessation is the single most effective intervention in COPD prevention and treatment. Bronchodilators are central to symptomatic treatment, backed up if necessary by other interventions.

Key points

- COPD is a heterogeneous disease, with two main phenotypes: chronic bronchitis and emphysema.
- A strong genetic component, in conjunction with environmental insult, probably accounts for the development of COPD.
- Smoking cessation is the single most effective intervention in COPD prevention and treatment.
- Bronchodilators are central to symptomatic treatment, backed up if necessary by other interventions.
airflow limitation by many years. Inflammation and secretions provide the obstructive component of the disease. In contrast to emphysema, chronic bronchitis is associated with a relatively undamaged pulmonary capillary bed. Emphysema is present to a variable degree but is usually centrilobular rather than panlobular. The body responds by decreasing ventilation and increasing cardiac output (ventilation/perfusion (\(V/Q\)) mismatch) leading to hypoxaemia, polycythaemia and increased \(CO_2\) retention, and eventually these patients develop signs of right heart failure.

The second major COPD phenotype is the emphysematous patient. Emphysema is defined by destruction of airways distal to the terminal bronchiole, gradual destruction of alveolar septae and of the pulmonary capillary bed, leading to decreased ability to oxygenate blood. The body compensates with lowered cardiac output and hyperventilation. This \(V'/Q'\) mismatch results in relatively limited blood flow through a quite well-oxygenated lung with normal blood gases and pressures. Eventually, due to low cardiac output, the rest of the body suffers from tissue hypoxia, pulmonary cachexia, muscle wasting and weight loss.

### Stages of severity

Airflow limitation in COPD is best measured by spirometry, the most widely available and reproducible lung function test. A simple spirometric classification of disease severity into five stages has been established by the Global Initiative for Obstructive Lung Disease (GOLD) and the criterion for airflow obstruction is a forced expiratory volume in 1 s (FEV1)\/forced vital capacity (FVC) ratio \(<0.7\), regardless of age (table 1). The FEV1\/FVC ratio in normal subjects declines with age, thus an alternative cut-off for diagnosing obstruction without over-diagnosing in younger subjects, is using values outside the 95% confidence intervals for predicted FEV1\/FVC ratios ("below the lower limit of normal").

Newer publications on reference equations give explicit upper and lower limits of the normal range, or provide a method for its calculation. Normal values are most difficult to predict in older, shorter people, who may not be well represented in the reference population from which the prediction equation was derived.

### Risk factors

Although smoking is the best studied COPD risk factor, it is not the only one and there is

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>FEV1/FVC</th>
<th>Reference FEV1%pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>At risk</td>
<td></td>
<td>FEV1/FVC &gt;0.70</td>
<td>FEV1 (\geq) 80% pred</td>
</tr>
<tr>
<td>Stage I: mild</td>
<td></td>
<td>FEV1/FVC &lt;0.70</td>
<td>FEV1 (\geq) 80% pred</td>
</tr>
<tr>
<td>Stage II: moderate</td>
<td></td>
<td>FEV1/FVC &lt;0.70</td>
<td>50% &lt; FEV1 &lt;80% pred</td>
</tr>
<tr>
<td>Stage III: severe</td>
<td></td>
<td>FEV1/FVC &lt;0.70</td>
<td>30% &lt; FEV1 &lt;50% pred</td>
</tr>
<tr>
<td>Stage IV: very severe</td>
<td></td>
<td>FEV1/FVC &lt;0.70</td>
<td>FEV1 &lt;30% pred or FEV1 &lt;50% pred plus chronic respiratory failure*</td>
</tr>
</tbody>
</table>

FVC: forced vital capacity; % pred: % predicted. *Respiratory failure is defined as an arterial partial pressure of oxygen \(<60\text{ mmHg}\) with or without arterial partial pressure of \(CO_2\) \(>50\text{ mmHg}\) while breathing air at sea level. Respiratory failure may also lead to effects on the heart such as cor pulmonale (right heart failure). Clinical signs of cor pulmonale include elevation of the jugular venous pressure and pitting ankle oedema. Patients may have stage IV chronic obstructive pulmonary disease even if their FEV1 is \(>30\%\) pred whenever these complications are present. At this stage, quality of life is significantly impaired and exacerbations may be life threatening. Reproduced from the Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, with permission.
consistent evidence from epidemiological studies that nonsmokers may develop chronic airflow obstruction (table 2). Other factors, such as indoor air pollution from burning biomass fuels for cooking and heating, are important causes of COPD in many developing countries, especially among women. Nevertheless, not all subjects exposed to a noxious agent develop COPD. Thus, a strong genetic component in relation with an environmental insult (gene–environment interaction) accounts, most probably, for the development of the disease (table 2). Familial clustering of COPD has been observed and twin studies have supported the concept of a genetic predisposition to COPD. Different strategies have been used to identify genes containing mutations or polymorphisms that contribute to the development of COPD due to smoking. Linkage analysis has revealed regions suggestive for COPD on chromosomes 1, 2 and 12. In addition, linkage of FEV1 and/or FEV1/FVC ratio with various loci in the genome has been reported (i.e. chromosomes 1, 2q, 4, 6, 8, 12p, 17, 18, 19 and 21). Among the candidate genes that have been studied in COPD are genes that regulate the production of proteases and antiproteases, genes that modulate the metabolism of toxic substances in cigarette smoke, genes involved with mucociliary clearance and genes that influence inflammatory mediators.

However, the genetic risk factor that is best documented is the hereditary deficiency of α1-antitrypsin (α1-AT), a serum protein made in the liver that is capable of inhibiting the activity of specific proteolytic enzymes, the serine proteases. The α1-AT gene is located within the serpin cluster, on the chromosome 14q23.1-3. Neutrophil elastase is the main target of α1-AT; if not inactivated by α1-AT, neutrophil elastase destroys lung connective tissue, particularly elastin, and this leads to the development of emphysema. >90 phenotypes of α1-AT have been described. The common gene variants are M, S and Z. M1, M2, M3, M4 are wild types found in 90% of the population. Different genotypes, ZZ, SZ, M2, SS and MS, cause average serum α1-AT concentration reduced to 16, 51, 83, 93 and 97%, respectively, of the wild-type MM genotype. ZZ homozygous have the most severe α1-AT deficiency. Emphysema associated with α1-AT deficiency is typically panlobular, characterised by uniform destruction of the pulmonary lobule. Cigarette smoking is the biggest risk factor for the development of emphysema and airflow obstruction in α1-AT deficiency, and current smokers have an accelerated decline in FEV1, compared with ex-smokers and never-smokers and α1-AT deficiency. Homozygous Z patients have a very low α1-AT and generally show rapid decline in FEV1 even without smoking. In homozygous Z smokers, COPD is developed at a younger age. However, this homozygous state is rare in the general population (one in 5,000 live births) and thus as genetic risk factor can explain <1% of COPD.

Recently, epigenetic mechanisms, such as acquired somatic mutations, have been explored in COPD. Somatic mutations are not heritable, although the susceptibility to acquiring such mutations might be controlled by inherited genes. In normal conditions, cells are equipped with a number of repair pathways that remove the damage and restore DNA. However, increased and persistent oxidative stress (e.g. due to cigarette smoking) may inactivate the human DNA mismatch repair system leading to acquired mutations. Smoking-induced acquired somatic alterations have been detected in COPD patients.

Management

The overall approach to managing stable COPD is based on an individualised assessment of disease severity and response to various therapies. The patient who still smokes should be encouraged to quit. Smoking cessation is the single most effective intervention to reduce the risk of developing COPD and stop its progression, and can have a substantial effect on subsequent mortality.

The goals of therapy are to prevent and control symptoms, reduce the frequency and severity of exacerbations and improve exercise
tolerance, thus improving overall the quality of life (fig. 1). Bronchodilator medications are central to the symptomatic management of COPD. These drugs improve emptying of the lungs, tend to reduce dynamic hyperinflation and improve exercise performance. There is choice of β₂-agonists, anticholinergics and methylxanthines used either singly or in combination. Inhaled therapy is preferred and bronchodilators are prescribed on either an as-needed or a regular basis, although it is evident that regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting ones. Treatment with a long-acting inhaled anticholinergic drug reduces the rate of COPD exacerbations and improves the effectiveness of pulmonary rehabilitation. A combination of a short-acting β₂-agonist and an anticholinergic produces better and more sustained improvements in FEV1 than either drug alone. The addition of inhaled glucocorticosteroids is appropriate for symptomatic patients with COPD stage III and IV and repeated exacerbations according to the guidelines (fig. 1). This treatment does not modify the long-term decline of FEV1, but it has been shown to reduce the frequency of exacerbations and improve the health status of COPD patients. Recent data, however, based on a single large study of patients with FEV1 <60% pred, indicate that regular treatment with inhaled glucocorticosteroids can decrease the rate of decline of lung function. Long-term treatment with oral glucocorticosteroids should be avoided in COPD because side-effects such as steroid myopathy may contribute to muscle weakness, decreased functionality and respiratory failure in patients with advanced COPD. The regular use of mucolytic and antioxidant agents has been evaluated in COPD patients without significant overall benefit, although there has been a study reporting reduced frequency of exacerbations. The regular use of antibiotics, other than for treating infectious exacerbations of COPD is not recommended. The regular use of antitussive medications is also not recommended since cough, although a troublesome symptom, has a significant protective role. There has been some recent evidence regarding the use of statins and long-term macrolide treatment in decreasing COPD exacerbations, but these are not standard recommendations.

Influenza vaccination is strongly recommended for all COPD patients; it can reduce serious illness and death by ~50% and should be given once a year. Pneumococcal polysaccharide vaccine is recommended for COPD patients who are aged ≥65 yrs.

Pulmonary rehabilitation aims at improving exercise capacity, reducing symptoms and overall improving quality of life. It is a multidisciplinary programme ideally involving several types of health professionals. COPD patients at all stages of disease appear to benefit from exercise training programmes, although benefit decreases after a rehabilitation programme ends. Pulmonary rehabilitation improves dyspnoea, improves quality-of-life scores, reduces the number of hospitalisations and days in hospital, reduces anxiety and depression related with COPD and improves survival. A comprehensive rehabilitation programme includes exercise training, education and nutrition counselling.

### Table 2. Risk factors for chronic obstructive pulmonary disease

<table>
<thead>
<tr>
<th>Genes</th>
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<tbody>
<tr>
<td>Tobacco smoke</td>
</tr>
<tr>
<td>Occupational dusts, organic and inorganic</td>
</tr>
<tr>
<td>Indoor air pollution (heating and cooking with biomass fuel)</td>
</tr>
<tr>
<td>Outdoor air pollution</td>
</tr>
<tr>
<td>Lung growth</td>
</tr>
<tr>
<td>Oxidative stress</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Respiratory infections</td>
</tr>
<tr>
<td>Socioeconomic status</td>
</tr>
<tr>
<td>Nutrition</td>
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</tbody>
</table>

Reproduced from the Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, with permission.
Nutritional status is an important factor in determining symptoms, respiratory function and prognosis in COPD. Both extremes (overweight and underweight) are detrimental. A reduction in body mass index, seen in \( \sim 25\% \) of stage III and IV COPD patients, is an independent risk factor for mortality. Present evidence suggests a combination of nutritional support and exercise regimes, to induce anabolic action.

**References**


**Figure 1.** Chronic obstructive pulmonary disease (COPD) treatment by severity. FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; % pred: % predicted. Reproduced from the Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, with permission.


EXACERBATIONS OF COPD

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Definition
Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory airway condition associated with episodes of acute deterioration termed exacerbations. An exacerbation of COPD is defined as an event in the natural course of the disease characterised by a change in the patient’s baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.

Burden
Exacerbations are important events in the natural history of COPD; they have been shown to drive lung function decline and are responsible for much of the morbidity and mortality associated with this highly prevalent condition. Exacerbations are also among the most common causes of medical admission and are costly to health services.

Patients hospitalised with exacerbations of COPD are a particularly vulnerable group with a poor long-term outlook, with all-cause mortality approaching 50% at 3 yrs post-discharge. Advanced age and severe lung function impairment, in addition to diabetes and poor health status, are particular risk factors for mortality. Inpatient mortality of patients admitted with COPD exacerbations in the UK is 7.4%, and rises to 25% for those patients with hypercapnic respiratory failure treated with noninvasive ventilation. Thus prevention, early diagnosis and prompt, effective management is vital to improve exacerbation recovery, ameliorate the effects on quality of life and reduce the risk of hospitalisation.

Causes
Exacerbations are associated with increased systemic and airway inflammation, and may be precipitated by environmental factors. However, the majority of COPD exacerbations are triggered by bacterial and/or respiratory viral infections (fig. 1).

Infection Bacteria are isolated from sputum in 40–60% of acute exacerbations of COPD and respiratory viruses are identified in 40–60% of exacerbations, rhinovirus being the most prevalent species identified. Experimental
infection models provide direct evidence that the symptomatic and physiological changes seen in acute exacerbations of COPD can be precipitated by rhinovirus infection. Furthermore, viral and bacterial infections demonstrate a synergistic effect at exacerbation; exacerbation symptoms, forced expiratory volume in 1 s (FEV1) decline and inflammation being more severe in the presence of both bacteria and viruses. These subjects are discussed further in the chapter entitled “Infective exacerbations of COPD”.

FIGURE 1. Triggers of chronic obstructive pulmonary disease exacerbations and associated pathophysiological changes leading to increased exacerbation symptoms. Reproduced from Wedzicha and Seemungal (2007) with permission from the publisher.
**Air pollution**  Extensive data exists to support a role for air pollution in the aetiology of some COPD exacerbations. The Air Pollution and Health, a European Approach (APHEA) collaboration examined short-term effects of air pollution on mortality and morbidity of COPD in six European cities and found that increased levels of environmental pollutants (sulphur dioxide, nitrogen dioxide, ozone and particles) were associated with elevated relative risks of daily admissions for COPD.

**Low temperature**  COPD exacerbations are more common and may be more severe in the winter months with colder temperatures; small but significant falls in lung function occur with reductions in outdoor temperature during winter in COPD patients. The mechanisms behind these observations are not clearly understood but may relate to increasing prevalence of respiratory viruses in low temperature winter months and/or increased susceptibility to upper respiratory tract virus infections in cold weather.

**Frequent exacerbator phenotype**  Patients with a history of frequent exacerbations have worse quality of life, increased risk of hospitalisation and greater mortality (fig. 2). Frequent exacerbators also exhibit faster decline in lung function and may have worse functional status, as measured by time outdoors. Thus, it is vital to identify patients at risk of frequent exacerbations.

Exacerbations become more frequent and severe as COPD severity increases. However, one distinct group of patients appears to be susceptible to exacerbations, irrespective of disease severity. This phenotype of susceptibility to exacerbations is a history of prior exacerbations. This phenomenon is seen across all Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages, including patients with stage 2 disease, of whom 22% had frequent exacerbations in the first year of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study. Thus suggesting that patients with the frequent exacerbator phenotype are prone to exacerbations as a result of intrinsic susceptibility, and develop exacerbations when exposed to particular triggers, like respiratory viruses.

**Susceptibility to exacerbations**  Respiratory viruses are more likely to be detected in patients with a history of frequent COPD exacerbations, suggesting that frequent exacerbators may be more

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![Figure 2](image_url)  
**FIGURE 2.** Effect of chronic obstructive pulmonary disease exacerbations in the group with frequent exacerbations. Reproduced from **Wedzicha and Seemungal (2007)** with permission from the publisher.
susceptible to respiratory viral infections. Cells from patients with COPD manifest increased viral titre and copy number following rhinovirus infection compared to controls and intercellular adhesion molecule (ICAM)-1, the rhinovirus major group receptor, is upregulated on the bronchial epithelium of patients with COPD.

Frequent exacerbators also have elevated airway inflammation when stable, as measured by sputum interleukin (IL)-6 and IL-8 levels, in addition to a higher incidence of lower airway bacterial colonisation.

*Haemophilus influenzae* enhances rhinovirus serotype 39-induced protein expression of IL-8 and epithelial-derived neutrophil attractant-78, chemokines which are increased in the sputum and airways of patients with COPD exacerbations. *Haemophilus influenzae* also increases expression of ICAM-1 and Toll-like receptor-3 and augments binding of rhinovirus to cultured cells. Through such mechanisms, patients colonised with bacteria may be more susceptible to the development of virally triggered exacerbations.

**Exacerbation prevention**

**Vaccines** In retrospective cohort studies of community-dwelling elderly patients, influenza vaccination is associated with a 27% reduction in the risk of hospitalisation for pneumonia or influenza and a 48% reduction in the risk of death. Pneumococcal polysaccharide vaccine has been shown to reduce the incidence of community-acquired pneumonia in COPD patients under the age of 65 yrs and those with severe airflow obstruction, although no mortality benefit was demonstrated. As a result, influenza and pneumococcal vaccines are recommended in the majority of patients with COPD.

**Inhaled corticosteroids and long-acting bronchodilators** The ISOLDE (Inhaled Steroid in Obstructive Lung Disease in Europe) study showed a 25% reduction in exacerbation frequency with inhaled corticosteroids (ICS). Long-acting β-agonists (LABAs) also reduce exacerbation frequency and in the TORCH (Towards a Revolution in COPD Health) study, in which 6,112 patients were followed over 3 yrs, both inhaled fluticasone and salmeterol reduced exacerbation frequency when administered separately in comparison to placebo. The combination of fluticasone and salmeterol reduced exacerbation frequency further, in addition to improving health status and lung function in comparison to placebo. The combination of ICS and LABA also resulted in fewer hospital admissions over the study period and trended towards a mortality benefit, although this did not reach statistical significance. Reduction in exacerbation frequency has been also found with other LABA/ICS combinations, such as formoterol and budesonide.

Long-acting antimuscarinics (LAMAs) also reduce exacerbation frequency. In the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial, 5,993 patients were randomised to tiotropium or placebo for a duration of 4 yrs, with concomitant therapy allowed. Although the primary end-point of the trial (reduction in rate of decline in FEV1) was negative, tiotropium was associated with a reduction in exacerbation risk, related hospitalisations and respiratory failure.

**Phosphodiesterase inhibitors** Phosphodiesterase-4 inhibitors inhibit the airway inflammatory processes associated with COPD. Evidence from a pooled analysis of two large placebo-controlled, double-blind multicentre trials revealed a significant reduction of 17% in the frequency of moderate (glucocorticoid treated) or severe (hospitalisation/death) exacerbations. However, only patients with an FEV1 <50% (GOLD stage 3 and 4), presence of bronchitic symptoms and a history of exacerbations were enrolled. There are no comparator studies with ICS. Weight loss was also noted in the roflumilast group, with a mean reduction of 2.1 kg after 1 yr, and was highest in obese patients. Therefore, following
treatment with roflumilast, weight needs to be carefully monitored.

Mucolytics The routine use of these agents is not recommended as only a few patients with viscous sputum appear to derive some small benefit from mucolytics.

Long-term antibiotics At present there is insufficient evidence to recommend routine prophylactic antibiotic therapy in the management of stable COPD, but some studies have shown promise. Erythromycin reduced the frequency of moderate and/or severe exacerbations (treated with systemic steroids, treated with antibiotics, or hospitalised) and shortened exacerbation length when taken twice daily over 12 months by patients with moderate to severe COPD. The macrolide azithromycin has been used as prophylaxis in patients with cystic fibrosis and is also suitable for use in COPD patients for exacerbation prevention. A large US trial of long-term azithromycin therapy in COPD will report shortly. Furthermore, intermittent pulsed moxifloxacin when given to stable patients has been shown to significantly reduce exacerbation frequency in a per-protocol population, and in a post hoc subgroup of patients with bronchitis at baseline. However, this reduction did not meet statistical significance in the intention to treat analysis and further work is required in this area.

Pulmonary rehabilitation and home oxygen and ventilatory support There is some evidence from clinical trials that pulmonary rehabilitation programmes reduce hospital stay. There is evidence from epidemiological studies that home oxygen and ventilatory support may reduce hospital admission, but controlled trials have not yet addressed these issues. These subjects are discussed in detail in the chapters entitled "Pulmonary rehabilitation" and "Oxygen therapy and ventilatory support" (table 1).

References


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Table 1. Strategies to prevent exacerbations

<table>
<thead>
<tr>
<th><strong>Pharmacological therapies for exacerbation prevention</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccines</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
</tr>
<tr>
<td>Long-acting bronchodilators (LABA and LAMA)</td>
</tr>
<tr>
<td>Combinations of LABA and inhaled corticosteroids</td>
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<tr>
<td>Phosphodiesterase-4 inhibitors</td>
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<tr>
<td>Mucolytics</td>
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<td>Long-term antibiotics</td>
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<table>
<thead>
<tr>
<th><strong>Nonpharmacological therapies</strong></th>
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</thead>
<tbody>
<tr>
<td>Pulmonary rehabilitation</td>
</tr>
<tr>
<td>Home oxygen therapy</td>
</tr>
<tr>
<td>Home ventilatory support</td>
</tr>
</tbody>
</table>


EXTRAPULMONARY EFFECTS OF COPD

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Chronic obstructive pulmonary disease (COPD) is an inflammatory disease of the lungs that is characterised by a fixed airflow limitation. Over the past few years, the understanding of COPD has evolved, and it is no longer justified to consider COPD as a disease restricted to the lungs. COPD has become a complex and multicomponent disorder, and the majority of patients die from cardiovascular diseases or cancer, and not primarily respiratory diseases. Extrapulmonary comorbidities significantly complicate the management of, and influence the prognosis of, patients with COPD. The broad range of clinical presentations, ranging from chronic bronchitis to hyperinflation and severe emphysema, also illustrates that the term “COPD” describes patients with very different clinical phenotypes.

The main recognised extrapulmonary manifestations include cardiovascular disease and heart failure, musculo-skeletal wasting, osteoporosis, metabolic syndrome and depression (table 1). While some of these comorbidities share risk factors with COPD, such as cigarette smoking, other frequently observed comorbidities cannot be attributed to smoking. There is increasing evidence that chronic inflammation is a key factor in COPD and is present in many other chronic diseases associated with COPD. The theory that COPD could be considered part of a “chronic systemic inflammatory syndrome” takes these different aspects into account.

Local and systemic inflammation

In industrialised countries of the western world, cigarette smoking accounts for most cases of COPD. Smoking triggers a local inflammatory response throughout the whole tracheobronchial tree. The cellular pattern is rather heterogenous and inflammatory cells

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Key points

- There is clear evidence that COPD is not simply a disease limited to the airways but should be considered a complex and multicomponent syndrome.
- Forced expiratory volume in 1 s (FEV1) is not just a lung function parameter for grading COPD severity, but is also a marker for premature death from any cause.
- The course of the disease and the prognosis is influenced by extrapulmonary pathology and accompanying comorbidities.
- Patients with COPD show comorbidities that are not only related to smoking but also to other lifestyle factors, including diet and inactivity: chronic systemic inflammation seems to link them and might explain why they often occur together.
- Future research has to answer the question of whether the successful treatment of comorbidities associated with COPD positively influences the course of the disease itself.
are found in the proximal and peripheral small airways, the lung parenchyma and the pulmonary vasculature. Apart from these local effects, smoking may significantly contribute to or cause systemic inflammation. COPD patients suffering from an acute exacerbation or having severe disease show increased markers of interleukins (IL-6, IL-8 and tumour necrosis factor-\(\alpha\)), acute-phase proteins (C-reactive protein (CRP) and fibrinogen) and circulating inflammatory cells (monocytes, neutrophils and lymphocytes). Whether this systemic inflammation is the result of a “spill-over” of local inflammation in the lungs, is a systemic inflammatory effect that affects multiple organ systems, or is attributable to some comorbid conditions that affect the lungs, remains debatable (fig. 1).

Systemic inflammation is actually not only present in patients with COPD, but is also a common feature in various other chronic diseases. Compared to healthy individuals, elevated levels of inflammatory markers such as CRP and IL-6 are observed in patients with stable coronary artery disease, peripheral arterial disease and diabetes. These findings have to be taken into account when the causative role of COPD in systemic inflammation is investigated because these conditions often occur together. Systemic inflammation might be the common pathway leading to these chronic diseases and might explain the high prevalence of multiple chronic diseases in the same patient.

**Impact on patient care**

Comorbidities and systemic effects in patients with COPD not only have prognostic value but also have implications for medical treatment. Medical care should focus on comorbidities that are easier to prevent and treat than COPD itself. A diagnosis of COPD can easily be performed by spirometry but the severity of the disease is clearly dependent on the presence of comorbidities. Therefore, it has been proposed that any patient older than 40 yrs with a positive smoking history (>10 packyrs), symptoms and a lung function compatible with COPD should be carefully evaluated for more general disorders associated with the chronic systemic inflammatory syndrome (table 2).

**Therapeutical implications**

Pharmacological treatment targeting the lungs has only a minor impact on the course of the disease, and the treatment of COPD should no longer be centred just on controlling symptoms and reducing exacerbations. Large clinical trials have shown that available drugs for COPD (bronchodilators and inhaled corticosteroids) do not significantly influence the long-term decline in forced expiratory volume in 1 s. Another approach would be to target the underlying systemic disease itself. A few observational studies have shown that the treatment of extrapulmonary manifestations (e.g. muscle weakness) and comorbid diseases (e.g. heart disease and peripheral arterial disease) positively influences morbidity and mortality in COPD patients. Even though these studies have clear limitations they suggest so far that statins, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers might have dual cardiopulmonary properties and be able to positively influence the course of the disease. However, these findings have to be confirmed.
in prospective and carefully controlled trials before any conclusions regarding the management of COPD patients can be drawn.

Assuming that systemic inflammation is a key factor in COPD and other chronic diseases, pulmonary rehabilitation addresses important extrapulmonary components that are not targeted by any pharmacological treatment, and might be the reason for its overwhelming efficacy. Lifestyle interventions in general, and pulmonary rehabilitation specifically, are essential components of patient care and should be evaluated in any patient with COPD GOLD stage II or higher (Global Initiative for Chronic Obstructive Lung Disease). Appropriate education about the disease itself, its time course and treatment options, as well as psychosocial support, including smoking cessation and nutritional interventions, are part of a successful rehabilitation programme.

Conclusions

Chronic diseases, including COPD, share common aspects, and chronic systemic inflammation seems to be one of the linking elements. Extrapulmonary effects of COPD not only influence the prognosis but also have an impact on disease management. The treatment of patients with COPD must become truly multidisciplinary and has to move from an organ-specific to a more holistic approach.
References

Bronchiectasis is a disorder characterised by abnormal bronchial wall thickening and luminal dilatation of the central and medium-sized bronchi due to a vicious circle of transmural infection and inflammation with mediator release. The prevalence varies between countries but seems to increase with age and is more common in females. Frequent symptoms are chronic cough and production of mucopurulent sputum. Less frequent are haemoptysis, pleuritic pain, recurrent fever, wheeze and dyspnoea. Exacerbations of bronchiectasis are characterised by increase in symptoms, i.e. increase in cough and change in purulence and volume of sputum associated with increase in malaise. These exacerbations are almost always associated with infections of bronchiectasis (table 1).

Underlying causes of bronchiectasis may be acquired or inherited, and include post-infective, mechanical obstruction, excessive immune response, deficient immune response, inflammatory pneumonitis, abnormal mucus clearance and fibrosis. Conditions associated with bronchiectasis include infertility, inflammatory bowel disease, connective tissue disorders, malignancy, diffuse panbronchiolitis, α₁-antitrypsin deficiency and mercury poisoning. In adults the aetiology is idiopathic in ~50%, and in children 25%; however, these figures may differ in time and between countries due to the availability of diagnostics and antibiotics (including vaccinations).

**Work-up**

The work-up of bronchiectasis comprises:

- blood tests: C-reactive protein, white blood count;
- differentiation, immunoglobulin (Ig)G, IgM, IgA, total IgE, IgG, aspergillus serology, α₁-antitrypsin;
specific tests to identify underlying causes or contributing conditions dependent of the clinical setting;

- spirometry;

- sputum smear and cultures for bacteria, mycobacteria and fungi; and

- radiography of chest and sinus, if necessary a high-resolution computed tomography (HRCT) scan of the lung.

The chest radiograph is abnormal in most patients; however, a normal chest radiograph does not exclude bronchiectasis. HRCT is nowadays the "gold standard" for bronchiectasis. Characteristic findings include internal bronchial diameters 1.5 times greater than that of the adjacent pulmonary artery (signet ring sign, fig. 1), lack of bronchial tapering, visualisation of bronchi within 1 cm of the costal pleura, visualisation of the bronchi abutting the mediastinal pleura, and bronchial wall thickening. The distribution of bronchiectasis on HRCT scan may give diagnostic clues for allergic bronchopulmonary aspergillosis, cystic fibrosis (CF), primary ciliary dyskinesia, and idiopathic bronchiectasis. Severity of bronchiectasis on HRCT scan is poorly correlated with clinical indices.

Management

Management of bronchiectasis should aim at fast resolution and prevention of infective exacerbations, no sputum infections, optimal bronchial clearance, minimal respiratory symptoms, normal lung function, high quality of life and no treatment-related adverse effects. Obviously, the prompt recognition and treatment of the underlying cause(s) and/or condition(s) is important for both short- and long-term outcomes. For the specific treatment of CF-related bronchiectasis see next chapter on Cystic fibrosis. Unfortunately, there are only limited high-quality studies on the management of non-CF bronchiectasis. Several reviews list a large number of treatment options; however, due to small study samples, different study populations and outcome variables, and other methodological issues, it is difficult to draw definitive conclusions.

Acute exacerbations

Antibiotic treatment is the mainstay of acute exacerbations and is targeted at likely organisms (table 1) or the results of sputum culture(s). A fluoroquinolone is recommended over 7-10 days in outpatients without history of recurrent exacerbations or sputum cultures (Barker, UpToDate; see Weblinks). Hospitalised patients may be treated with two i.v. antibiotics with efficacy for Pseudomonas (Barker, UpToDate; see Weblinks). Supportive

Table 1. Microbiology of bronchiectasis

<table>
<thead>
<tr>
<th>Bacterial</th>
<th>Mycobacterial</th>
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<tbody>
<tr>
<td><em>Haemophilus influenza</em></td>
<td><em>Avium-intracellular</em> complex</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td><em>Kansasi</em></td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td><em>Fortuitum</em></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td></td>
</tr>
<tr>
<td><em>Mycobacterial</em></td>
<td><em>Fungal</em></td>
</tr>
<tr>
<td><em>Avium-intracellular</em> complex</td>
<td><em>Aspergillus fumigatus</em></td>
</tr>
</tbody>
</table>

The pattern of microbiology is quite stable; however, resistance against antibiotics may increase in time. *Pseudomonas* is associated with more severe disease. Nontuberculous mycobacteria associates frequently with *Aspergillus*. Taken from *ILOWITE et al.* (2009).

Figure 1. Signet ring sign. Cross-sectional computed tomography scan of the right lung in a patient with bronchiectasis. White arrow indicates a signet ring sign. Taken from *OUELLETTE* (1999).
management may consist of inhaled bronchodilators, systemic corticosteroids, and measures to improve bronchial clearance (physical therapy, hydration, mucolytic agents).

**Prevention of exacerbations** Prolonged use of antibiotics (>4 weeks) may be considered in patients who quickly relapse (>4–6 times per year) or demonstrate progressive lung function decline. Several treatment strategies are described:

- oral antibiotic 2–3 times daily,
- oral macrolide three times weekly,
- aerosolised tobramycin, gentamycin, colistin, ceftazidime, or aztreonam twice daily (aerosolised antibiotics in non-CF bronchiectasis are frequently not licensed or stopped because of side-effects),
- intravenous antibiotics, 2–3-week courses with 1–2-month intervals (Barker, UpToDate; see Weblinks).

A Cochrane review concluded that there is a small benefit on overall clinical response scores, but not on exacerbation rates. Clearly the indication for prolonged use of antibiotics should be based on a benefit–risk evaluation, also taking possible adverse effects into account.

**Sputum and bronchial clearance** Inhaled rhDNase administered to stable non-CF bronchiectasis patients has been associated with increased exacerbation frequency and greater forced expiratory volume in 1 s decline and therefore should not be given. Oral bromhexine improved expectoration, quantity and quality of sputum, and auscultatory findings during acute infective exacerbations. Macrolides improved sputum production and sputum inflammatory markers. 12-day inhalation of mannitol improved the tenacity and hydration of sputum. Inhaled fluticasone improved sputum production and sputum inflammation, but not its microbiological profile. Nebulised 0.9 and 7% saline as an adjunct to physiotherapy improved sputum production, sputum viscosity and ease of sputum expectoration; however, 7% saline was superior to 0.9%. Two systematic reviews found insufficient evidence to either support or refute bronchial hygiene physical therapy.

**Symptoms and quality of life** Haemoptysis is treated with bronchial embolisation; however, surgical resection is sometimes inevitable. Surgical resection may also be considered if the area of the bronchiectatic lung is localised and if the patient’s symptoms are debilitating or life threatening. In this case, surgery can even be curative if there is absence of an ongoing underlying cause. Although surgery is widely used, there are no randomised controlled trials (RCTs). Inhaled fluticasone improved dyspnoea, sputum production, days without cough, β2-agonist use and health-related quality of life.

**Lung function** RCTs on short-acting β2-agonists, long-acting β2-agonists, anticholinergic therapy, oral methyl-xanthines, leukotriene antagonists and oral corticosteroids were not selected in Cochrane reviews. Nevertheless, bronchodilator therapy may be considered if a patient has proven airway obstruction. Macrolides may improve methacholine reactivity, airway obstruction and carbon monoxide diffusion. However, if macrolides are considered, the presence of nontuberculous mycobacteria must be excluded first, and patients must be warned about ototoxicity.

**Exercise tolerance** Pulmonary rehabilitation is effective in improving exercise capacity and endurance, whereas simultaneous inspiratory muscle training may be important in the longevity of these training effects.

**References**


**Weblinks**


The autosomal recessive condition cystic fibrosis (CF) is the most common inherited disease of white races; the prevalence varies across Europe. Although commonest in white people, it has been found in virtually every ethnic group. The gene, on the long arm of chromosome 7, encodes a multifunctional protein, cystic fibrosis transmembrane regulator (CFTR), which is active at the apical membrane of epithelial cells. Different classes of mutation have been described (fig. 1); severe mutations (classes I–III) are usually associated with pancreatic insufficient CF and a worse prognosis, whereas those with milder mutations (IV–VI) are more usually pancreatic sufficient. The combination of a mild and severe gene usually leads to a mild pancreatic phenotype; however, there is only a poor correlation between genotype and pulmonary phenotype. In many parts of Europe, the most common mutation is DF508, but there are marked ethnic differences.

CFTR functions as a chloride channel and regulates other ion channels, such as the epithelial sodium channel (ENaC). Most of the morbidity and mortality of CF is due to chronic bronchial infection, but as adults survive longer, multisystem complications are becoming more important. The airways of the newborn with CF are effectively normal at birth, but from an early age, cycles of infection and inflammation supervene, leading ultimately to severe bronchiectasis and respiratory failure. The most popular hypothesis for the pathophysiology of CF lung disease is airway surface liquid dehydration due to uncontrolled activity of ENaC, possibly triggered by viral infection. Median survival is predicted to be ~50 yrs, longer for males. In parts of Europe there are now more adult than paediatric CF patients.

Key points

- Adult pulmonologists need to know about cystic fibrosis; it is common across Europe, patients are surviving into middle age and beyond, and new diagnoses are being made even in old age.
- Cystic fibrosis is now a true multisystem disease; to the well-known complications of chronic respiratory infection and malabsorption has been added conditions such as cirrhosis, insulin deficiency and diabetes, osteopenia, stress incontinence and infertility.
- Furthermore, with longevity is coming new complications, including the selection of resistant microorganisms and antibiotic allergy. Other organ systems will likely be affected in the aging cystic fibrosis population.
- Treatment of cystic fibrosis thus requires a dedicated multidisciplinary team, comprising physicians, specialist nurses, physiotherapists, dieticians, clinical psychologists and pharmacists.
- The increasing knowledge of the molecular pathophysiology of cystic fibrosis is leading the way in the development of genotype specific therapies, which will be a paradigm for other diseases.
Figure 1. Classes of cystic fibrosis (CF) mutations. Class I: no cystic fibrosis transmembrane regulator (CFTR) synthesis (mutation, premature stop codon) (G542X); class II: CFTR processed incorrectly and does not reach apical cell membrane (DF508); class III: CFTR reaches apical membrane, but channel regulation is abnormal (G551D); class IV: CFTR reaches apical membrane, but channel open time is reduced (R334W); class V: reduced CFTR synthesis (R117H); class VI: CFTR reaches apical cell membrane, but has a shortened half-life due to more rapid turnover (1811+1.6 kb A>G).
Adult physicians will encounter CF patients by two routes:

- referral from a paediatric clinic of an already diagnosed patient. Transition to a new and strange adult clinic from the familiar staff and surroundings of the paediatric clinic may be a difficult time, and needs to be handled with sensitivity. Increasingly, young adult handover clinics, staffed by paediatricians and adult physicians, are being set up.
- a new diagnosis made in adult life.

CF is usually diagnosed in early childhood, increasingly by newborn screening, but mild atypical cases may be missed. ~10–15% of CF patients present in adult life (see table 1). Conversely, always consider the possibility that the diagnosis of CF made in childhood is incorrect, and whether a repeat diagnostic workup should be done.

**Diagnostic testing for CF**

Once the diagnosis is suspected, it is usually easily confirmed by a sweat test, which must be performed in an experienced centre. Other diagnostic modalities that are employed include:

- Genetic testing: more than 1,300 variants are described, and rare ones are usually undetected in the routine clinical laboratory, so a negative genotype cannot exclude disease.
- Nasal transepithelial potential difference measurement: only available in a few centres.
- Ancillary testing: human faecal elastase (pancreatic insufficiency), high-resolution computed tomography for occult bronchiectasis, scrotal ultrasound or semen analysis for congenital bilateral absence of the vas deferens (CABVD).

**Management of CF (table 2)**

CF has now become a true multisystem disease. Treatment can only be optimally conducted with the help of a full multidisciplinary team (CF physician, specialist nurse, physiotherapist, dietician, clinical psychologist and pharmacist) and the help of ancillary specialists with expert

**Table 1. Late presentation of cystic fibrosis (CF; such patients are usually but not invariably pancreatic sufficient)**

| Recurrent respiratory infections | Consider especially with ‘suggestive’ microorganisms such as Staphylococcus aureus, Pseudomonas aeruginosa, Burkholderia cepacia |
| Atypical ‘asthma’ | Especially if chronic productive cough, and a poor response to standard asthma therapy |
| Bronchiectasis | Especially if any extrapulmonary features, a positive family history, or infection with atypical microorganisms |
| Male infertility | Azospermia due to congenital bilateral absence of the vas deferens (CABVD) |
| Electrolyte disturbance | Classically as acute heat exhaustion leading to sodium, chloride and potassium depletion |
| Atypical mycobacterial infection | Always consider the possibility of CF if these organisms are isolated from sputum |
| Acute pancreatitis | Typically seen in pancreatic sufficient CF |
| CF liver disease | Portal hypertension and variceal haemorrhage; liver cell failure is a late manifestation |
| Cascade screening | Diagnosis made in a relative leading to extended family screening |

New diagnoses of CF have been made even in old age; CF diagnosis should always be considered.
Table 2. Management of cystic fibrosis (CF) lung disease

<table>
<thead>
<tr>
<th>Disease stage</th>
<th>Pulmonary status</th>
<th>Aim</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (unusual but seen in adults with CF)</td>
<td>Pre-infection</td>
<td>Mucus clearance</td>
<td>Airway clearance techniques (physiotherapy and adjuncts; these include exercise and mucolytics, <em>e.g.</em> rhDNase, hypertonic saline)</td>
</tr>
<tr>
<td></td>
<td>Intermittent isolation of <em>Pseudomonas aeruginosa</em></td>
<td>Prevent infection</td>
<td>Segregation and cohorting to prevent cross-infection. Prophylactic antibiotics controversial; used against <em>Staphylococcus aureus</em> in the UK; avoid cephalosporins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eradication of infection. Energetic treatment is essential</td>
<td>High doses of appropriate antibiotics. <em>P. aeruginosa</em> eradication protocols include both topical (nebulised) and systemic (usually oral ciprofloxacin). Eradication achieved in 80–90%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Chronic infection with usual organisms (<em>P. aeruginosa</em>: eventually present in 80% of patients; <em>S. aureus</em> (methicillin resistant and sensitive), less usually <em>Haemophilus influenzae</em>)</td>
<td>Suppression of bacterial load and thus limitation of inflammatory response</td>
<td>Depends on organism: <em>P. aeruginosa</em>: nebulised high-dose tobramycin (300 mg b.i.d.) or colomycin. Use the new, faster nebuliser devices, for example, e-Flow (PARI) and iNeb (Profile Pharma)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treat infective exacerbations</td>
<td>Oral or IV antibiotics (some centres use regular elective courses, but no evidence to prefer this over symptomatic use) Culture results usually guide choice, but no evidence that this improves outcome</td>
</tr>
</tbody>
</table>
Table 2. Continued

<table>
<thead>
<tr>
<th>Infection with less common organisms (Burkholderia cepacia complex, Stenotrophomonas maltophilia, Achromobacter xylosoxidans)</th>
<th>Reduce inflammation (it is controversial whether the CF airway is intrinsically pro-inflammatory, or there is merely a greater airway inflammatory response to infection than normal)</th>
<th>No evidence for a role for corticosteroids except in treating ABPA, because of efficacy but adverse side-effect profile (oral) or lack of benefit (inhaled) Ibuprofen not much used in most of Europe; beware synergistic nephrotoxicity with intravenous aminoglycosides Azithromycin is useful, but mode of action unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABPA</td>
<td>Eradication if early; suppression of bacterial load most commonly</td>
<td>Confirm diagnosis in a reference laboratory; treat on an individual basis with specialist microbiological advice</td>
</tr>
<tr>
<td>Nontuberculous Mycobacterial infection</td>
<td>Eradication or suppression (Mycobacterium abscessus may be very difficult to eradicate)</td>
<td>Oral corticosteroids (long course often required), consider pulsed methyl prednisolone Addition of an antifungal agent common but evidence limited</td>
</tr>
<tr>
<td>Lobar or segmental atelectasis (may be seen at any stage of CF)</td>
<td>Re-inflation of the lung</td>
<td>Diagnosis and management difficult; seek specialist advice, especially for M. abscessus infection Prolonged courses of multiple chemotherapies will be needed: ethambutol, rifampicin, azithromycin, amikacin, ciprofloxacin, moxifloxacin are among the agents used</td>
</tr>
<tr>
<td>Late</td>
<td>Major haemoptysis (may be seen also in those with well preserved lung function)</td>
<td>Prevent or halt acute bleeding</td>
</tr>
<tr>
<td></td>
<td>Pneumothorax (carries a very bad prognosis)</td>
<td>Control air leak, prevent recurrence</td>
</tr>
<tr>
<td></td>
<td>End-stage respiratory failure</td>
<td>Optimise conventional treatment Refer for lung transplant</td>
</tr>
</tbody>
</table>

ABPA: allergic bronchopulmonary aspergillosis; COPD: chronic obstructive pulmonary disease.
knowledge of CF (ear, nose and throat surgeon, obstetrician and endocrinologist). CF patients should be seen at least every 3 months by the core CF team. A large number of treatment guidelines have been published.

**Respiratory tract disease** The main issues are the prevention of infection where possible by cohort segregation of patients with particular infections, and the aggressive use of antibiotics; although conventional teaching is that airway infection occurs with a relatively

<table>
<thead>
<tr>
<th>Organ</th>
<th>Manifestation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>Exocrine insufficiency: malabsorption, steatorrhoea</td>
<td>High-fat diet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Supplementation with enteric-coated microsphere pancreatic enzymes and fat-soluble vitamins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fat absorption may be aided by alkaline environment (H₂-blockers or proton pump inhibitors)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastrostomy feeds if in nutritional failure (parenteral nutrition only rarely required)</td>
</tr>
<tr>
<td></td>
<td>Acute pancreatitis (pancreatic sufficient patients)</td>
<td>As for other causes; oral pancreatin powder (anecdotal evidence only)</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>Gastro-oesophageal reflux (especially common post-lung transplant)</td>
<td>Proton pump inhibitors, prokinetic agents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surgery if refractory symptoms</td>
</tr>
<tr>
<td>Small bowel</td>
<td>Distal intestinal obstruction syndrome</td>
<td>Oral gastrografin (Schering) or klean prep (Norgine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Review dose of, and adherence to, pancreatic enzyme replacement therapy, perform 3-day faecal fat collection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider pro-kinetic agents</td>
</tr>
<tr>
<td></td>
<td>Coeliac disease (increased incidence in CF)</td>
<td>Gluten-free diet, as for isolated coeliac disease</td>
</tr>
<tr>
<td></td>
<td>Crohn’s disease (any part of the bowel)</td>
<td>Management as for isolated Crohn’s disease, seek specialist gastroenterology advice</td>
</tr>
<tr>
<td>Colon</td>
<td>Constipation</td>
<td>Laxatives, high-fibre diet; must not be confused with distal intestinal obstruction syndrome</td>
</tr>
<tr>
<td>Rectum</td>
<td>Rectal prolapse</td>
<td>Rare in adults, usually related to uncontrolled fat malabsorption</td>
</tr>
<tr>
<td>Liver</td>
<td>Fatty liver (usually asymptomatic)</td>
<td>Liver ultrasound at least every 2 yrs</td>
</tr>
<tr>
<td></td>
<td>Macronodular cirrhosis (variceal bleeding, splenomegaly, hypersplenism)</td>
<td>Ursodeoxycholic acid, taurine (seek specialist advice)</td>
</tr>
<tr>
<td></td>
<td>Hepatocellular failure a late manifestation</td>
<td>Severe cases may need transplantation</td>
</tr>
</tbody>
</table>

DIOS: distal intestinal obstruction syndrome.

---

**Table 3. Management of gastrointestinal manifestations of cystic fibrosis (CF) in the adult**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Manifestation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>Exocrine insufficiency: malabsorption, steatorrhoea</td>
<td>High-fat diet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Supplementation with enteric-coated microsphere pancreatic enzymes and fat-soluble vitamins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fat absorption may be aided by alkaline environment (H₂-blockers or proton pump inhibitors)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastrostomy feeds if in nutritional failure (parenteral nutrition only rarely required)</td>
</tr>
<tr>
<td></td>
<td>Acute pancreatitis (pancreatic sufficient patients)</td>
<td>As for other causes; oral pancreatin powder (anecdotal evidence only)</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>Gastro-oesophageal reflux (especially common post-lung transplant)</td>
<td>Proton pump inhibitors, prokinetic agents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surgery if refractory symptoms</td>
</tr>
<tr>
<td>Small bowel</td>
<td>Distal intestinal obstruction syndrome</td>
<td>Oral gastrografin (Schering) or klean prep (Norgine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Review dose of, and adherence to, pancreatic enzyme replacement therapy, perform 3-day faecal fat collection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider pro-kinetic agents</td>
</tr>
<tr>
<td></td>
<td>Coeliac disease (increased incidence in CF)</td>
<td>Gluten-free diet, as for isolated coeliac disease</td>
</tr>
<tr>
<td></td>
<td>Crohn’s disease (any part of the bowel)</td>
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<tr>
<td></td>
<td>Hepatocellular failure a late manifestation</td>
<td>Severe cases may need transplantation</td>
</tr>
</tbody>
</table>

DIOS: distal intestinal obstruction syndrome.
### Table 4. Treatment of other manifestations of cystic fibrosis (CF) in the adult

<table>
<thead>
<tr>
<th>Organ</th>
<th>Manifestation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upper airway</strong></td>
<td>Nasal polyps (can cause obstructive sleep apnoea)</td>
<td>Topical steroids. Long courses of antibiotics. Surgery if medical management fails, re-operation often needed.</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
<td>Most patients have asymptomatic changes on radiography or computed tomography scan, and require no treatment. Topical steroids. Antibiotics.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surgery if medical management fails, but results often disappointing. Some use sinus drainage tubes and repeatedly instil antibiotics into the sinuses.</td>
</tr>
<tr>
<td><strong>Endocrine pancreas</strong></td>
<td>Insulin deficiency, which causes reduced lung function and nutrition before overt hyperglycaemia</td>
<td>Screen regularly with annual glucose tolerance test, or continuous glucose monitoring.</td>
</tr>
<tr>
<td></td>
<td>Frank diabetes; although there may be an element of peripheral insulin resistance, the main root cause is diminished insulin secretion</td>
<td>Have a low threshold for starting insulin. Continue high-fat diet, adjust insulin doses accordingly. Diabetic ketoacidosis is very rare. Oral hypoglycaemic agents not to be used outside a randomised controlled trial.</td>
</tr>
<tr>
<td><strong>Sweat gland</strong></td>
<td>Electrolyte depletion, often leading to acute collapse</td>
<td>Sodium and potassium chloride supplementation.</td>
</tr>
<tr>
<td><strong>Bones and joints</strong></td>
<td>Osteopenia (cystic fibrosis transmembrane regulator is expressed in bones)</td>
<td>Measure bone mineral density at least every 2 yrs. Prevention: weight bearing exercise, high dairy intake, vitamin D and K therapy. Treat with bisphosphonates if severe.</td>
</tr>
<tr>
<td></td>
<td>Pathological fracture</td>
<td>Nonsteroidal anti-inflammatory agents, prednisolone; seek specialist rheumatological advice if more than mild.</td>
</tr>
<tr>
<td></td>
<td>CF arthropathy (large or small joint)</td>
<td></td>
</tr>
<tr>
<td><strong>Male reproductive tract</strong></td>
<td>Bilateral absence of vas deferens leading to male infertility</td>
<td>Sperm aspiration and <em>in vitro</em> fertilisation; genetic counselling prior to procedure.</td>
</tr>
<tr>
<td><strong>Female reproductive tract</strong></td>
<td>Vaginal candidiasis</td>
<td>Topical anti-fungal agents.</td>
</tr>
<tr>
<td></td>
<td>Stress incontinence</td>
<td>Seek gynaecological advice.</td>
</tr>
<tr>
<td></td>
<td>Pregnancy (not an illness, but may be a major therapeutic challenge); women with severe CF may be subfertile, but normal conception is usual</td>
<td>Pre-pregnancy genetic counselling advisable. Continue standard CF medications; close collaboration with obstetric unit; may need regular admissions to hospital for intravenous antibiotics. Especially beware if low lung function prior to pregnancy, and CF related diabetes on insulin.</td>
</tr>
</tbody>
</table>
narrow spectrum of microorganisms, recent work, including the use of molecular techniques, suggests that anaerobes in particular may be more important than previously thought. Sputum clearance using a choice of many chest physiotherapy techniques and the identification and aggressive management of late complications are also important. If the patient has poor lung function, early discussion with the local transplant centre is advisable. Routine respiratory care at every clinic visit should include spirometry and pulse oximetry, and sputum or cough swab culture.

**Gastrointestinal disease (table 3)** The main issues are to ensure optimal nutrition, and be alert to gastrointestinal causes of weight loss that are unrelated to pancreatic insufficiency. Bad nutrition is a very poor prognostic feature. CF patients have higher than normal energy requirements because of subclinical malabsorption and a higher energy consumption secondary to infection. Increased metabolic rate is thought by some to be part of the underlying defect. Weight should be measured, and body mass index calculated, 3-monthly.

**Other organ system disease (table 4)** It is important to be aware that new complications are being described as CF patients survive longer. A full systems review is essential at each clinic visit. Finally, the psychological aspects of CF and the effects of chronic illness and the burden of disease and its treatment should not be underestimated; see the poignant stories and poetry on the Breathing Room website.

**Future developments**

A large number of novel therapies are currently being trialled in CF. Gene therapy, using as vectors either liposomes, viruses or nanoparticles, has been the subject of proof of concept trials, and a large therapeutic trial is about to start. The age of genotype specific therapy dawned with the use of agents such as topical aminoglycosides or oral PTC124 to over-ride premature stop codons (class I mutations). Other approaches include the use of molecular chaperones ("correctors") to transport abnormal (class II mutations) CFTR to the apical cell membrane, and potentiators to improve activity when they reach this site. There is ongoing mutation-specific work to increase chloride channel activity of class III and IV mutations, as well as the use of compounds that activate alternative epithelial chloride channels. There is no doubt that we are on the verge of a CF treatment revolution. Most important, however, is to ensure that the basic therapy, which has so greatly improved prognosis, is not neglected here and now.

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Weblinks
• www.ukneqas.org.uk.
• www.genet.sickkids.on.ca/cftr.
• www.thebreathingroom.org/cg.
• www.cfgenetherapy.org.uk.
# CHAPTER 10: OCCUPATIONAL AND ENVIRONMENTAL LUNG DISEASES

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WORK-RELATED AND OCCUPATIONAL ASTHMA

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Definition

Work-related asthma (WRA) is the most common form of occupational lung disease, causing significant morbidity and disability. WRA accounts for 9–15% of cases of asthma in adults of working age.

WRA may be categorised into: occupational asthma (OA), which refers to asthma caused specifically by exposure to an agent present at the workplace; and work-aggravated or work-exacerbated asthma (WEA), in which pre-existing asthma is exacerbated by conditions in the work environment. The American College of Chest Physicians consensus document and British Occupational Health Research Foundation guidelines therefore define WRA to include OA (i.e. asthma induced by sensitizer or irritant work exposures) and WEA (i.e. pre-existing or concurrent asthma worsened by work factors).

OA can occur in workers with or without prior asthma and can be subdivided into: 1) sensitizer-induced OA, characterised by a latency period between first exposure to a respiratory sensitizer at work and the development of symptoms; and 2) irritant-induced OA that occurs typically within a few hours of a high-concentration exposure to an irritant gas, fume or vapour at work. When the causal exposure consists of a single inhalation incident, the condition is commonly called reactive airways dysfunction syndrome.

In clinical practice, it is often difficult to differentiate between “true” OA and aggravation of pre-existing asthma. Conversely, aggravation of symptoms related to work exposure, even in the absence of new sensitisation, requires individual and collective measures at the workplace, similar to OA. A recent consensus definition therefore is that

Key points

- The burden of work-related asthma (WRA) is still very high, accounting for one in ten cases of adult asthma, and causing morbidity, disability and high costs.
- Prevention is very important. Health officials, work managers and doctors must be aware of the problem, strict measures for exposures to known sensitizers should always be followed, conditions at work examined and, when necessary, amended.
- Better education of workers and managerial staff as well as medical professionals is key to the prevention and prompt diagnosis and management of WRA and occupational asthma (OA). When WRA is diagnosed, prompt management is required and consists of removing or reducing exposure through elimination or substitution of causative agents and, where this is not possible, by effective control of exposure.
- Pharmaceutical treatment of OA follows the general asthma guidelines.
OA is defined as asthma induced by exposure in the working environment to airborne dusts, vapours or fumes, with or without pre-existing asthma (Francis (2007)). Physicians involved in adult asthma care need to be aware of the high prevalence of WRA and the importance of inducing or exacerbating factors at work.

**Sensitising and triggering agents**

More than 250 agents causing OA have been described and are categorised into high molecular weight (HMW) and low molecular weight (LMW) agents, according to whether their molecular weight is above or below 1 kD. HMW agents are usually proteins of animal and vegetal origin such as flour, laboratory animal proteins and enzymes. LMW agents include a wide variety of chemicals, such as acid anhydrides, platinum salts and reactive dyes. Sensitisation to most HMW and some LMW factors is through an immunoglobulin (Ig)E mechanism and can be tested by skin tests. An immunological mechanism is suspected for LMW agents but has not been demonstrated, and an antigen-specific immune response cannot easily be tested in most affected workers.

The most frequently reported agents of occupational asthma are:

- Isocyanates
- Flour and grain dust
- Colophony and fluxes
- Latex
- Animal and plant proteins
- Aldehydes
- Wood dust
- Metal salts

Epidemiological studies have demonstrated that the level of exposure is the most important determinant of OA. This implies that preventive measures should be aimed at reducing workplace exposure. Prevention through elimination/reduction of exposure is the most effective approach for reducing the burden of OA. However, the relationship between the levels of exposure and the induction of OA is not always clear and the methodology of exposure assessment requires standardisation. Atopy increases the risk of developing OA in workers exposed to various sensitisers including enzymes, bakery allergens, laboratory animals, crab, prawn and acid anhydrides. The latent interval between first exposure and the onset of symptoms varies depending on the agent, the level of exposure/management and biological variability of exposure. The latent interval can extend to many years; however, the risk of OA appears to be highest soon after first exposure to laboratory animal allergens, isocyanates, platinum salts and enzymes. See Table 1 for a list of agents frequently identified by inhalational challenge.

**Diagnosis**

The clinical presentation and symptoms of OA are no different from non-OA. Patients experience attacks of breathlessness, wheezing, cough, chest tightness and limitations in their daily activities. In any working adult patient presenting with such symptoms, the diagnosis of WRA should be considered. In individuals with suspected WRA, the physician should obtain a history of job duties and possible exposures, the use of protective devices and the presence of respiratory disease in co-workers. Table 2 shows examples of occupations/industries with sentinel health events for sensitisers-induced OA.

Symptoms may get worse when the patient enters the work environment, but very often the patients experience delayed symptoms and therefore may get worse after leaving work. A clinically useful approach, therefore, is not asking whether the patients experience worsening of their symptoms when at work but rather whether they feel better after a weekend or a holiday away from work. However, this is difficult to describe, as most people feel rested and happier at the end of a holiday. The diagnosis requires first spirometry, with a positive bronchodilation test and/or histamine, methacholine or...
exercise testing of airway hyperresponsiveness for the confirmation of asthma. Furthermore, the patient should be asked to record symptoms, use of medication and peak expiratory flow (PEF) measurements when working and off work. PEF should be measured at least four times a day for a period of a month while times on and off work should be noted (the recommendation is at least 2 weeks on and 2 weeks off work). The sequential self-measurements of PEF can be complemented by repeated measurements of provocative concentration of histamine or methacholine causing a 20% fall in forced expiratory volume in 1 s. Allergic sensitisation to some inducers such as animal proteins can be examined by skin prick testing or in vitro assays of specific IgE. When the diagnosis cannot be confirmed by serial PEF measurements and skin tests or IgE assays, the “gold standard” for diagnosing sensitiser-induced OA is a specific bronchial provocation test (specific inhalation challenge), which may demonstrate a direct relationship between exposure to a test agent and an asthmatic response. The response may be early or late and may carry a risk to the patient of a severe reaction. Therefore, these tests should be performed only when necessary and only in specialised centres under medical supervision.

**Management**

Ideally, causal agents should be eliminated from the workplace, an option that is not often available. The second-best option is to remove the workers from exposure; however, many patients cannot quit their job. In such cases, the early institution of preventive measures, including the replacement of specific reagents where possible, the strict monitoring of exposure levels, and the use of extractor fans and masks, is necessary. The EU has allocated a high priority to safeguarding the health and safety of workers. Existing EU health and safety legislation aims to minimise the health risks from dangerous substances in the workplace, placing the emphasis on their elimination and substitution in order to protect workers. There are four important directives in this field, containing the basic provisions for health and safety at work, and further defining the risks related to exposure to chemical agents, to biological agents and to carcinogens at work. Medical surveillance programmes are very important and may include symptom questionnaires, spirometry and skin prick testing at regular intervals (e.g. every 6 or 12 months), as well as monitoring of exposure levels.

Once OA has developed, recovery is directly dependent on the duration and level of exposure to the causative agent. Depending on the severity of the case, the condition of the patient can substantially improve during the first year after removal from exposure. Conversely, asthma may persist even after removal from exposure to the causative workplace agent. The likelihood of improvement or resolution of symptoms or

### Table 1. Low molecular weight (LMW) and high molecular weight (HMW) agents frequently identified by inhalational challenge

<table>
<thead>
<tr>
<th>LMW agents</th>
<th>HMW agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isocyanates</td>
<td>Flour</td>
</tr>
<tr>
<td>HDI</td>
<td>Plants and grain dust</td>
</tr>
<tr>
<td>MDI</td>
<td>Seafood/fish</td>
</tr>
<tr>
<td>TDI</td>
<td>Latex</td>
</tr>
<tr>
<td>Metals</td>
<td>Animal-derived allergens</td>
</tr>
<tr>
<td>Plicatic acid (white or red</td>
<td>Leather</td>
</tr>
<tr>
<td>cedar)</td>
<td>Enzymes</td>
</tr>
<tr>
<td>Wood dust</td>
<td>Talc</td>
</tr>
<tr>
<td>Hairdresser products</td>
<td></td>
</tr>
<tr>
<td>Epoxy</td>
<td></td>
</tr>
<tr>
<td>Gums</td>
<td></td>
</tr>
<tr>
<td>Dyes and fabrics</td>
<td></td>
</tr>
<tr>
<td>Chemicals</td>
<td></td>
</tr>
<tr>
<td>Perfume</td>
<td></td>
</tr>
</tbody>
</table>

preventing deterioration is greater in workers who have no further exposure to the causative agent, have relatively normal lung function at diagnosis, and those who have shorter duration of symptoms prior to diagnosis and prior to avoidance of exposure.

Trigger avoidance is pivotal in preventing asthma symptoms and progression of severity. Nevertheless, pharmacological treatment is also required to control symptomatic patients. Pharmacological treatment follows the general asthma treatment guidelines, and inhaled steroids and β-agonists are the cornerstone of management. Treatment follows a stepwise approach, based on asthma control and severity and the approach is identical to that of non-OA.

### Socioeconomic impact of WRA

The economic impact of WRA is due not only to direct healthcare costs but also to indirect costs from impaired work productivity and compensation/rehabilitation costs, as well as to the intangible costs from impaired quality of life. Income loss is more likely when avoidance of exposure leads to a change of job and this income loss is not offset by compensation. In many European countries, compensation does not include rehabilitation or retraining, perhaps accounting for the relatively high proportion (30%) of workers who continue to be exposed to the causative agent.

Moreover, when considering the cost of OA and/or compensation, it is not only lung function impairment and optimal asthma treatment that

### Table 2. Examples of occupations/industries with sentinel health events for sensitiser-induced occupational asthma

<table>
<thead>
<tr>
<th>Industry, process or occupation</th>
<th>Selected agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jewellery, alloy and catalyst makers</td>
<td>Platinum</td>
</tr>
<tr>
<td>Polyurethane, foam coatings, adhesives production and end-use settings (e.g. spray painters, and foam and foundry workers)</td>
<td>Isocyanates</td>
</tr>
<tr>
<td>Alloy, catalyst, refinery workers</td>
<td>Chromium, cobalt</td>
</tr>
<tr>
<td>Solderers</td>
<td>Soldering flux (colophony)</td>
</tr>
<tr>
<td>Plastics industry, dye, insecticide makers, organic chemical manufacture</td>
<td>Phthalic anhydride, trimetallic anhydride (used in epoxy resins)</td>
</tr>
<tr>
<td>Foam workers, latex makers, biologists, and hospital and laboratory workers</td>
<td>Formaldehyde</td>
</tr>
<tr>
<td>Printing industry</td>
<td>Gum arabic, reactive dyes and acrylates</td>
</tr>
<tr>
<td>Metal plating</td>
<td>Nickel sulphate and chromium</td>
</tr>
<tr>
<td>Bakers</td>
<td>Flour, amylase and other enzymes</td>
</tr>
<tr>
<td>Woodworkers and furniture makers</td>
<td>Red cedar (plicatic acid) and other wood dusts</td>
</tr>
<tr>
<td>Laboratory workers and animal researchers</td>
<td>Animal proteins</td>
</tr>
<tr>
<td>Detergent formulators</td>
<td>Detergent enzymes such as protease, amylase, and lipase</td>
</tr>
<tr>
<td>Seafood (crab, snow crab and prawn) workers</td>
<td>Crab, prawn and other shellfish proteins</td>
</tr>
<tr>
<td>Healthcare workers and nurses</td>
<td>Psyllium, natural rubber latex, glutaraldehyde, methacrylates, antibiotics and detergent enzymes</td>
</tr>
<tr>
<td>Laxative manufacture and packing</td>
<td>Psyllium</td>
</tr>
<tr>
<td>Hairdressers and manicurists</td>
<td>Persulphates and acrylates (artificial nails)</td>
</tr>
</tbody>
</table>

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need to be taken into account, but also psychogenic factors. These can play an important role in the quality of life of OA patients, and significant prevalence of anxiety and depression has been shown in that population.

References

RESPIRATORY DISEASES CAUSED BY ACUTE INHALATION OF GASES, VAPOURS AND DUSTS

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Acute inhalation injury may occur in the workplace, but also at home or in the community, e.g. as a result of fires and explosions, volcanic eruptions, industrial disasters, and accidents involving trains or trucks transporting chemicals. Inhalation accidents may be of catastrophic proportions, as occurred with the release of methyl isocyanate in Bhopal, India, in 1984. Mass casualties with inhalation injuries may also result from chemical warfare, and from conventional warfare or terrorist actions involving explosions, fires and building destructions.

The clinical presentation and severity of inhalation injury range from self-limited inhalation fever to life-threatening chemical pneumonitis with lung oedema and evolution to acute respiratory distress syndrome (ARDS) and multiorgan failure. Following inhalation injury, the lesions may heal completely or there may be persisting structural or functional sequelae.

Key points

- An influenza-like response (“inhalation fever”) may follow the inhalation of high quantities of zinc fumes (“metal fume fever”) or organic aerosols (“organic dust toxic syndrome”).
- After inhalation of poorly water-soluble agents, such as nitrogen dioxide, phosgene or cadmium fumes, pulmonary oedema becomes clinically manifest only 4–12 h after exposure.
- Acute inhalation injury may be followed by various structural lesions in the airways, but also by asthma. Such asthma induced by a single inhalation injury is called acute irritant-induced asthma, or RADS.

Inhalation fever

Inhalation fever is the name given to a group of nonallergic, noninfectious flu-like clinical syndromes caused by the acute inhalation of metal fumes, organic dusts or some plastic fumes.

Metal fume fever is caused by a single exposure to high amounts of some metallic fumes, most notably those emitted when heating zinc. Organic dust toxic syndrome (ODTS) is caused by the inhalation of large quantities of agricultural and other dusts of biologic origin (bio-aerosols), which are generally heavily contaminated with toxin-producing microorganisms. Polymer fume fever occurs after exposure to the fumes of heated fluorine-containing polymers.
The clinical features of the inhalation fevers are those of a beginning influenza. The actual exposure may or may not have been experienced as irritant for the eyes and respiratory tract. 4–8 h after the exposure, the subject begins to feel unwell with fever (up to 40°C), chills, headaches, malaise, nausea and muscle aches. Respiratory symptoms are usually mild and consist mainly of cough and/or sore throat, but occasionally subjects may have more severe responses with dyspnoea.

The diagnosis of inhalation fever rests essentially on the recent exposure history and the clinical condition, and when these clearly point to inhalation fever, no sophisticated investigations are required. In general, chest auscultation and chest radiograph are normal, but in more severe cases crackles may be heard and there may be transient infiltrates on chest radiograph. Pulmonary function is often within normal limits; in severe cases there may be a decrease in diffusing capacity and arterial hypoxaemia. Increased peripheral blood leukocytosis, with a rise in neutrophils, is a consistent finding until 24 h after the exposure; other blood tests should be normal, except for indices of an inflammatory response. Bronchoalveolar lavage studies have shown pronounced and dose-dependent increases in polymorphonuclear leukocytes on the day after exposure to zinc fumes or organic dust.

Inhalation fever must not be confused with other more serious conditions, including chemical pneumonitis, which in its early phases could be mistaken for inhalation fever. A differential diagnosis must also be made with various types of infectious pneumonias and with acute extrinsic allergic alveolitis.

Inhalation fever is a self-limited syndrome and recovery normally takes place after a night’s rest. Tolerance exists against re-exposures occurring shortly after a bout of metal fume fever or ODTS.

**Acute chemical pneumonitis**

**Major causes** The response to acute chemical injury in the respiratory tract is rarely compound-specific (table 1). The main agents that may cause acute inhalation injury are as follows:

- **Watersoluble irritants**, such as ammonia (NH₃), sulphur dioxide (SO₂), hydrochloric acid (HCl), formaldehyde, acetic acid, have good warning properties and mainly affect the upper respiratory tract, unless massive quantities have been inhaled.

- **Cases of intermediate water solubility**, such as chlorine (Cl₂) and hydrogen sulphide (H₂S), penetrate deeper into the bronchial tree. Accidental release of gaseous chlorine is one of the most frequent causes of inhalation injury, not only in industry, but also in the community as a result of transportation accidents, the use of chlorine for disinfecting swimming pools, or the mixing of bleach (NaClO) with acids; mixing bleach with ammonia leads to the release of volatile and irritant chloramines (including trichloramine, NCl₃). Hydrogen sulphide (H₂S), which is formed by the putrefaction of organic material in sewage drains, manure pits or ship holds, and is also a frequent contaminant in the petrochemical industry, does not only cause mucosal irritation, but it also leads to chemical asphyxia by mechanisms that are somewhat similar to those of cyanide.

- **Poorly watersoluble agents**, such as nitrogen dioxide (NO₂), phosgene (COCl₂), ozone (O₃), mercury vapours (Hg), cadmium oxide (CdO) fumes, are particularly hazardous because they cause little sensory irritation and are, therefore, hardly noticed, and they reach the distal airways thus potentially causing noncardiogenic pulmonary oedema, which develops over the course of several hours.

- **Exposure to organic solvents** is rarely a cause of toxic pneumonitis. However, exposure to very high concentrations of solvent vapours in confined spaces (e.g. in chemical tanks) may cause chemical
pneumonitis and pulmonary oedema, often in victims who have been unconscious. Pneumonia and respiratory distress syndrome caused by loss of alveolar surfactant may also result from the aspiration of solvents or fuels ingested unintentionally (e.g. from siphoning petrol) or intentionally (e.g. by “fire eaters”). Severe acute respiratory illness may also be caused by spraying solvent-propelled fluorocarbon-containing water-proofing agents and leather conditioners.

- Some agrochemicals (such as paraquat and organophosphate or carbamate insecticides) may cause toxic pneumonitis after ingestion or dermal exposure.
- The commonest cause of toxic pneumonitis is smoke inhalation caused by domestic, industrial or other fires. Respiratory morbidity is often the major complication in burn victims. It may be caused by direct thermal injury (particularly if hot vapours have been inhaled), but more generally the lesions are caused by chemical injury. The toxic components of smoke include gaseous asphyxiants (CO, HCN) and irritants, as well as particulates.

**Clinical presentation** Depending on the circumstances of the accident, there may be thermal or chemical facial burns. Signs of mucosal irritation include cough, hoarseness, stridor or wheezing, retrosternal pain, discharge of bronchial mucus, possibly with blood, mucosal tissue and soot. Auscultation of the chest may or may not be abnormal, with wheezing, rhonchi or crepitations. Mucosal oedema, haemorrhage and ulcerations may be visible in the air passages. Victims of inhalation accidents with poorly soluble agents may feel – and look – perfectly well initially, but then experience progressive dyspnoea, shallow breathing, cyanosis, frothy pink sputum and eventually ventilatory failure. A clinical picture of ARDS may thus develop gradually over 4–72 h, even after a period of clinical improvement.

Pulmonary function can be used to monitor ambulatory subjects who have been exposed. Arterial blood gases show varying degrees of hypoxaemia and respiratory acidosis, depending on the severity of the injury. The chest radiograph is usually normal if only the conducting airways are involved, but there may be signs of peribronchial cuffing. After exposure to deep lung irritants the chest radiograph is unremarkable in the first hours after presentation, but signs of interstitial and alveolar oedema may become visible and, with time, patchy infiltrates, areas of atelectasis and even “white lungs” may develop. These changes may be due to tissue damage and organisation or they may reflect superimposed infectious (broncho)pneumonia.

In some instances, particularly in the later stages of chemical pneumonitis, there may be pathological (and radiological) features of organising pneumonia with or without

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**Table 1. Possible causes of toxic tracheobronchitis or pneumonitis**

| Irritant gases | High water-solubility: NH₃, SO₂, HCl, etc. | Moderate water-solubility: Cl₂, H₂S, etc. | Low watersolubility: O₃, NO₂, COCl₂, etc. |
| Organic chemicals | Organic acids: acetic acid, etc. | Aldehydes: formaldehyde, acrolein, etc. | Isocyanates: methylisocyanate (MIC), toluene diisocyanate (TDI) |
| | Amines: hydrazine, chloramines, etc. | | |
| | Riot control agents (CS) and vesicants (mustard gas) | Organic solvents | Leather treatment sprays |
| | | Some agrochemicals (paraquat, cholinesterase inhibitors) | |
| Metallic compounds | Mercury vapours | Metallic oxides: CdO, V₂O₅, MnO, Os₃O₄, etc. | Halides: ZnCl₂, TiCl₄, SbCl₅, UF₆, etc. |
| | Ni(CO)₄ | Hydrides: B₂H₆, LiH, AsH₃, SbH₃ | |
| Complex mixtures | Fire smoke | Pyrolysis products from plastics | Solvent mixtures |
| | | Spores and toxins from microorganisms | |
bronchiolitis obliterans. Following resolution of the acute pulmonary oedema, a relapse in the clinical condition may occur after 2–6 weeks with dyspnoea, cough, fine crackles, a radiographic picture of miliary nodular infiltrates, arterial hypoxaemia and a restrictive or mixed impairment, with low diffusing capacity. This relapse phase has been attributed to bronchiolar scarring with peribronchiolar and obliterating fibrosis of the bronchioli.

Management At the scene of the accident, appropriate medical intervention includes removal from exposure, resuscitation and supportive treatment. In some instances, emergency personnel must also be protected from chemicals that remain present on victims or their clothes and decontamination procedures must be available. For some types of exposures asymptomatic persons must remain under observation for 24 h; they should not exercise, nor should they be overfilled by intravenous fluids. Oxygen treatment should be given as required by the level of arterial oxygen saturation.

The further management of acute inhalation injury will be governed by the severity of the patient’s condition and will involve intensive care treatment with intubation and artificial ventilation, as required. Antibiotics are only to be given if there are signs of infection. In victims of smoke injury, bronchoscopic removal of soot from the airways may be necessary. The administration of (systemic) corticosteroids is probably justified to prevent complications arising from (excessive) inflammation, such as bronchiolitis obliterans, although there are no controlled studies on this issue.

Physicians treating victims in the early days after the incident must document accurately the clinical condition and all relevant data in these patients. Documentation of the damage by bronchoscopy and high-resolution computed tomography may be justified. Repeated measurements of ventilatory function and arterial blood gases must be carried out, and victims of acute inhalation injury should never be discharged without a comprehensive assessment of their pulmonary function.

Subacute toxic pneumonitis

Although the concept of chemical-induced lung injury is used only for disorders resulting from a single, acute exposure to a toxic chemical, the term “subacute toxic pneumonitis” may be used to refer to lung injury caused by repeated peaks of toxic exposures or a more prolonged toxic exposure over weeks to months. This is the case with exogenous lipid pneumonitis, which may be caused by inhalation of natural or synthetic mineral oils, and with pulmonary alveolar proteinosis, which may be caused by heavy exposure to silica (“acute silico-proteinosis”) and possibly by other agents.

The “Ardystil syndrome” is an example of subacute toxic pneumonitis. This outbreak of severe organising pneumonia occurred in 1992 in Spain, and involved several workers from factories where textiles were air-sprayed with dyes.

Another recently described form of subacute toxic lung injury is “popcorn worker’s lung”. This severe lung disease, characterised as bronchiolitis obliterans, occurred in subjects occupationally exposed to vapours of butter flavouring (containing diacetyl) used for making microwave-popcorn and other food.

Possible sequelae of acute inhalation injury

Following acute inhalation injury, there is often complete recovery. However, this is not always the case. Various persistent anatomical lesions such as constrictive bronchiolitis, bronchiectases, bronchial strictures or polyps, may be identified by imaging studies or through bronchoscopy.

Moreover, even in the absence of such structural sequelae or in the absence of significant defects in basal spirometry, a state of permanent nonspecific bronchial hyperreactivity may be observed. This condition of adult-onset, nonallergic asthma known as “reactive airways dysfunction syndrome” (RADS) or “acute irritant-induced asthma” occurs in a proportion of survivors of inhalation injury. Observations in fire-fighters
and other personnel involved in rescue operations during and following the collapse of the World Trade Center on September 11, 2001, suggest that RADS may occur even without the occurrence of clinically serious injury.

**References**

Hypersensitivity pneumonitis (HP), also known as allergic alveolitis, is an immunologically mediated inflammatory lung disease in the lung parenchyma induced by the inhalation of a variety of organic or inorganic antigens and characterised by hypersensitivity to the antigens. The disease is usually named colourfully after the environment in which it occurs (e.g. farmer’s lung and bird fancier’s lung) and has been reported from over 30 different occupations and environments.

Epidemiology

In a large, general-population-based cohort of HP patients from the UK, the overall incidence rate was approximately one per 100,000 population, and in Japan the summer-type HP occurs every year in approximately one per million population. Most other studies have focused on the risk of developing clinical disease among subsets of the population with high levels of exposure to particular antigens. For example, the incidence of farmer’s lung in Sweden in the 1980s was ~20 per 100,000 person-yrs. However, there has been a decrease in the incidence of farmer’s lung due to changes in farming practice (hay making replaced by silage bags). A recent study from North America showed that the most common cause was bird or hot-tub exposure.

Risk factors

The first reported HP was farmer’s lung, caused by inhalation of microorganisms from infested crops. The disease was first described among farmers in the Nordic parts of the globe; however, it has since been described in a range of farming operations all over the world, making farming-like operations with decaying organic material one of the important exposures to look for when
confronted with a case of HP. One of the most common appearances of HP is bird fancier’s lung, caused by exposure to birds, e.g. pigeons or parakeets. Among pigeon breeder’s HP, intestinal mucin, a high molecular weight glycoprotein, has been identified as a major antigen.

**Host factors**

Smoking seems to give protection towards HP, although the disease has been described in a few smokers. The reason behind this protection might be the downregulation of the immune system by tobacco smoke and nicotine.

Virus infection seems to increase the susceptibility of mice towards the antigens, and a higher number of virus antigens have been found in the bronchial lavage of HP patients.

**Pathological mechanism**

Although HP is a well known disease, the pathogenesis is still only partly understood. When PEPYS (1978) found precipitating antibodies to mould antigen in many cases, it was believed for many years that the immune complexes were the basis of the lung changes. It is now believed that the cellular immune response is driving the disease. Following inhalation of antigen, a complex formed by soluble antigens and immunoglobulin G antibodies triggers the complement cascade and alveolar macrophage activation is induced, resulting in an increase in macrophages. These cells secrete cytokines and chemokines that attract neutrophils in alveoli and small airways. The number of T-lymphocytes is also increased, with a predominance of the CD8+ T-lymphocytes subset, resulting in a decrease in the CD4+/CD8+ ratio (in contrast to what is seen in sarcoidosis). Different upregulatory mechanisms result in a stronger interaction between macrophages and T-cells and a more effective antigen-presenting capacity.

**Symptoms and findings**

The predominant symptoms in HP are tiredness, dyspnoea, fever, shivering, flu-like feeling, cough, muscle and joint aches and headache. Radiography of the thorax shows diffuse, fine, nodular shadows, either general or predominantly in the bases. In the early stages the changes can be difficult to detect, but widespread patchy opacities may also be seen. Lung function is decreased, with a typical restrictive pattern and a decreased diffusing capacity.

**Environmental assessment**

The origin of the disease is an adverse reaction towards an occupational or environmental factor, so it is imperative to search the patient’s environment for this exposure, and to minimise further contact to the offending agent. Often it is obvious what the reason might be, e.g. a mouldy hay problem occurring after a wet harvest season. In some instances the causal agent might be difficult to find and techniques for the assessment of microorganisms should be employed in order to assess the exposure to which the patient is exposed.

**Diagnosis**

The diagnosis of HP relies on an array of nonspecific clinical symptoms and signs developed in an appropriate setting, with demonstration of bilateral patchy infiltrates on chest radiographs, and serum precipitating antibodies against offending antigens. Several different diagnostic criteria for HP have been proposed; all have significant problems that limit their utility. After studying a total of 661 HP patients with a stepwise logistic regression, a panel of clinical experts identified six significant predictors of HP.

Diagnostic criteria of extrinsic hypersensitivity pneumonitis:

- Exposure to a known offending antigen
- Symptoms occurring 4–8 h after exposure
- Positive precipitating antibodies to the offending antigen
- Inspiratory crackles on physical examination
Recurrent episodes of symptoms

Weight loss

However, diagnosing HP often poses challenges, even to expert clinicians. Additional investigations (including surgical biopsy) are indicated in patients with interstitial diseases in whom the diagnosis remains unclear after initial assessment.

**Treatment**

The only treatment for allergic diseases is to avoid the exposure to the offending allergen. This can be done in many circumstances, *e.g.* when the occurrence is sporadic and not part of the daily work of the patient. However, in some cases, *e.g.* farmers, it might be difficult to avoid the exposure totally for a range of different reasons. Under such circumstances respiratory protection can be used to minimise the exposure as much as possible.

It has been discussed whether medical treatment has an effect on the outcome of HP. Cortisone has been found to reduce interleukin-8 synthesis. Cortisone treatment seems to improve the radiological findings and should be given to severely ill patients to ameliorate symptoms, but no apparent benefit

<table>
<thead>
<tr>
<th>HP type</th>
<th>Exposure</th>
<th>Antigen</th>
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<tbody>
<tr>
<td>Farmer's lung</td>
<td>Mouldy hay</td>
<td><em>Saccharopolyspora rectivirgula</em></td>
</tr>
<tr>
<td>Bagassosis</td>
<td>Mouldy bagasse</td>
<td><em>Thermoactinomyces sacchari</em></td>
</tr>
<tr>
<td>Mushroom worker's lung</td>
<td>Mushroom spores, mushroom compost</td>
<td><em>Thermophilic actinomycetes</em></td>
</tr>
<tr>
<td>Malt worker's lung</td>
<td>Mouldy barley</td>
<td><em>Aspergillus clavatus, Faenia rectivirgula</em></td>
</tr>
<tr>
<td>Humidifier/airconditioner lung</td>
<td>Contaminated water reservoirs</td>
<td><em>Thermophilic actinomycetes</em></td>
</tr>
<tr>
<td>Grain handler's lung</td>
<td>Mouldy grain</td>
<td><em>Saccharopolyspora rectivirgula, Thermactinomycetes vulgaris</em></td>
</tr>
<tr>
<td>Cheese worker's lung</td>
<td>Cheese mould</td>
<td><em>Penicillium casei</em></td>
</tr>
<tr>
<td>Paprika splitter's lung</td>
<td>Paprika dust</td>
<td><em>Mucor stoloni</em></td>
</tr>
<tr>
<td>Compost lung</td>
<td>Compost</td>
<td><em>Aspergillus spp.</em></td>
</tr>
<tr>
<td>Peat moss worker's lung</td>
<td>Peat moss</td>
<td><em>Monocillium spp., Penicillium citreonegrum</em></td>
</tr>
<tr>
<td>Suberosis</td>
<td>Mouldy cork dust</td>
<td><em>Penicillium frequentans</em></td>
</tr>
<tr>
<td>Maple bark stripper's lung</td>
<td>Mouldy wood bark</td>
<td><em>Cryptostroma corticale</em></td>
</tr>
<tr>
<td>Wood pulp worker's lung</td>
<td>Mouldy wood pulp</td>
<td><em>Alternaria spp.</em></td>
</tr>
<tr>
<td>Wood trimmer's disease</td>
<td>Mouldy wood trimmings</td>
<td><em>Rhizopus spp.</em></td>
</tr>
<tr>
<td>Japanese summertype HP</td>
<td>Indoor air</td>
<td><em>Trichosporon cutaneum</em></td>
</tr>
<tr>
<td>Metal grinding</td>
<td>Metalworking fluids</td>
<td><em>Mycobacteria</em></td>
</tr>
<tr>
<td>Hot tub lung</td>
<td>Mist from hot tubs</td>
<td><em>Mycobacteria</em></td>
</tr>
<tr>
<td>Bird breeder's lung</td>
<td>Pigeons, parakeets, fowl, rodents</td>
<td><em>Avian or animal proteins</em></td>
</tr>
<tr>
<td>Mollusc-shell hypersensitivity</td>
<td>Sea snail shells</td>
<td><em>Shell dust</em></td>
</tr>
<tr>
<td>Chemical worker's lung</td>
<td>Manufacture of plastics, polyurethane foam, rubber</td>
<td><em>Trimellitic anhydride, diisocyanate, methylene diisocyanate</em></td>
</tr>
</tbody>
</table>
is derived from long-term treatment. The cortisone treatment should be given for about 2 months.

**Prognosis**

If the exposure ceases, the symptoms usually subside rapidly, but the lung function impairment may persist for a longer period and become permanent, with a restrictive pattern and decreased diffusing capacity. Repeated attacks increase the risk of sequelae. It is therefore important to treat the patient as soon as possible in order to avoid more damage to the lung parenchyma than is already the case at the time of diagnosis.

**Differential diagnosis**

Infectious lung diseases, both of virological and bacteriological origin, as well as other lung diseases such as sarcoidosis, have to be ruled out. Another differential diagnosis is the organic dust toxic syndrome (ODTS) also known as “inhalation fever” or “toxic pneumonitis”: acute, febrile, noninfectious, flu-like, short-term reactions that can be produced by inhalation of bio-aerosols and organic dusts as well as plastic hardeners and metal (zinc) fumes. Symptoms are caused by the release of inflammatory cytokines from the lungs caused by an inhalatory overexposure to aerosols. ODTS is quite a common condition, but the prognosis is good and most people have recovered totally without any sequels after 24 h. No treatment is required if the exposure is terminated.

**References**

Asbestos, coal and silica exposures are the main causes of pneumoconiosis relevant to current clinical and medico-legal practice. Although these exposures have greatly diminished in recent years, many patients still present to pneumologists with disease resulting from exposure that occurred in previous years. This article will consider the effects of dust inhalation both on lungs and pleura.

**Asbestos**

The mining and use of amphibole forms of asbestos, mainly crocidolite and amosite, has ceased worldwide, but chrysotile, the serpentine form, is still used in Africa, South America and Asia, both because of a lack of cheaper substitutes and because it is less harmful than the amphiboles. Some ceiling boards still contain chrysotile and people who live near chrysotile mines experience environmental exposure. There is a high incidence of mesothelioma in women who lived in the chrysotile mining region of Quebec, Canada, where contamination of chrysotile by the amphibole tremolite increases toxicity.

**Pleural plaques**

Pleural plaques, which are discrete areas of thickening on the parietal pleura, are the commonest manifestation of asbestos exposure. They are usually discovered incidentally on plain chest radiographs or computed tomography scans. They do not become evident radiographically in <15 yrs from first exposure. Previously, plaques were thought to have no effect on lung function, but a recent statement from the American Thoracic Society claimed that studies of large cohorts showed a reduction in lung function attributable to pleural plaques.

**Key points**

- Pleural plaques are benign and do not predispose to malignancy.
- Asbestosis is a disappearing disease.
- Diffuse pleural thickening is the sequel to benign asbestos pleurisy and may cause restricted ventilation.
- New cases of coal workers’ pneumoconiosis are still occurring.
- Silicosis increases the risk of both TB and lung cancer.

However in the majority of cases, any such effect is unlikely to be of clinical significance. Some studies have suggested that plaques predispose to the development of mesothelioma, but the consensus view is that they are not pre-malignant. Until recently in the UK, pleural plaques were accepted as justifying compensation. However, in 2007, the House of Lords ruled that plaques did not constitute an injury and that compensation would no longer be awarded to affected individuals.

**Benign asbestos pleurisy and diffuse pleural thickening**

Asbestos pleurisy was first described in 1964. Many episodes are asymptomatic but some patients experience pain, fever and dyspnoea. Typically the pleurisy is associated with a blood-stained effusion but some cases are of “dry pleurisy”. Spontaneous recovery is usual although recurrence on the other side is common. Asbestos pleurisy may occur after a latency of <10 yrs, but in another study the mean latency was 26 yrs.
Diffuse pleural thickening (DPT) involves the visceral pleura and may be unilateral or bilateral. It is now thought to follow earlier episodes of benign pleurisy. The fibrosis may be extensive and cause restricted ventilation. It may be difficult to distinguish from confluent pleural plaques but in DPT, obliteration of the costophrenic angle has usually occurred and this does not happen with plaques.

**Asbestosis**

Asbestosis is diffuse interstitial pulmonary fibrosis secondary to severe asbestos exposure. In the USA, it is becoming a disappearing disease because of the great reduction in exposure. Disease progression was a feature of severe disease after heavy exposure, but after mild exposure, the disease tends to become quiescent. It is therefore very rare nowadays to see patients with severe asbestosis.

The relevance of asbestosis in current practice is almost entirely medico-legal. Patients with pulmonary fibrosis and a history of asbestos exposure seek compensation, but many of them had limited exposure and have coincidentally developed idiopathic pulmonary fibrosis of the usual interstitial pneumonia (UIP) sub-type. The two important distinguishing features are the more progressive nature of UIP in terms of radiographic changes and declining lung function and the presence of pleural plaques which occur in ~95% of patients with asbestosis.

An international meeting was held in Helsinki in 1997 and criteria for the diagnosis of asbestosis were developed, which in addition to radiological features, included data on analysis of lung tissue for asbestos bodies and fibres.

There is agreement that asbestosis increases the risk of lung cancer but there is still no consensus about whether asbestos exposure in the absence of asbestosis also increases the cancer risk.

**Coal workers’ pneumoconiosis**

**Populations at risk**

Over the past 30 yrs, the prevalence of coal workers’ pneumoconiosis (CWP) has fallen consistently as the numbers of coal miners and the dust levels in mines have decreased. Nevertheless, mining is still a major industry in many parts of eastern Europe, India, China, South America and Africa. Increased mechanisation results in higher dust levels. New cases of CWP are still being diagnosed in miners who have worked exclusively under current exposure limits. The risk of CWP depends on the total dust burden and is also related to the coal rank, which is based on carbon content. Anthracite has a higher rank than bituminous. Therefore, this disease is not disappearing as definitely as asbestosis and continued vigilance is necessary in assessing respiratory symptoms in miners.

**Clinical features**

Simple CWP is a radiological and pathological diagnosis. The characteristic lesion is the coal macule, which is a centrilobular accumulation of macrophages. This lesion causes no signs or symptoms and dyspnoea in a patient with simple CWP must prompt a search for another diagnosis. This may be associated emphysema due to coal dust or smoking, or the development of progressive massive fibrosis, but it may also be a treatable disease unrelated to CWP.

It is now accepted that CWP causes bronchitis due to coal dust resulting in cough and mucus production. In addition, CWP is recognised as being associated with airflow obstruction independent of smoking. *Postmortem* examination suggests that coal mine dust causes centrilobular emphysema, especially when pneumoconiosis is present. In the UK, chronic bronchitis and emphysema are classified as an occupational disease for which industrial injuries benefit can be paid.

**Silicosis**

**Prevalence**

Silicosis is a major worldwide disease even in developed countries. It affects miners and workers in the construction industry and foundries. There is some evidence that prevalence in South Africa is rising. A recent study claimed that exposure
over a working lifetime to the commonly used standard of 0.1 mg·m⁻³ results in significant radiological silicosis with death both from silicosis and from lung cancer.

**Clinical features** Like CWP, uncomplicated silicosis is not associated with signs or symptoms. Dyspnoea usually indicates the development of progressive massive fibrosis or tuberculosis but may reflect associated airway disease or emphysema. Silicosis often continues to progress after exposure has ceased.

**Lung cancer** Traditionally lung cancer was not associated with silicosis, but recent authoritative reviews have concluded that the data are sufficient to support an association between silicosis and lung cancer. It remains unclear whether the increased risk derives from exposure to silica or requires the presence of silicosis.

**Tuberculosis** It is well known that silicosis predisposes to tuberculosis which may be two- to 30-fold more common than in controls without silicosis. HIV status adds a further complication. In black South African gold miners, HIV infection increased tuberculosis incidence by five times, whereas silicosis increased incidence by three times. When HIV and silicosis were both present, the tuberculosis incidence increased multiplicatively by 15 times. In addition to tuberculosis, patients with silicosis have an increased incidence of infection with environmental mycobacteria and also of extrapulmonary tuberculosis.

**Chronic obstructive pulmonary disease** Emphysema is a common feature of long-term silica exposure and along with bronchitis may develop with or without radiological signs of silicosis. Smoking may potentiate the effect of silica on airflow obstruction.

**References**

Air pollution is a well-established hazard to human health. Air quality is particularly important for subpopulations that are more susceptible (i.e., children, the elderly, subjects with cardiopulmonary diseases or those who are socioeconomically deprived) or at higher risk of specific exposures (workers exposed to inorganic dust, wood dust, fumes, gases and cleaning agents). Children are particularly vulnerable since they inhale a higher volume of air per body weight than adults, the lungs are growing, the immune system is incomplete, and defense mechanisms are still evolving. Air pollution can affect the cells in the lung by damaging those that are most susceptible, and if the damaged cells are important in the development of new functional parts of the lung, the lung may not achieve its full growth and function as a child matures to adulthood. This can lead to enhanced susceptibility during adulthood to the effects of aging and infections as well as to pollutants. Air pollution is mostly produced by human activities. Other pollutants derive from natural sources, such as biological allergens (e.g., acarids, house dust mites, pets, moulds), and natural phenomena (e.g., volcanic activity, forest fires).

**Key points**

- Recent epidemiological studies have clearly shown that outdoor and indoor air pollution affects respiratory health worldwide, causing an increase in the prevalence of respiratory symptoms/diseases (i.e., COPD, asthma, hay fever, lung function reduction) and of mortality, both in children and in adults.

- Rapid industrialisation and urbanisation have increased air pollution and, consequently, the amount of exposed people.

- Conservative estimates show that between 1.5 and 2 million deaths per year could be attributed to indoor air pollution in developing countries.

- The abatement of the main risk factors for respiratory diseases and the support of health care providers and general community to public health policy for improving outdoor/indoor air quality can achieve huge health benefits.

**Outdoor pollution**

The most important outdoor pollutants derive from fossil fuel combustion. Primary pollutants directly emitted into the atmosphere are carbon monoxide (CO), sulphur dioxide (SO₂), nitrogen dioxide (NO₂) and particulates (PM). Ozone (O₃) is a secondary pollutant, mainly produced by chemical reaction of NO₂ and hydrocarbons in the presence of sunlight at warm temperature. Rapid industrialisation and urbanisation in many parts of the world have increased air pollution and,
consequently, the number of people exposed to it. In China, for instance, rapid economic development has led to severe environmental degradation, particularly due to coal combustion (it provides 70–75% of energy) and vehicular traffic. Chinese mortality and morbidity associated to outdoor pollution are very high: more than 300,000 deaths and 20 million cases of respiratory illnesses annually. The main effects of the more common outdoor pollutants are summarised in Table 1.

Exposure–response relationships for outdoor pollutants, especially PM, have been confirmed by epidemiological studies in recent decades. Short-term exposure, due to acute increase in air pollution, may cause premature mortality and increase hospital admissions for exacerbations of chronic obstructive pulmonary disease (COPD) or asthma. Long-term cumulative health effects of chronic exposure comprise an increase in morbidity and mortality for cardiovascular and respiratory diseases, including COPD and lung cancer, and impaired development of the lungs in children. In COPD patients, continued exposure to noxious agents promotes a more rapid decline in lung function and increases the risk of repeated exacerbations. Air pollution can harm the foetus if the mother is exposed to high levels during pregnancy (i.e. intra-uterine growth retardation), and it can increase respiratory neonatal mortality. PM, NO₂ and O₃ are the most important pollutants today. The health effects of PM are more serious for fine (aerodynamic diameter <2.5 μm, PM₂.₅) and ultrafine (aerodynamic diameter <0.1 μm, PM₀.₁) particles, as they penetrate deeper into the airways of the respiratory tract, reaching the alveoli. Vehicular exhausts are responsible for small-sized airborne PM air pollution in urban areas.

Table 1. Major outdoor pollutants and related health effects

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Major sources</th>
<th>Health effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particulate matter</td>
<td>Vehicular traffic</td>
<td>Lung cancer</td>
</tr>
<tr>
<td></td>
<td>Wood stoves</td>
<td>Premature death</td>
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<tr>
<td></td>
<td>Organic matter/fossil fuel combustion</td>
<td>Mortality from cardiorespiratory diseases</td>
</tr>
<tr>
<td></td>
<td>Power plants/industry</td>
<td>Reduced lung function</td>
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<tr>
<td></td>
<td>Wind-blown dust from roads,</td>
<td>Lower airways inflammation</td>
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<tr>
<td></td>
<td>agriculture and construction</td>
<td>Upper airways irritation</td>
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<tr>
<td></td>
<td>Bush fires/dust storms</td>
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<tr>
<td>Nitrogen dioxide</td>
<td>Vehicular traffic</td>
<td>Exacerbation of asthma</td>
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<td></td>
<td>Power plants/industry</td>
<td>Airway inflammation</td>
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<td>Bronchial hyperresponsiveness</td>
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<td></td>
<td></td>
<td>Increased susceptibility to respiratory infection</td>
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<td>Ozone</td>
<td>Sunlight: chemical reaction between other pollutants</td>
<td>Lung tissue damage</td>
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<td></td>
<td>Vehicular traffic</td>
<td>Reduced lung function</td>
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<td></td>
<td>Power plants/industry</td>
<td>Reduced exercise capacity</td>
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<td></td>
<td>Consumer products</td>
<td>Exacerbation of asthma</td>
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<td></td>
<td>Upper airway and eye irritation</td>
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<tr>
<td>Carbon monoxide</td>
<td>Organic matter/fossil fuel combustion</td>
<td>Death/coma at very high levels</td>
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<td></td>
<td>Vehicular traffic</td>
<td>Headache, nausea, breathlessness</td>
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<td></td>
<td>Wood stoves</td>
<td>Confusion/reduced mental alertness</td>
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<td></td>
<td>Bronchial hyperresponsiveness</td>
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<tr>
<td>Sulphur dioxide</td>
<td>Coal/oil burning power plants</td>
<td>Exacerbation of respiratory diseases</td>
</tr>
<tr>
<td></td>
<td>Industry/refineries</td>
<td>including asthma</td>
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<tr>
<td></td>
<td>Diesel engines</td>
<td>Respiratory tract irritation</td>
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<tr>
<td></td>
<td>Metal smelting</td>
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areas. A recent Chinese study showed that long-term exposure to PM2.5 increases the risk of mortality from lung cancer by 15–21% per 10 μg m⁻³ increase. O₃ significantly increases annual mortality rates from respiratory causes, as demonstrated by a very large cohort study performed in the USA (~450,000 subjects from 96 metropolitan areas). Even in Sweden, with overall low levels of traffic-related air pollution, adults living near a road with higher traffic show significantly higher risk for diagnosis of asthma (OR 1.40, 95% CI 1.04–1.89) and COPD (OR 1.64, 95% CI 1.11–2.40) and for related symptoms. In Italy, the current authors have recently reported that people living in an urban area show a higher risk of having increased bronchial responsiveness (OR 1.41, 95% CI 1.13–1.76) than people living in a rural area.

The role of air pollution in the epidemics of allergies is still debated, even if experimental studies have suggested that the effects of air pollutants on the development and worsening of allergies are biologically plausible. Asthma shows a strong familial association, but genetic factors alone are unlikely to account for the rapid rise in its prevalence seen in recent decades. The rapid increase in the burden of atopic diseases occurred along with rapid urbanisation/industrialisation. Thus, genetic and environmental factors may interact to cause asthma. A growing number of studies shows significant associations of traffic with new-onset asthma, or asthma symptoms/exacerbations, in children. A recent study on a very large sample of German children suggests that recent exposure to NO₂ and O₃ may reduce the efficacy of short-acting β-agonists in producing bronchodilation.

Furthermore, European Community Respiratory Health Survey data suggest that NO₂ traffic-related pollution causes asthma symptoms and possibly asthma incidence in adults.

Indoor pollution

Indoor environments contribute significantly to human exposure to air pollutants. People spend most of their time indoors: up to 90% in industrialised countries. Further, levels of some pollutants are higher inside than outside buildings. Even at low concentrations, indoor pollutants may have an important biological impact because of long exposure periods (e.g. at home/school, in working places). Conservative estimates show that 1.5–2 million deaths per year could be attributed to indoor air pollution. There is consistent evidence that exposure to indoor pollutants increases the risk of several respiratory/allergic symptoms/diseases (table 2). Relevant indoor pollution sources are environmental tobacco smoke (ETS), a common source of indoor PM, biomass (wood/coal) fuel use and mould/damp.

ETS is associated with increased risk of acute respiratory or irritation symptoms, infectious diseases, chronic respiratory illnesses, lung function reduction and even lung cancer. It has been estimated to be a significant pooled risk for chronic cough in never-smokers heavily exposed to ETS, both in males (OR 1.60, 95% CI 1.22–2.10) and females (OR 1.68, 95% CI 1.17–2.34). In nonsmoking males, the mortality risk for respiratory diseases is about double for those living with smokers than for those who do not. A few studies performed worldwide suggest higher risk for ETS exposure in females than in males. In China, about 80% of the cardiorespiratory burden caused by ETS exposure concerns women, and the number of deaths from ETS due to cardiovascular diseases and lung cancer in women is about two-thirds of that from active smoking. The induction period of lung cancer being long, its risk is probably related to cumulative lifetime ETS exposure. Meta-analyses on spousal ETS exposure estimated a
pooled risk for lung cancer of OR 1.23 (95% CI 1.13–1.34). ETS exposure is a risk factor for new-onset asthma among both nonsmoking adults and children; it exacerbates pre-existing asthma and increases symptom burden and morbidity. In children, ETS also increases the risk of sudden infant death syndrome, middle-ear disease, lower respiratory tract illnesses, wheeze and cough.

About half of the world’s population burns biomass for cooking, heating and lighting, in open fires or with inefficient stoves, and in poorly ventilated rooms, especially in developing countries. There is very high production of PM and CO. Indoor air pollution from biomass fuels is strongly poverty-related and represents an important risk factor for acute respiratory illness morbidity and mortality, especially in children and women. The evidence that biomass use increases the risk of COPD in women is very strong (about threefold higher risk in those exposed than in those unexposed). Besides COPD, observed health effects include weakening of the immune system, impaired lung function and lung cancer.

Based on meta-analyses, building dampness and mould are associated with approximately 30–50% increases in respiratory and asthma-related health outcomes. In adults, a pooled risk for cough by indoor mould/dampness was estimated at OR 2.10, 95% CI 1.27–3.47. There is also evidence on the association of mould exposure with new-onset asthma, and worsening of pre-existing asthma (wheezing, cough, shortness of breath) in both children and adults. Allergic symptoms are commonly related to mould exposure (sneezing, nose/mouth/throat irritations, nasal stuffiness/runny nose, red/itchy/watery eyes). In children, a population attributable risk for asthma of 6.7% has been estimated.

Finally, exposure to VOCs may result in a spectrum of illnesses ranging from mild (irritations) to very severe effects, including cancer. Many studies indicate that the effects are related to very low levels of exposure. VOC exposure also seems a significant risk factor for asthma (especially benzene, ethylbenzene and toluene).

Table 2. Major indoor pollutants and related health effects

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Major sources</th>
<th>Health effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particulate matter</td>
<td>Wood stoves, organic matter/fossil fuel combustion for heating/cooking,</td>
<td>Lung cancer</td>
</tr>
<tr>
<td></td>
<td>Environmental tobacco smoke</td>
<td>Premature death</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality from cardiorespiratory diseases</td>
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<tr>
<td></td>
<td></td>
<td>Reduced lung function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower airways inflammation</td>
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<tr>
<td></td>
<td></td>
<td>Upper airways irritation</td>
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<tr>
<td>Nitrogen dioxide</td>
<td>Unvented gas/kerosene appliances</td>
<td>Exacerbation of asthma</td>
</tr>
<tr>
<td></td>
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<td>Airway inflammation</td>
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<td></td>
<td></td>
<td>Bronchial hyperresponsiveness</td>
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<tr>
<td>Carbon monoxide</td>
<td>Organic matter/fossil fuel combustion for heating/cooking, wood stoves,</td>
<td>Death/coma at very high levels</td>
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<tr>
<td></td>
<td>unvented gas/kerosene appliances</td>
<td>Headache, nausea, breathlessness</td>
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<td>Confusion/reduced mental alertness</td>
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<td>Low birth weight (foetal exposure)</td>
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<tr>
<td></td>
<td></td>
<td>Bronchial hyperresponsiveness</td>
</tr>
<tr>
<td>Volatile organic</td>
<td>Building materials and products such as new furniture, solvents, paint,</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>compounds</td>
<td>adhesives, insulation, cleaning activities and products, office materials</td>
<td>Asthma, dizziness, respiratory and lung diseases</td>
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<tr>
<td></td>
<td></td>
<td>Chronic eye, lung or skin irritation</td>
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<td></td>
<td></td>
<td>Neurological and reproductive disorders</td>
</tr>
</tbody>
</table>

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**Biological mechanisms**

Many recent studies have shown that oxidative stress, induced by air pollutants, plays a central role in the impact of air pollution. The first contact of inhaled ambient pollutants is with the fluid layer that covers the respiratory epithelium, and the responses following the exposure are mediated through oxidation reactions occurring within this fluid air–lung interface. These reactions can result in oxidative stress and consequent increased production of inflammatory mediators from human airway epithelial cells. Oxidative stress is a situation in which the oxidant–antioxidant balance is disturbed. This imbalance can occur when the generation of oxidant molecules (free radicals) exceeds the available antioxidant defences.

The three pollutants of most concern that can cause oxidative stress include NO, which is a free radical, PM10, and O3. The majority of human genetic association studies of air pollutants have examined O3 exposure. O3 is a powerful oxidant and reacts with the bronchial epithelium lining fluid to generate free radicals. It depletes levels of protective antioxidants and increases the production of inflammatory mediators.

The size and the surface of PM determine the potential to elicit oxidative damage. In general, the smaller the size of PM the higher the toxicity through mechanisms of oxidative stress and inflammation. Nanoparticles (ultratine particles with diameter <100 nm) are more toxic and inflammmogenic than fine particles. They generate reactive oxygen species to a greater extent and exacerbate pre-existing respiratory and cardiovascular disease, also through a dose–response effect.

Pulmonary impairment related to pollutants exposure may be higher in individuals who are genetically at risk for greater susceptibility to oxidative stress. The formation of reactive oxygen species is an important aspect of the inflammatory process of asthma, and genetic aberrations associated with antioxidants might explain the reason why some people with asthma seem at higher risk of exacerbations due to air pollution exposure.

**Conclusion**

Outdoor and indoor pollution greatly affect respiratory health worldwide as shown by many recent epidemiological studies.

Patient education about the importance of good indoor air quality in the home and workplace is essential. The support of healthcare providers and the general community for public health policy aimed at improving outdoor air quality through programmes to abate/reduce polluting emissions is also important. Moreover, there is evidence that increased antioxidant intake may protect against the effects of air pollution.

Hopefully, these actions will reduce the negative effects of air pollution on the respiratory health status and quality of life of the general population, in particular of the more susceptible individuals.

**References**

- Valavanidis A, et al. Airborne particulate matter and human health: toxicological assessment and importance of size and composition of particles for oxidative damage and carcinogenic


Tobacco use is by far the single largest avoidable cause of chronic illness and premature death worldwide. Smokers die of cancer of the lung and of other organs as well as of respiratory and cardiovascular diseases. In the European Union (EU), tobacco use kills at least 650,000 people (more than one in seven of all deaths) each year. Nearly 50% of these deaths involve diseases of the respiratory system, mainly lung cancer and chronic obstructive pulmonary disease (COPD). Given the relatively long period between time of smoking initiation (“first puff”) and time of onset of smoking-related lung disease (≥10 yrs), young people who start smoking often disregard future health risks of tobacco use. Unfortunately, while male smoking is declining in most European countries, female smoking rates are still on the rise in some parts of the EU, and in most other countries of the world, due to tobacco industry activism.

Tobacco smoke

Almost all tobacco-associated lung cancer and respiratory diseases result from smoke inhalation. In this respect, studies have shown that people who only use oral tobacco (such as Swedish snus, for example) during their lifetime are at no greater risk of developing these diseases than nonsmokers; however, the use of oral tobacco is related to several health problems, such as gum and pancreatic cancer and, possibly, cardiovascular diseases. Given that cigarette smoking is by far the most common method of tobacco consumption, the following data mainly concern diseases related to active cigarette smoking.

Cigarette smoke is composed of >4,000 substances, including nicotine, chemical poisons, toxic gases, small particles and carcinogens. The nicotine present in tobacco leaves is highly addictive but has little toxicity on the respiratory tract. Thus, people smoke for the psychoactive effects of nicotine, but die from the high toxicity of the other components present in smoke. Even if tobacco smoke composition varies slightly (due to tobacco type, substances added during manufacturing, filter type) the health risks and effects of tobacco smoking are quite constant from one cigarette brand to another. Furthermore, previously labelled “low tar/low nicotine” cigarettes have been shown to be as hazardous as “regular” ones. Likewise, hand-rolled cigarette, bidi, and water-pipe smoking are at least as dangerous as cigarette smoking. Finally, while pipe and cigar smoke is more toxic than cigarette smoke, cigar and pipe smokers are seldom deep inhalers. This explains the lower incidence of respiratory disease in these “noninhaling” smokers. Nevertheless, this rate is still higher than in nonsmokers.

Key points

- Tobacco use is responsible for more than one in seven out of all deaths in the EU.
- About 50% of tobacco-related deaths are due to lung cancer and COPD.
- Female smoking is still on the rise in some parts of the EU.
- Preventing tobacco use and treating tobacco addicts should be given top priority.
Cannabis smoke

In respect to effects on the respiratory tract, cannabis smoking is at least as dangerous as tobacco smoking. Moreover, since cannabis is usually smoked mixed with tobacco, young people often become addicted to tobacco for life, even occasional users merely seeking to experience the relaxing effects of tetrahydrocannabinol. This co-consumption of cannabis and tobacco complicates characterisation of the specific health effects of cannabis smoking. Nevertheless, it has been shown that cannabis smoking causes lung cancer and COPD.

Lung cancer

Lung cancer is the most frequent cause of death due to tobacco use: 85–90% of the 225,000 lung cancer deaths occurring each year in the EU are the consequence of tobacco smoking. Lung cancer is one of the deadliest cancers, with 5-yr survival rates ranging from 10–15%. Lung cancer incidence and mortality increase roughly in proportion to the first power of smoking intensity (number of cigarettes smoked per day) and, most importantly, to the second power of smoking duration (total number of years of smoking). Tobacco smoking results in all major histological types of lung cancer. Lung cancer risk is similar in males and females with comparable smoking histories. With such a highly specific cause and terrible prognosis, the best “treatment” of lung cancer is to avoid it through tobacco smoking prevention and treatment. Indeed, the relative risk of lung cancer steadily decreases when smokers give up smoking. For example, in the UK, for males who stopped smoking at ages 30, 40, 50 and 60, the risk of lung cancer by age 75 yrs was 2, 3, 6 and 10%, respectively; whereas for males who smoked up to 75 yrs of age this cumulative risk reached 16%. In the same way, an increase in overall tobacco consumption by a population is followed by an increase of lung cancer incidence, while a fall in consumption is followed by a drop in lung cancer incidence, as shown for males in France between 1950 and 2006 (fig. 1).

Figure 1. Trends in cigarette smoking (—) and death by lung cancer (-----) by sex in France, 1950–2006. Modified from Hill et al. (2010).

COPD and asthma

In 2000, ~30% of the 371,000 deaths from nonmalignant respiratory diseases occurring in the EU were caused by cigarette smoking. Among these cases, COPD was the most frequent cause of death. Nearly two-thirds of these COPD deaths were caused by tobacco smoking. The COPD mortality rate is roughly 20 times higher among heavy smokers (male or female) than nonsmokers. According to international guidelines for COPD classification (American Thoracic Society, 1987).
European Respiratory Society), up to 60% of current smokers aged >65 yrs suffer from COPD. Measurement of forced expiratory volume in 1 s (FEV1) and of its decline is the best marker of airflow limitation in COPD, and FEV1 value is directly related to COPD morbidity and mortality. Physiological decline of FEV1 with age is accelerated by tobacco smoking, whereas, in contrast, smoking cessation slows lung function decline in smokers (fig. 2). Cessation also improves COPD patient quality of life, and is the only measure that definitively improves COPD patient survival. Asthmatic patients who smoke have a higher risk of hospitalisation for their disease and experience more severe symptoms with poor clinical control and poorer quality of life. Finally, active cigarette smoking is a direct cause of asthma onset, and causes more severe symptoms and lung function decline.

**Respiratory infectious diseases**
Bronchial and lung infectious diseases, including tuberculosis, acute bronchiolitis, pneumonia, the common cold, and influenza are more frequent and more severe in smokers.

**Interstitial lung diseases**
Several interstitial lung diseases, namely, respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonia, and pulmonary Langerhans’ cell histiocytosis are strongly associated with cigarette smoking.

**Passive smoking**
In addition to its direct harmful effects on active smokers, exposure to tobacco combustion products from smoking is dangerous to nonsmokers, as environmental tobacco smoke is highly toxic. In the EU, in

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**Figure 3. Survival of male doctors who stopped smoking at ages 25–34 and 45–54 yrs. Modified from Doll et al. (2004).**
2002, an estimated 79,449 deaths were attributable to passive smoking from various diseases caused by second-hand smoking, including lung cancer (13,241 deaths), chronic non-neoplastic respiratory disease (5,275 deaths), ischaemic heart disease (32,342 deaths), and stroke (28,591 deaths).

Furthermore, COPD, asthma, and several infectious diseases are more severe in nonsmokers exposed to passive smoking.

**Conclusion**

Since current treatments of lung cancer and COPD are poorly efficient, it is obvious that preventing tobacco use through tobacco control and treating tobacco addiction are by far the most efficient means to prevent and "cure" these respiratory diseases. This conclusion is also true for most other diseases related to cigarette smoking. Indeed, the overall impact of smoking cessation on survival is significant for all smokers at any age, as shown in fig. 3.

**References**

TREATMENT OF TOBACCO DEPENDENCE

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Tobacco dependence is a disease that would be of little consequence if it were not for adverse effects of smoking. Instead it causes 30–40% of all cancers and is the principal cause of lung cancer. It is the biggest cause of preventable respiratory disease, even if lung and other respiratory cancers are excluded: smoking is linked causally or as an important risk factor to chronic obstructive pulmonary disease (COPD), emphysema, asthma and respiratory infections including tuberculosis. Nevertheless, to speak of smoking as an occupational or environmental disease is perhaps not entirely accurate. Without doubt, however, smoking prevalence has a strong occupational bias. Exposure to second-hand smoke at work is also a significant occupational hazard. This situation has been greatly improved by the enactment of smoke-free laws in many countries, especially within the European Union. Second-hand smoke remains, however, the most significant indoor pollutant, especially in homes and motor cars.

Treating tobacco dependence is an important issue for respiratory physicians. An interest in the prevention of dependence through tobacco control mechanisms should also be a priority.

Prevention

As always, prevention is the primary intervention to be considered. The mechanisms for tobacco control are well established and incorporated in the Framework Convention for Tobacco Control (FCTC), which is the first medical treaty of the World Health Organization (WHO) and has been ratified by 168 countries. The WHO has also proposed a strategy, MPOWER, for these mechanisms' implementation and monitoring. It is clearly stated in the FCTC that price is the most effective tobacco control measure but that interventions such as workplace restrictions on smoking, protection from exposure and product regulation by various means are important. It is also agreed that proper information about the dangers of smoking needs to be made known. The value of health warnings, especially graphic image warnings is emphasised and there is a realisation that packaging and labelling are important methods of advertising for the tobacco industry. This is especially so in countries where direct advertising and

Key points

- Tobacco dependence is a disease and is an important issue for respiratory physicians.
- The prevention of tobacco dependence through tobacco control mechanisms is a priority.
- Effective and cost-effective treatments for tobacco dependence exist in the form of motivational support and pharmacotherapy.
- The treatment of tobacco dependence benefits from knowledge, experience and training, which is not provided in medical schools at undergraduate level, and that should be a priority.
promotion and sponsorship are banned. However the role of treating smoking in the plan, although regarded as important, is left unclear. The reasons for this are many and include considerations of availability, cost, efficacy and efficiency. This is not surprising but is challenging. Even more challenging is the fact that the costs of other evidence-based interventions are usually much smaller than those of treatment. This may also be true of some other diseases, for which treatments are much better developed. The cost-effectiveness of treatment of tobacco dependence as a disease in patients without other diseases may not be obvious: the time lag between the treatment and the prevention of serious physical disease may obscure comparisons with the treatments of other diseases. However, effective treatments are available, are very cost-effective and compare very well with treatment of other diseases in this regard. Despite this, interest in supplying this service seems to be low among policymakers. Smoking was, and to some extent still is, not accepted as a disease by many people. This is in no small part due to the tobacco industry. For generations, it denied that smoking was harmful and addictive and emphasised the free choice argument and the apparent glamour of smoking. It is now becoming widely accepted that smoking is a disease and that it is based on addiction. It is very difficult to treat but the rewards for treating it successfully are enormous.

One-third of the population of the world smokes. If this disease is to be tackled by treating all smokers, the implications are daunting: treatment alone will probably never become the appropriate response to this epidemic, unless much better and cheaper treatments can be developed to make this possible in the future. At present treatment has a defined role. Its importance in tobacco control will vary from time to time and from country to country depending on the stage of implementation of tobacco control policies. Our first responsibility as doctors is probably to know what treatments exist, then to examine the evidence base for their usefulness and consider how they could be made available to our patients.

Evidence-based treatments

Effective and cost-effective treatments for smoking exist. The two treatment modalities proven to be effective consist of motivational support, in the form of counselling, and pharmacotherapy. Present knowledge suggests that a combination of the two is more effective than either alone. The duration of counselling seems to be important. Within limits, longer seems better – for instance, brief intervention by a general practitioner of some 3 min increases success rates by ~2.5% when compared with those who did not receive such advice. Sessions lasting ~10 min and repeated three to four times at intervals according to present knowledge seem to be near optimal, but these considerations need further defining and application.

As regards pharmacological therapies, a number of preparations have been shown to have measurable success rates. These include nicotine replacement therapy (NRT), which approximately doubles success rate. Varenicline and bupropion also have established success rates. Varenicline seems to be more effective than NRT, while bupropion’s success rate is similar to that of NRT. The use of these preparations and their safety profiles need to be studied carefully. They provide the clinician with pharmacotherapy which has proven efficacy and should be used knowledgably by physicians. Tønnessen (2009) recently reviewed the evidence for smoking cessation, concluding that with the most optimal drugs and counselling a 1-yr abstinence rate of ~25% can be expected in smoking cessation. This compares very favourably with the treatment of any other chronic relapsing disease. Caponnetto and Pulos (2008) recently outlined the predictors of success and failure in treatment. Factors which influence outcomes include degree of nicotine dependence, age at initiation, how many cigarettes are smoked per day, social support and family circumstances, such as a nonsmoking partner, sex and comorbidities.
such as alcoholism and depression. They also point out the complex relationship with previous attempts and of course the importance of motivation to quit.

In addition, evidence suggests that quit attempts are more frequent in subjects with high baseline body-mass index and low weight concerns. Innovative approaches, such as brief isometric exercise and the cognitive technique of body scanning, may be effective for reducing desire to smoke and withdrawal symptoms in temporarily abstaining smokers.

**Conclusion**

The treatment of tobacco dependence benefits from knowledge, experience and training. This is not provided in medical schools at undergraduate level. We expect that the structure of training for the management of this disease and particularly its treatment will improve and increase in the short term. Knowledge of general tobacco control principles will also need attention if we are to succeed in this important endeavour.

**References**


**Weblink**

HIGH-ALTITUDE DISEASE

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Physiological response to altitude

The low barometric pressure at altitude results in a reduced inspiratory and arterial oxygen tension. The immediate physiological response comprises a rise in heart rate and pulmonary arterial pressure. Chemoreceptor-mediated hyperventilation tends to mitigate hypoxaemia but the associated hypocapnia with an arterial carbon dioxide tension close to the apnoeic threshold promotes ventilatory instability with periods of hyperpnoea alternating with central apnoea/hypopnoea. This pattern, termed high-altitude periodic breathing, is observed in healthy subjects at altitudes >2,000 m mostly during sleep. It may cause intermittent dyspnoea and sleep disturbances (figs 1 and 2).

Prolonged altitude exposure triggers various acclimatisation mechanisms including an increased chemoreceptor sensitivity to hypoxia and hypercapnia, enhanced erythropoesis and alterations in the endocrine system, metabolism and in fluid balance.

The reduced air density at altitude lowers airflow resistance. Vital capacity is slightly reduced due to respiratory muscle weakness and pulmonary congestion. Oxygen uptake through the lungs is affected by a reduced alveolar-capillary oxygen gradient and a reduced transit time of blood through pulmonary capillaries due to increased cardiac output. This causes diffusion limitation leading to hypoxaemia especially during exercise.

High-altitude-related disease

Acute mountain sickness (AMS) is the most common altitude-related illness. It affects 10–40% of lowlanders ascending to 3,000 m and 40–60% at 4,500 m. A lack of prior acclimatisation, rapid ascent, high sleeping altitude and individual susceptibility predispose to AMS. Symptoms start within 6–12 h after arrival at altitude and include headache, loss of appetite, nausea or vomiting, weakness, fatigue and insomnia. The diagnosis relies on the constellation of typical symptoms in the setting of altitude exposure. Different scores (e.g. the Lake Louise Score) help to establish the diagnosis and to grade AMS severity. If additional neurological signs such as ataxia, cognitive deficits and impaired vigilance develop, a

Key points

- A low barometric pressure at altitude results in reduced inspired and arterial oxygen partial pressures.
- Hypoxaemia triggers adaptive physiological responses termed acclimatisation.
- Respiratory acclimatisation includes hyperventilation and periodic breathing, which typically prevails during sleep.
- Acute mountain sickness, high-altitude cerebral oedema and high-altitude pulmonary oedema may affect travellers after rapid ascent to altitude. Chronic mountain sickness occurs in long-term residents of high mountain areas.
- Treatment of high-altitude related illness consists of descent, supplemental oxygen and drugs.
potentially life-threatening high-altitude cerebral oedema (HACE) must be considered. Treatments of AMS include descent to lower altitude, analgesics for headache and acetazolamide. More severe forms of AMS and HACE require dexamethasone and oxygen if available. Inflatable hyperbaric bags simulating descent to 1,500–2,500 m are also used.

High-altitude pulmonary oedema (HAPE) is a noncardiogenic and noninflammatory oedema resulting from excessive elevation of pulmonary capillary pressure, uneven distribution of blood flow and impaired alveolar fluid clearance. HAPE is rare below 3,500 m but occurs in 2–4% of mountaineers within hours to 4 days after arrival at 4,500 m. It is promoted by rapid ascent, physical exertion and individual susceptibility. Manifestations of HAPE include excessive dyspnoea, dry cough, tachycardia, cyanosis, pulmonary crackles and low-grade fever. Chest radiography shows interstitial or alveolar opacities but a normal-sized heart. Descent, supplemental oxygen or both are nearly always successful in HAPE. If oxygen is not available or descent not possible, pharmaceuticals become necessary (table 1). Pulmonary vasodilators such as nifedipine or phosphodiesterase inhibitors (sildenafil) lower pulmonary artery pressure. If descent is

Figure 1. Mechanisms of high-altitude periodic breathing.

Figure 2. Periodic breathing associated with oscillations in oxygen saturation and heart rate recorded in a 28-yr-old women resting after a climb at 6,850 m. Modified from Bloch et al. (2010), with permission from the publisher.
impossible and oxygen unavailable a hyperbaric bag may be life-saving.

Table 1 summarises prevention and treatment of altitude related diseases.

Chronic mountain sickness, a condition observed in long-term high altitude residents, is characterised by severe hypoxaemia, excessive erythrocytosis and pulmonary hypertension. Affected people suffer from fatigue, dizziness, headache and confusion. Descent to low altitude leads to prompt relief.

Patients with lung disease at altitude

Little is known about the risks of altitude exposure in patients with pre-existing lung disease. Recommendations are largely based on anecdotal evidence.

Chronic obstructive pulmonary disease In patients with impaired gas exchange, arterial oxygen tension may drop to low levels at altitude so that the use of supplemental oxygen should be considered. It seems reasonable that patients with severe disease (forced expiratory volume in 1 s <50% predicted) with an arterial oxygen saturation <95% at low altitude should have an individual assessment before travelling to altitude. Acetazolamide should be used with caution in patients with severe airflow obstruction since carbon dioxide retention may lead to worsened dyspnoea or respiratory failure.

Asthma A reduced allergen burden with increasing altitude can be expected at >1,500 m. Conversely, inhalation of cold air may worsen asthma, especially in combination with exercise or hypoxia-induced hyperventilation. Asthma patients with controlled disease are advised to take their usual medications when travelling to altitude, to avoid

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Table 1. Prevention and treatment of high-altitude disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevention</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>Acute mountain sickness (AMS)</td>
<td>Acclimatisation</td>
<td>Analgesics, antiemetics</td>
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<tr>
<td></td>
<td>Slow ascent</td>
<td>Acetazolamide 2 × 125-250 mg·day⁻¹,</td>
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<td></td>
<td>Acetazolamide 2 × 125-250 mg·day⁻¹,</td>
<td>starting 24 h before ascent</td>
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<tr>
<td></td>
<td>or dexamethasone 2 × 4 mg·day⁻¹ 24 h</td>
<td>before ascent</td>
</tr>
<tr>
<td>High-altitude cerebral oedema (HACE)</td>
<td>As for AMS</td>
<td>Immediate descent. If not possible: Oxygen (2-6 L·min⁻¹),</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Portable hyperbaric chamber</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dexamethasone (initially 8 mg i.v., then 4 × 4 mg·day⁻¹ p.o.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acetazolamide (2 × 250 mg·day⁻¹), eventually in combination with dexamethasone</td>
</tr>
<tr>
<td>High-altitude pulmonary oedema (HAPE)</td>
<td>Acclimatisation</td>
<td>Immediate descent. If not possible: Oxygen (2-6 L·min⁻¹),</td>
</tr>
<tr>
<td></td>
<td>Slow ascent</td>
<td>Portable hyperbaric chamber</td>
</tr>
<tr>
<td></td>
<td>Avoid overexertion</td>
<td>Dexamethasone (initially 8 mg i.v., then 4 × 4 mg·day⁻¹ p.o.)</td>
</tr>
<tr>
<td></td>
<td>Nifedipine 30–60 mg·day⁻¹ (extended-release formulation)</td>
<td>Check for accompanying HAPE, acetazolamide if descent delayed</td>
</tr>
</tbody>
</table>

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ERS Handbook: Respiratory Medicine
strenuous exercise in a cold environment and to treat any exacerbation appropriately. Patients with uncontrolled, severe asthma should be cautioned against travelling to altitude.

**Obstructive sleep apnoea syndrome** Untreated patients residing at sea-level and travelling to moderate altitude (2,500 m) revealed an exacerbation of sleep apnoea with pronounced hypoxaemia and frequent central events. Sleep quality was worse at altitude and daytime testing revealed impaired vigilance and elevated blood pressure. Combined treatment with continuous positive airways pressure ventilation and acetazolamide seems advisable.

**Pulmonary hypertension** In general, patients with more than mild pre-existing pulmonary hypertension should be counselled against high-altitude travel because pre-existing pulmonary hypertension may predispose to HAPE. In patients not on medical therapy, prophylaxis with nifedipine and supplemental oxygen should be considered.

**Conclusions**

Physiological adaptation allows humans to tolerate exposure to even very high altitudes. Rapid ascent, inappropriate time for acclimatisation, strenuous physical exertion and individual susceptibility predispose to high-altitude-related illnesses, which may be prevented with appropriate precautions.

**References**

DIVING-RELATED DISEASES

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Professional divers are engaged in underwater construction and inspection, and compressed air workers (Caisson workers) work at increased ambient pressure in a dry environment, mostly in tunnel construction. Military forces, police and fire brigades have teams of divers for specialised underwater operations. Recreational divers make up by far the largest group of divers. The physical environment in which these divers are operating is different, but common to all groups is exposure to increased ambient pressure and the exposure factors associated with pressure.

Pulmonary limitations at depth

Gas density increases proportionately with ambient pressure when air is used as the gas breathed. Airway resistance is proportional to gas density and maximal expiratory flow rates are inversely proportional to the square root of gas density. This means that at a depth of 30 m, when relative gas density is four times that of air at atmospheric pressure, maximal expiratory flow rates and maximal voluntary ventilation are reduced by 50%. Most experimental data are close to this theoretical relationship, as illustrated in fig. 1.

When diving to depths >50 m, the gas breathed is often a mixture of helium and oxygen to compensate for the mechanical limitations of ventilatory capacity due to gas density. The partial pressure of oxygen in these gas mixtures is usually 30–50 kPa, corresponding to a fraction of oxygen of 2–5% at depths of ≥100 m.

Physical work under water is demanding. A normal ventilatory capacity and physical work capacity evaluated by exercise testing are required. External resistance and static load related to breathing apparatus and submersion adds to the increased load imposed by gas density. The gas breathed at depth has to be dry to prevent icing in the pressure regulators and evaporative heat loss is high. The gas breathed has the temperature of ambient water and, because of increased gas density, convective heat loss is increased. Subjects with bronchial hyperreactivity may be at increased risk of bronchoconstriction at depth. There are, however, no definite studies confirming this risk as subjects with asthma traditionally have been excluded from diving.

Pulmonary barotrauma

Intra-alveolar gas volume will expand during decompression. If there is any obstruction to the free flow of gas out of the alveoli or a decrease in lung compliance, there will be an increase in intra-alveolar pressure imposing a risk for lung rupture or pulmonary barotrauma. Any processes in the lung associated with airway obstruction or

Key points

- Normal lung function and physical work capacity are required for underwater work.
- Normal lung function is required to reduce the risk of pulmonary barotrauma.
- Cumulative diving exposure is associated with a long-term reduction in lung function of an obstructive pattern, which at some time in the career may preclude further diving.
decreased compliance locally or generally are considered to increase the risk. Lung rupture may cause pneumothorax, pneumopericardium, mediastinal emphysema and most seriously arterial gas embolism, which may be fatal. A pneumothorax or pneumopericardium encountered at depth may be fatal because of an increase in the transpulmonary pressure difference during decompression that obstructs venous return. The lowest pressure drop associated with diving causing pulmonary barotrauma described in the literature was 20 kPa (or 200 cmH₂O). The volume expansion for a given pressure reduction is larger close to the surface (Boyle–Mariotte’s law).

**Pulmonary effects of a single dive**

A dive is associated with exposure to hyperoxia and a decompression stress, and both are related to ambient pressure and time. Hyperoxia at partial pressures of oxygen >40 kPa has well known toxic effects on the lung causing acute reductions in diffusion capacity, vital capacity and maximal expiratory flow rates. The decompression stress is related to the amount of inert gas dissolved in the tissues during the bottom phase of the dive and the rate of decompression. Supersaturation resulting in formation of venous gas bubbles has been demonstrated when the tension of inert gas in the tissues exceeds ambient pressure by ~30 kPa. Venous gas microemboli have been shown to be common with the decompression procedures routinely used in commercial and military diving operations.

The venous gas microemboli are filtered in the pulmonary circulation and are associated with inflammatory responses that add to toxic effects of hyperoxia. Venous gas microemboli may be shunted over to the systemic circulation through intrapulmonary and intracardiac shunts. A patent foramen ovale is present in 20–30% of the general population. Local circulatory disturbances due to gas bubbles that are either formed in situ or transported by the systemic circulation to other areas like joints, skin, brain and spinal cord may cause decompression sickness.

The combination of added static and dynamic respiratory load, immersion and exercise results in a large increase in pulmonary arterial pressure. Undue breathlessness after diving, or even swimming only, may be related to pulmonary oedema.

**Long-term effects of diving**

The exposure to hyperoxia and the accumulation of gas microemboli in the lung are associated with inflammatory responses. Several cross-sectional studies of divers’ lung function indicate that residual effects of single dives accumulate to a long-term effect characterised by an obstructive spirometric pattern and a reduction in diffusion capacity. There are only a few longitudinal studies of divers’ lung function, but these studies confirm the findings in the cross-sectional studies by demonstrating a negative relationship between cumulative diving exposure and maximal expiratory flow rates and forced expired volume in 1 s.

**References**

Radiotherapy plays an important role in the treatment of tumours located in the thoracic area. The cure rate for these tumours is, however, limited by the low radiation dose that can be tolerated by the lungs. The presently set dose already results in pulmonary complications in about one-fifth of patients.

Radiation-induced lung injury develops in an early inflammatory phase termed radiation pneumonitis (RP) followed by a late fibroproductive phase (fig. 1). These phases lead to compromised lung perfusion, increased vascular resistance, reduced gas-exchange interphase between air and blood, and suboptimal blood oxygenation. Symptoms range from dyspnoea on effort to respiratory failure, oxygen dependency, right heart failure and death.

Several inflammatory responses contribute to RP. Acute alveolar and interstitial inflammation and loss of type I epithelial induces proliferation of type II epithelial cells. This leads to a cascade of induction of inflammatory cytokines (fig. 1), potentially aggravated by chemotherapeutic agents. Subsequently, an influx of inflammatory cells,

**Key points**

- Radiotherapy for tumour treatment results in pulmonary complications in about 20% of patients.
- Radiation-induced lung injury develops from an early, inflammatory phase to a late fibrotic phase.

Figure 1. Radiation-induced lung injury develops in an early inflammatory and late fibrotic phase. Black line: pneumonitis; red line: fibrosis; blue line: cytokine response.
such as leukocytes, lymphocytes, neutrophils and macrophages, is induced. Though macrophages are a hallmark, T-lymphocytes and matured dendritic cells also play an important role in RP.

Radiation-induced lung disease is a consequence of:

- loss of type I epithelial and endothelial cells
- inflammatory responses
- malfunction of microvasculature
- lung fibrosis.

In addition, malfunction of the microvasculature due to endothelial injury and subsequent increased permeability with protein exudation contributes to the development of RP. Depending on the irradiated region and volume, the inflammatory response may affect only pulmonary blood vessels (low dose, large volumes) or vessels and parachyma (high dose, low volumes) to induce complications.

Following or even without prior symptomatic pneumonitis, chronic radiation-induced pulmonary fibrosis (RF) may develop depending on the irradiated lung volume. RF is caused by accumulation of collagen and other extracellular matrix fibres in the interstitium under persistent cytokine stimuli in combination with arterio-capillary sclerosis.

References

CHAPTER 11:

INTERSTITIAL LUNG DISEASE

SARCOIDOSIS
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D. Olivieri, S. Chiesa and P. Tzani 311

EOSINOPHILIC DISEASES
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DRUG-INDUCED RESPIRATORY DISEASE
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Sarcoidosis is a multisystem granulomatous disorder of unknown aetiology, which commonly affects young and middle-aged adults. The disease frequently presents with bilateral hilar lymphadenopathy, pulmonary infiltration, and ocular and skin lesions. Any organ of the body may be involved. The prevalence rates of Sarcoidosis vary widely, from <1 case to 40 cases per 100,000 population. Sarcoidosis is common in Scandinavia, Central Europe, the USA and Japan. It is less frequently seen in other Asian countries, Central and South America, and Africa. Sarcoidosis in Afro-Americans is more severe, while Caucasians are more likely to present with asymptomatic disease. Overall mortality is 1–5%.

The cause of sarcoidosis remains unknown. Available evidence strongly supports the hypothesis that the disease develops when a specific environmental exposure with antigenic properties occurs in a genetically susceptible individual. Potential aetiologic agents include mycobacteria and Propionibacterium acnes. Sarcoidosis susceptibility or chronicity has been associated with a number of human leukocyte antigen alleles. Some genetic associations have been found with specific disease subsets, most notably with Löfgren’s syndrome. A polymorphism of the BTN2L gene has been linked with sarcoidosis. The immunological abnormalities are characterised by the accumulation of activated T-cells of the T-helper cell type 1 and macrophages at sites of ongoing inflammation.

Clinical presentation

The clinical presentation of sarcoidosis varies widely. 30–50% of patients are asymptomatic at the time of diagnosis. Symptoms of sarcoidosis are largely nonspecific. Low-grade fever (sometimes up to 40°C), weight loss (usually limited to 2–6 kg during the 10–12 weeks before presentation), night sweats and arthralgias can be found in about 20–30% of patients. Sarcoidosis is an important and frequently overlooked cause of fever of unknown origin. Fatigue and skeletal muscle weakness are more common; present in ≤70% of patients when carefully looked for. According to their initial presentation, sarcoidosis patients can be divided into two

Key points

- Sarcoidosis is a multisystem granulomatous disorder of unknown aetiology, which commonly affects young and middle-aged adults.
- Prevalence of sarcoidosis varies from <1 case to 40 cases per 100,000 population, and overall mortality is 1–5%.
- Clinical presentation varies widely, though fever, fatigue and skeletal muscle weakness are often noted.
- Decision to treat should be carefully assessed based on benefit to the patient and disease severity; treatment should mainly be considered if symptoms develop or lung function deteriorates.
- The clinical course of sarcoidosis can be unpredictable, so regular monitoring of signs of disease progression is advised.
distinct subgroups: acute and chronic. The acute form can present as classical Löfgrens syndrome, which is characterised by fever, bilateral hilar lymphadenopathy, ankle arthritis and erythema nodosum. The chronic form shows an insidious onset, and organ-related symptoms predominate, such as cough, dyspnoea, and chest pain.

**Diagnostic approach**

The criteria of the American Thoracic Society (ATS), European Respiratory Society (ERS), and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) for the diagnosis of sarcoidosis include:

- The presence of a consistent clinical and radiological picture
- Histological evidence of non-caseating granulomas
- Exclusion of other conditions capable of producing a similar histological or clinical picture

The initial diagnostic work-up for patients with suspected sarcoidosis involves careful baseline assessment of disease distribution and severity by organ, with emphasis on vital target organs (table 1). Specifically, the diagnostic assessment should attempt to accomplish four goals:

- Provide histological confirmation of the disease
- Assess the extent and severity of organ involvement
- Assess whether the disease is stable or is likely to process
- Determine whether therapy will benefit a patient

Granuloma alone are never diagnostic proof of sarcoidosis.

An important step is choice of site for a proper biopsy. Transbronchial lung biopsy is the recommended procedure in most cases, with the diagnostic yield reaching 80%. This can be combined with transbronchial needle aspiration, which has the highest yield when guided by endobronchial ultrasound, and with biopsy of the bronchial mucosa. Other easily accessible sites for biopsy are the skin, lip, or superficial lymph nodes. In patients without biopsy, clinical and/or radiological features alone may be diagnostic in stage I (reliability of 98%) or stage II (89%), but are less accurate in stage III (52%) or stage 0 (23%). The classical Löfgren’s syndrome may not require biopsy proof. Bronchoalveolar lavage and studies of lymphocyte subpopulations showing an increase in the CD4/CD8 ratio may be helpful. Elevated serum angiotensin-converting enzyme and calcium levels may lend support to the diagnosis.

The chest radiogram is described in 4 stages (table 2). Computed tomography scanning describes much greater detail of mediastinal and parenchymal abnormalities, but is not an essential of baseline study. It is indicated when clinical presentation and/or chest radiographic findings are unclear or to detect complications of the lung disease.

**Natural history and prognosis**

The disease course is highly variable. Spontaneous remissions occur in nearly two thirds of patients. Serious extrapulmonary involvement (cardiac, central nervous system, hepatic) occurs in 4–7% of patients at time of presentation. Incidence becomes higher as the disease evolves. Adverse prognostic factors include lupus pernio, chronic uveitis, age at onset >40 yrs, chronic hypercalcaemia, nephrocalcinosis, African ethnic origin, progressive pulmonary sarcoidosis, nasal mucosal involvement, cystic bone lesions, neural sarcoidosis, cardiac sarcoidosis, and chronic respiratory insufficiency.

**Treatment and follow-up**

The indication to treat a patient depends on many factors, the most important being whether or not the patients is symptomatic. Except for life- and sight-threatening organ involvement, it should be carefully considered whether the patient might benefit from treatment. For asymptomatic pulmonary
patients, a watch-and-wait approach is appropriate; treatment should mainly be considered if symptoms develop or lung function deteriorates. The goal of treatment is to make the patient asymptomatic and to restore or preserve organ function. Initial therapy is still based on corticosteroids. For pulmonary sarcoidosis, the initial prednisone dose is 20–40 mg; higher doses may be needed for cardiac or neural sarcoidosis. The dose is slowly tapered to 5–10 mg per day; treatment should be continued for a minimum of 12 months. Patients with Löfgren’s syndrome do not require therapy with corticosteroids.

For patients with chronic disease requiring years of therapy, alternatives to corticosteroids include methotrexate, azathioprine and hydrochloroquine, all given usually in combination with low dose corticosteroids. For refractory sarcoidosis patients, new therapeutic approaches have begun to emerge through the use of immuno-modulatory agents. Based on current understanding of pathogenic mechanisms, these are tumour necrosis factor-α-blocking drugs, such as infliximab, thalidomide, and pentoxifyllin.

Because the clinical course of sarcoidosis can be unpredictable, regular monitoring for signs of disease progression is necessary, using the least invasive and most sensitive tools. For pulmonary sarcoidosis, this is spirometry and diffusion capacity. For stable stage I disease, follow-up every 6–12 months is usually adequate; more frequent evaluations (every 3–6 months) are advised for stage II, III or IV sarcoidosis. All patients should be monitored for a minimum of 3 yrs after therapy is discontinued. Follow-up needs to be more vigilant after corticosteroid-induced remissions, due to the high rate of relapses in this context, ranging 15–70%.

References


Table 1. Initial evaluation for sarcoidosis

<table>
<thead>
<tr>
<th>History (occupational and environmental exposure, symptoms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination</td>
</tr>
<tr>
<td>Chest radiography</td>
</tr>
<tr>
<td>Pulmonary function tests: vital capacity, FEV₁, carbon monoxide diffusion capacity</td>
</tr>
<tr>
<td>Peripheral blood counts</td>
</tr>
<tr>
<td>Serum chemistries: calcium, liver enzymes, creatinine, ACE</td>
</tr>
<tr>
<td>Urine analysis</td>
</tr>
<tr>
<td>Electrocardiography</td>
</tr>
<tr>
<td>Eye investigation</td>
</tr>
<tr>
<td>Tuberculin skin test</td>
</tr>
<tr>
<td>Selection of site for biopsy</td>
</tr>
</tbody>
</table>

FEV₁: forced expiratory volume in 1 s; ACE: angiotensin-converting enzyme.

Table 2. Chest radiographic stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>Findings</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>5–10%</td>
</tr>
<tr>
<td>I</td>
<td>BHL</td>
<td>50%</td>
</tr>
<tr>
<td>II</td>
<td>BHL and parenchymal infiltrates</td>
<td>25%</td>
</tr>
<tr>
<td>III</td>
<td>Parenchymal infiltrates without BHL</td>
<td>15%</td>
</tr>
<tr>
<td>IV</td>
<td>Sign of fibrosis</td>
<td>5–10%</td>
</tr>
</tbody>
</table>

BHL: bilateral hilar lymphadenopathy
Idiopathic interstitial pneumonias (IIPs) represent a heterogeneous group of disorders with different clinical and histological features and prognoses. They are considered as inflammatory disorders of the interstitium without extrapulmonary involvement.

The most recent American Thoracic Society (ATS) and European Respiratory Society (ERS) classifications of IIPs include seven different diseases identified by a typical histological pattern; each histological pattern meets precise clinical and radiological features and corresponds to a particular prognosis.

**Epidemiology**

The incidence of IIPs has been estimated at 7–11 cases per 100,000 persons while the prevalence ranges between 27–29 cases per 100,000 persons. The disease typically affects adults, peaking after the sixth decade of life, with a higher incidence in males and smokers. There is a familial variant of idiopathic pulmonary fibrosis (IPF), which accounts for 0.5–3% of cases of IIPs; this form is indistinguishable from the nonfamilial forms, except that patients tend to be younger in the former.

**Clinical features and treatment**

The IIPs include IPF, nonspecific interstitial pneumonia (NSIP), cryptogenic organising pneumonia (COP)/bronchiolitis obliterans organising pneumonia (BOOP), acute interstitial pneumonia (AIP), respiratory bronchiolitis/interstitial lung disease (RB/ILD), desquamative interstitial pneumonia (DIP)/alveolar macrophage pneumonia (AMP) and lymphoid interstitial pneumonia (LIP) (table 1).

Some of these entities have been well identified clinically, as well as the appropriate corresponding treatments. In particular, when the inflammatory component dominates, such as in DIP/AMP, AIP and COP/BOOP, prompt corticosteroid therapy may lead to a significant improvement and sometimes to complete resolution of the disease.

LIP and AIP require prompt intervention by the haematology and intensive care units (ICU) respectively, because of their particular onset and the necessity of a specific therapeutical approach.

Nowadays the terms IPF and NSIP should be used only for chronic fibrosing interstitial

---

**Key points**

- IIPs represent a heterogeneous group of disorders with different clinical and histological features and prognoses.
- The most recent ATS and ERS classifications of IIPs include seven different diseases identified by a typical histological pattern: NSIP, COP/BOOP, AIP, RB/ILD, DIP/AMP and LIP.
- The terms IPF and NSIP should only be used for chronic fibrosing interstitial pneumonia of unknown cause limited to the lungs. The prognosis in IPF is worse with a histological pattern of UIP.
pneumonia of unknown cause limited to the lungs. This distinction is particularly relevant because of the different clinical aspects and therapeutic approaches. Moreover, the prognosis is worse in these forms and particularly in IPF with a histological pattern of usual interstitial pneumonia (UIP).

**Desquamative interstitial pneumonia/alveolar macrophage pneumonia**

DIP is characterised by its insidious onset, with a worsening dry cough and progressive dyspnoea. There is a strong correlation between this disease and cigarette smoking. The term “desquamative” originated from the belief that the principal histological feature was desquamation of epithelial alveolar cells; in fact, intra-alveolar macrophage accumulation and the presence of hyperplastic epithelial cells seem to be the dominant aspects of the disease. Radiological features include ground-glass opacities with a lower zone predilection. The pathogenesis is unclear and the clinical course may vary: most patients improve with steroid treatment, but some may develop fibrosis.

**Respiratory bronchiolitis/interstitial lung disease**

This form affects primarily current or former smokers, especially males. Symptoms are mild and aspecific. The principal histological aspect is the presence of clusters of brown macrophages in the respiratory bronchioles, alveolar ducts and peribronchial alveolar space. Usually, smoking cessation leads to a complete resolution of the lesions. Steroid treatment may be necessary.

**Acute interstitial pneumonia**

AIP is a rare fulminating form of lung injury, with clinical and radiological findings similar to those seen in acute respiratory distress syndrome (ARDS). The disease evolves through three phases. First the exudative phase (from the onset to the 7th day) showing oedema, hyaline membranes and acute interstitial inflammation. The proliferative phase (30th day) is then characterised by hyperplasia of type 2 pneumocytes. Finally, the organising phase shows loose organising fibrosis mostly with type II alveolar septa. Hypoxaemia develops early and progresses rapidly to respiratory failure, which may be refractory to supplemental oxygen, whereby AIP requires prompt treatment in the ICU.

**Cryptogenic organising pneumonia/bronchiolitis obliterans organising pneumonia**

COP/BOOP is a rare form of IIP of unknown aetiology. Features of the organising pneumonia pattern are organisation within alveolar ducts and alveoli, with or without organisation in bronchioles. The clinical onset is aspecific and includes dyspnoea, dry cough, fever and inspiratory crackles. Radiological aspects are bilateral diffuse alveolar opacities with a lower zone predilection and peripheral predominance. The characteristic histopathological lesion includes an excessive proliferation of granulation tissue within small airways and alveolar ducts associated with chronic inflammation in the surrounding alveoli. Systemic steroid therapy is the gold standard treatment when other causes of

<table>
<thead>
<tr>
<th>IPF/UIP</th>
<th>Idiopathic pulmonary fibrosis/usual interstitial pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIP/AMP</td>
<td>Desquamative interstitial pneumonia/alveolar macrophage pneumonia</td>
</tr>
<tr>
<td>RB/ILD</td>
<td>Respiratory bronchiolitis/interstitial lung disease</td>
</tr>
<tr>
<td>AIP</td>
<td>Acute interstitial pneumonia</td>
</tr>
<tr>
<td>COP/BOOP</td>
<td>Cryptogenic organising pneumonia/bronchiolitis obliterans organising pneumonia</td>
</tr>
<tr>
<td>NSIP</td>
<td>Nonspecific interstitial pneumonia</td>
</tr>
<tr>
<td>LIP</td>
<td>Lymphoid interstitial pneumonia</td>
</tr>
</tbody>
</table>

**Table 1. Classification of idiopathic interstitial pneumonias**

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bronchiolitis (i.e. infective bronchiolitis) are excluded.

**Lymphoid interstitial pneumonia**

LIP is more common in children than adults. The aetiology is unknown. Up to three quarters of patients present a monoclonal increase in gammaglobulin, whereas in childhood hypogammaglobulinemia may occur. LIP is associated with Sjögren's Syndrome in a quarter of cases. LIP is defined as an interstitial lymphoid infiltrate including lymphocytes, plasma cells and histiocytes, with associated type II cell hyperplasia and the presence of interstitial mononuclear cells and the formation of noncaseating granulomas. In LIP the infiltrate is characterised by the presence of polyclonal lymphocytes (T and B); by contrast, in the lymphomas the infiltrate is usually monoclonal. Radiological aspects are bilateral interstitial linear or nodular opacities; honeycombing may appear in the advanced phase of the disease. Spontaneous resolution is possible, but steroid and/or immunosuppressive therapy may be necessary.

**Idiopathic pulmonary fibrosis/usual interstitial pneumonia and nonspecific interstitial pneumonia**

**Pathogenesis** The pathogenetic mechanisms of IPF (pattern UIP) and NSIP are not completely clear. There are various hypotheses relative to the initial stimulus responsible for the pathogenetic process, such as exposure to toxic substances or viral infections. Regardless of the initial cause, the inflammatory-fibrotic process in UIP is characterised by injury to the alveolar epithelial cells, destruction of the subepithelial basement membrane, and the subsequent abnormal cicatrisation with increased fibroblastic response and excessive deposition of collagen and extracellular matrix.

The interplay between inflammatory and mesenchymal cells is regulated by a number of cytokines produced by fibroblasts and epithelial cells; the most important of these mediators are the transforming growth factor (TGF)-β, tumour necrosis factor (TNF)-α, platelet-derived growth factor, connective tissue growth factor, integrin-mediated intercellular adhesion molecules, proteases and oxygen radicals. Deficiency of interferon-γ may contribute to activating and perpetuating the fibroblastic process. As far as the histological aspect is concerned, the presence of fibroblastic foci is typical in UIP; the fibroblastic foci are formed by mesenchymal cells similar to myofibroblasts. Under the influence of TGF-β the cells increase the production of collagen, vimentin and actin, leading to an excessive deposition of extracellular matrix.

In the rare familial form, the transmission mode is unknown. It is likely to be autosomal dominant with variable penetration in two thirds of patients. Familial IPF has been associated with altered α1-antitrypsin inhibitor alleles on chromosome 14. Genetic polymorphism for interleukin (IL)-1 receptor antagonists or TNF-α may be involved.

**Physiology** The physiological aberrations in IPF are typical of a restrictive pattern and include reduced lung volumes (vital capacity and total lung capacity), and normal or increased expiratory flow rates. Transfer factor of the lung for carbon dioxide (TL,CO) is typically reduced, indicating damage to the interstitium causing impaired gas exchange. A further consequence of this alteration is hypoxaemia, which is exacerbated with exercise. Late in the course of the disease severe hypoxaemia may be observed also at rest; hypercapnia may be present as well.

**Clinical features and diagnosis** The initial insidious symptoms of IPF/UIP and NSIP are an insistent nonproductive cough and progressive dyspnoea. In most patients, physical examination reveals end-inspiratory crackles (velcro-type). The course of the disease may vary, in relation to the types of IIP. As far as UIP is concerned, prognosis is extremely severe; the course of the disease is rapid, even if some patients stabilise after an initial period of decline. Respiratory failure
appears in 3–8 yrs and mean survival from the onset of the disease is approximately 3–5 yrs. During the late phases of the disease, patients often show cor pulmonale. Respiratory failure is the main cause of death, followed by pulmonary embolism and heart failure.

Diagnosis of IPF and NSIP is the result of an integrated and multidisciplinary process, requiring cooperation among clinicians, radiologists and pathologists. International guidelines state that histology is necessary for diagnosis. A surgical lung biopsy has a higher diagnostic value compared to a transbronchial biopsy or bronchoalveolar lavage. However, it is an invasive approach with potential risks, and sometimes patients may present clinical and physiological contraindications to surgery. In some cases, an acute exacerbation of the disease follows surgery, leading to a general decline.

The most recent ATS/ERS guidelines present new clinical diagnostic criteria, which increase the likelihood of a correct diagnosis of IPF in the immunocompetent adult, in the presence of all the major criteria as well as at least three minor criteria, even without histological data (table 2).

High resolution computed tomography (HRCT) has become a crucial tool for the diagnostic process and allows an accurate and objective follow-up of the disease. HRCT scans consistent with IIP represent one of the major ATS/ERS guidelines diagnostic criteria. In particular, the HRCT scans in the case of UIP show a heterogeneous distribution with predilection for the peripheral, especially subpleural and basilar regions of the lung. The main radiological feature in UIP is honeycombing, that is cystic radiolucencies as expression of severe and irreversible fibrotic conversion of the parenchyma. Secondary features include coarse reticular opacities, thickened bronchial walls, bronchiectasis and bronchioloectasis.

NSIP is characterised by the presence of ground-glass areas, signifying an active inflammatory process. The main aspects to be considered for differential diagnosis between UIP and NSIP are the geographic and temporal histological and radiological heterogeneity, the high concentration of fibroblastic foci and honeycombing in the UIP form.

**Natural history and exacerbations** The course of the disease is characterised by a progressive decline in pulmonary function, leading to a worsening general condition and ultimately death. A subset of patients, particularly in cases of UIP, develops an accelerated and usually fatal course, showing an extremely rapid decline; this condition is known as an acute exacerbation.

---

**Table 2. American Thoracic Society/European Respiratory Society criteria for diagnosis of IPF**

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion of other known causes of IIP (environmental/professional exposures, drug toxicities, connective tissue diseases)</td>
<td>Age &gt;50 yrs</td>
</tr>
<tr>
<td>Abnormal lung function: restrictive pattern and impaired gas exchange</td>
<td>Duration of illness &gt;3 months</td>
</tr>
<tr>
<td>Bibasilar reticular abnormalities and ground glass opacities on HRCT scans</td>
<td>Insidious onset of dyspnoea on exertion</td>
</tr>
<tr>
<td>Transbronchial lung biopsy or BAL not consistent with other diseases</td>
<td>Bibasilar inspiratory crackles (“velcro”-type)</td>
</tr>
</tbody>
</table>
The criteria for defining an exacerbation are:

- progressive dyspnoea during the last 30 days
- new pulmonary infiltrates in chest radiographs
- worsening of hypoxaemia with a reduction in oxygen partial pressure >10 mmHg
- absence of pulmonary infection supported by negative bronchoalveolar lavage (BAL)
- absence of any other cause, such as heart failure, pulmonary embolism or conditions which may cause acute lung damage.

Diagnosis of exacerbation may be controversial, despite the codification of the diagnostic criteria; ground-glass opacities are not specific for IPF and NSIP and may be present in cases of infection. Nonintubated patients in the acute phase of the disease often cannot undergo BAL because of their unstable conditions and they are treated with antibiotics for precautionary measure. Lung biopsy shows diffuse alveolar damage, however the invasiveness of the procedure is a limiting factor and only few well-selected patients undergo surgical lung biopsy. It is our duty to mention the correlation between surgical lung biopsy or lung resection and acute exacerbation, however unclear, as far as causality is concerned. Risk factors involved in this accelerated phase may be a high concentration of oxygen (100%), hyperexpansion of the lung parenchyma and the use of mechanical ventilation in the post-operative phase.

Generally, the factors responsible for the exacerbations are still unknown; clinical presentation in some patients (fever, influenza-like symptoms, neutrophilia in BAL) may be consistent with a viral infection, however the pathogen has not been identified.

**Treatment** Poor understanding of the pathogenetic mechanisms underlies the ineffectiveness of the current treatment options. Initially, a pathogenetic theory considered IPF and NSIP as inflammatory processes justifying the use of anti-inflammatory drugs, such as corticosteroids, which were considered first-line drugs. Later, cytotoxic and immunosuppressive agents were used, usually in combination with corticosteroids.

The most recent revelations from the pathogenetic field identify the initial phase of the disease as injury to the alveolar epithelial cells and destruction of the subepithelial basement membrane, leading to abnormal wound healing with a vigorous fibroblastic response and excessive deposition of collagen and extracellular matrix. This new pathogenetic theory suggests a primary role for fibroblast deregulation. Thus, the fibroproliferative process became the therapeutic target, and new drugs which arrest the proliferation of fibroblasts and the deposition of extracellular matrix are being testing.

**Established treatment** Corticosteroids have been considered the mainstay of IPF treatment for decades, although there are no randomised placebo-controlled trials using corticosteroids alone. The ATS/ERS international consensus statement concludes that existing therapies are of unproven benefit.

In the past, high doses of prednisone or prednisolone (1 mg·kg⁻¹·day⁻¹), considering ideal body weight) for 4–6 weeks, with a gradual taper, were used. Given the high risk of systemic side-effects and the significant toxicity, especially when in combination with other drugs, the dose has been re-evaluated, and more recent therapeutic regimens recommend low doses of prednisone or prednisolone (0.5 mg·kg⁻¹·day⁻¹ for 4 weeks, followed by 0.25 mg·kg⁻¹·day⁻¹ for 8 weeks, then 0.125 mg·kg⁻¹·day⁻¹). The rate of taper depends on the patient’s individual characteristics. In the case of responders with clinical and radiological improvement, prolonged maintenance therapy with low dose alternate-day prednisone may be prescribed to reduce the chance of recrudescence disease.

In case of exacerbation, 2 mg·kg⁻¹·day⁻¹ of methylprednisolone for ~14 days should be
administered, depending on individual clinical response. The rapid decline of pulmonary function may lead to important respiratory failure; accordingly, patients require supplemental oxygen and noninvasive positive pressure mechanical ventilation. In the most severe cases, intubation may be necessary.

Azathioprine and cyclophosphamide are the most frequently used second-line drugs, alone or in combination with corticosteroids. Azathioprine is the most frequently used cytotoxic agent and usually is well tolerated. Its metabolism leads to the production of mercaptourine, similar to purine, which inhibits DNA synthesis. Azathioprine is administered per os, usually in combination with low-dose corticosteroids; initial dose is 25–50 mg-day\(^{-1}\) (2–3 mg·kg\(^{-1}\)·day\(^{-1}\)). If adverse effects do not appear, an increase of 25 mg every 7–14 days is recommended, until a maximum dose of 150 mg-day\(^{-1}\) is reached. There are no clinical trials which confirm a certain benefit of combination (corticosteroids + azathioprine) therapy. Given the minor toxicity compared to cyclophosphamide, azathioprine should be administered in patients with symptomatic or progressive disease for 6 months unless adverse effects which suggest interruption or modification of the treatment appear.

Cyclophosphamide is usually used as a second-line drug for patients who have presented adverse effects to high-dose corticosteroid therapy. The route of administration is usually oral or intravenous, but it can also be administered by intramuscular injection. Generally, cyclophosphamide is used in combination with low-dose corticosteroids. Scientific evidence confirming the efficacy of cyclophosphamide in the treatment of IIPs is lacking; no clinical benefit regarding survival and progression of the disease has been reported.

Cyclosporine is a fungus-derived peptide which exerts potent immunosuppressive effects; it inhibits lymphocyte T proliferation by inhibiting the release of IL-2. Cyclosporine is rarely used for IIP treatment and its use is limited for selected patients awaiting a lung transplant. There are no clinical trials showing that cyclosporine therapy is beneficial.

**Novel therapeutic strategies** Interferon (IFN)-\(\gamma\)-1b is a novel biological antifibrotic drug with a number of inhibitory effects on fibroblasts. In the literature there are only few studies relative to the real efficacy of IFN-\(\gamma\), either alone or in combination therapy with low dose corticosteroids.

Colchicine inhibits the synthesis of collagen and suppresses growth factors that are necessary for fibroblast proliferation. On the basis of these properties, the use of this drug is being tested. Data are limited, although there is no evidence that colchicine improves the progression of the disease and survival.

\(\alpha\)-Penicillamine is a thiolic compound which interferes with collagen turnover. Indeed, it inhibits collagen synthesis and deposition by interrupting cross-linking of collagen molecules. There are no controlled clinical trials showing any benefit of \(\alpha\)-penicillamine therapy. Given the frequent adverse effects, \(\alpha\)-penicillamine does not appear to be a treatment choice in IIPs.

Pirfenidone (5-methyl-1-phenyl-2\([1H]\)-pyridone) attenuates pulmonary fibrosis in animal models. It reduces synthesis of collagen (I and III) and TNF-\(\alpha\), and inhibits TGF-\(\beta\)-stimulated collagen synthesis. Moreover, it decreases synthesis of the extracellular matrix and blocks the mitogenic effect of profibrotic cytokines.

Experimental models in vitro and in vivo showed that angiotensin-converting enzyme inhibitors (ACEI) and statins possess antifibrotic properties. However, there is no evidence of improved survival in treated patients.

There is evidence that the production of oxidative agents increases in IIP. In particular, neutrophils, macrophages and fibroblasts release oxidative agents, such as reactive oxygen species (ROS), hydrogen peroxide (\(H_2O_2\)) and superoxide anion. These factors, in
addition to the reduction of antioxidants, facilitate fibroblast deregulation and deposition of extracellular matrix. N-acetylcysteine (NAC) is derived from the amino acid cysteine. It is considered a precursor of glutathione (GSH) and it stimulates GSH synthesis. GSH has strong antioxidative properties, as it removes free oxygen radicals and decreases H$_2$O$_2$. The route of administration is oral at a dose of 1,800 mg·die$^{-1}$ and only in association with conventional therapy with corticosteroids and azathioprine. A significant difference in the rate of decline of FVC and $Tl_{\text{co}}$ has been described in patients treated with NAC, even if no difference was observed in mortality.

Endothelin (ET)-1 is a potent mitogen for endothelial and smooth muscle cells. ET-1 is strongly upregulated in patients with IPF and is mainly expressed in epithelial cells. Some studies have suggested that inhibition of ET-1 could have antifibrotic effects. Bosentan is a non-selective ET(A) and ET(B) receptor antagonist which is used in patients with pulmonary hypertension and it could delay the progression of IPF. However, in the treatment of IPF, clinical trials have been disappointing.

TNF-$\alpha$ antagonist – etanercept has been found to be significantly elevated in bleomycin-induced pulmonary fibrosis (BIPF). TNF-$\alpha$ stimulates a series of cytokines, such as TGF-$\beta$, IL-5 and modifies eosinophil recruitment in the parenchyma. Both antibodies anti-TNF-$\alpha$ and TNF-$\alpha$ soluble receptor antagonists have been found to reduce fibrotic processes in animals. The typical fibroproliferative process in IPF seems to be related to inflammation and vascular injury. Indeed, endothelium damage causes exposition of the intimal tissue to circulation, thereby inducing thrombotic events. Pulmonary embolism is one of the most common causes of death in IPF patients and d-dimer levels often increase during exacerbation of the disease. Recently, the role of thrombotic events in the natural history of the disease and survival in IPF patients has been evaluated. Patients treated with warfarin added to corticosteroids had significantly higher survival after exacerbation when compared to patients treated with corticosteroids alone. d-dimer levels and number of days free of exacerbation did not differ between the two groups. The mechanisms underlying increased survival are unclear. Certainly extravascular deposition of fibrin and thrombotic events play main roles in the fibroproliferative process and acute lung injury. Hence, anticoagulant therapy may be considered as an important additional therapeutic support in IIP treatment.

**Lung transplantation** Lung transplantation is the only option which definitely improves survival in IPF patients and the only option for patients refractory to medical therapy. IIPs represent the second most frequent disease which requires lung transplantation. It is extremely important to decide when to list a patient for transplantation. Given the legal complexity of

<table>
<thead>
<tr>
<th>Table 3. International Society for Heart and Lung Transplantation guidelines</th>
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<tr>
<td><strong>For referral</strong></td>
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<tr>
<td>Radiographic or histological evidence of UIP irrespective of vital capacity</td>
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<tr>
<td>Histological evidence of fibrotic NSIP</td>
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<tr>
<td><strong>For listing</strong></td>
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<tr>
<td>Radiographic or histological evidence of UIP and any of the following: $Tl_{\text{co}} &lt; 39%$ predicted; $&gt;10%$ reduction in FVC in the last 6 months; oxygen saturation $&lt;88%$ during 6MWT; honeycombing on HRCT (fibrosis score $&gt;2$)</td>
</tr>
<tr>
<td>Histological evidence of NSIP and any of the following: $Tl_{\text{co}} &lt; 35%$ predicted; $&gt;10%$ reduction in PVC or $&gt;15%$ in $Tl_{\text{co}}$ in the last 6 months</td>
</tr>
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$Tl_{\text{co}}$: transfer factor of the lung for carbon dioxide; FVC: forced vital capacity; 6MWT: 6-min walk test.

Idiopathic interstitial pneumonias
the process, early listing is urged. Recently, the International Society for Heart and Lung Transplantation published guidelines for establishing the characteristics and the criteria for transplantation and listing (table 3).

Unfortunately, many patients die while awaiting a transplant because of the poor availability of donor organs. Post-operative mortality in transplanted patients is high, because of rejection, infections and other complications. Two- and 5-yr survival rates following single lung transplants are approximately 70% and 50%, respectively.

References

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EOSINOPHILIC DISEASES

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The exact role of the eosinophil has yet to be determined. It is believed to play a role in combating helminthic parasitic infections and, in health, eosinophils primarily reside within the gastrointestinal mucosa. Eosinophilic lung diseases cover a wide spectrum of pathology ranging from airways disease, such as eosinophilic bronchitis, to parenchymal disease, such as eosinophilic pneumonia, and also systemic diseases, such as the hyper-eosinophilic syndrome.

Nonasthmatic eosinophilic bronchitis

Eosinophilic bronchitis is a common and treatable form of chronic cough that was first identified in 1989. Nonasthmatic eosinophilic bronchitis is a condition that presents with a corticosteroid-responsive chronic cough in nonsmokers. These patients have evidence of eosinophilic airways inflammation without the variable airflow obstruction or airways hyperresponsiveness characteristic of asthma.

Eosinophilic bronchitis accounts for 10–30% of cases of chronic cough referred for specialist investigation. Eosinophilic bronchitis is defined as a chronic cough in patients with no symptoms or objective evidence of airflow obstruction, a histamine/methacholine provocative concentration causing a 20% fall in forced expiratory volume in 1 s of >16 mg·mL\(^{-1}\) and >3% sputum eosinophilia.

It is unclear why eosinophilic inflammation leads to asthma in some individuals and eosinophilic bronchitis in others. Studies by BRIGHTLING (2006) suggest that the key may be mast cell localisation. In asthmatics, mast cells infiltrate airways smooth muscle, resulting in airflow obstruction and hyperresponsiveness. In eosinophilic bronchitis, mast cells infiltrate the airway epithelium leading to bronchitis and cough.

Anti-inflammatory therapy with inhaled corticosteroids is the mainstay for the treatment of eosinophilic bronchitis. Inhaled corticosteroids produce a significant improvement in symptoms as well as a fall in sputum eosinophilia. There is no evidence to suggest that any one inhaled corticosteroid is more effective. Data is also not available to guide the dose or duration of inhaled corticosteroid therapy. Logically, antileukotrienes may be of benefit, but this hypothesis has not been tested in clinical trials. In very resistant cases, oral corticosteroids may be required for symptom control.

Little is known about the natural history of the condition, but it can be transient, episodic or persistent unless treated.

Key points

- Eosinophilic lung disease covers a wide spectrum of pathology from airways to parenchymal lung disease.
- Always exclude secondary causes of eosinophilia before diagnosing acute or chronic eosinophilic pneumonia.
- Novel therapies are being introduced for eosinophilia including tyrosine kinase inhibitors and monoclonal antibodies against interleukin 5.
**Acute and chronic eosinophilic pneumonia**

Acute eosinophilic pneumonia presents as an acute febrile illness of <5 days' duration. The average age at presentation is 30 yrs with symptoms of dyspnoea, cough, myalgia and fevers. Patients often present with severe type I respiratory failure requiring ventilation. Unlike other pulmonary eosinophilic syndromes, the blood eosinophil count is usually normal. The chest radiograph demonstrates diffuse alveolar and interstitial infiltrates. The diagnosis is confirmed by the presence of a bronchoalveolar lavage eosinophilia of >25% in the absence of parasitic, fungal or other infections and no history of drug hypersensitivity. Acute eosinophilic pneumonia responds quickly to oral corticosteroids with no relapse after stopping therapy.

Chronic eosinophilic pneumonia typically presents in middle-aged asthmatic women, but it can also develop in nonasthmatic individuals. The symptoms are gradually progressive and include shortness of breath, cough, fever and weight loss. Clinical examination demonstrates wheezing and hypoxia. Patients usually have a raised blood eosinophil count at the time of an acute exacerbation along with elevated inflammatory markers. The majority of patients have infiltrates visible on chest radiograph, and they are peripherally distributed in about two-thirds of cases (fig. 1).

High-resolution computed tomography is more sensitive at demonstrating infiltrates and ~50% of patients also have mediastinal adenopathy. Patients respond well to oral corticosteroids, but tend to relapse on discontinuation of therapy. Many patients require long-term, low-dose oral corticosteroids to control the condition; in a small minority, alternative steroid-sparing agents have been used. This condition is frequently misdiagnosed as asthma. Blood eosinophilia and pulmonary infiltrates respond to corticosteroids within 24-48 h, making it easy to miss this condition if the relevant investigations are not performed prior to starting steroids.

Both acute and chronic eosinophilic pneumonia are idiopathic conditions. It is important to exclude secondary causes of eosinophilia before diagnosing either condition. In clinical practice, this requires a careful travel history asking about residence in areas of endemic parasitic infection and a careful drug history including illicit substances. The other main causes of a pulmonary eosinophilic syndrome are as follows: allergic bronchopulmonary aspergillosis, the hypereosinophilic syndrome, and Churg–Strauss syndrome, which should also be excluded at the time of diagnosis.

**Hypereosinophilic syndrome**

The hypereosinophilic syndrome (HES) is a heterogeneous group of disorders characterised by the presence of marked blood and tissue eosinophilia resulting in a variety of clinical manifestations. The following criteria are used to define idiopathic HES: 1) blood eosinophilia >1,500-mm$^{-3}$ for ≥6 months; 2) absence of an underlying
cause for the eosinophilia; and 3) end-organ damage due to the eosinophilia.

Idiopathic HES can occur at any age, but tends to develop in the fourth or fifth decade of life, with a male predominance. Nonspecific systemic symptoms are common. More specific symptoms will depend upon which organs are affected. The lungs are involved in ~40% of patients, leading to cough and airflow limitation. Pulmonary function tests demonstrate an obstructive pattern in patients with cough. In patients with cardiac involvement, concomitant pulmonary fibrosis can occur leading to a restrictive or mixed pattern. The chest radiograph can be normal or demonstrate spontaneously clearing airspace shadowing in early disease. At a later stage with multi-organ involvement, up to one-third of cases will have diffuse, nonsegmental interstitial infiltrates.

The most important cause of morbidity and mortality in idiopathic HES is cardiovascular involvement. Thromboembolic disease and involvement of the nervous system are also common presentations.

Until recently, oral corticosteroids have been the mainstay of treatment. Better understanding of eosinophil biology has led to the use of more logical targeted therapies. Distinct HES subtypes are now recognised. The myeloproliferative variant is associated with the presence of a fusion tyrosine kinase, FIP1L1/PDGFRA. These patients historically had a poor prognosis with poor steroid responsiveness. The use of the tyrosine kinase inhibitor, imatinib, in this group of patients has significantly improved their outcome.

The lymphoproliferative variant is a consequence of increased production of eosinophilopoietic cytokines by clonal populations of phenotypically abnormal, activated T-lymphocytes. Identification of interleukin-5 (IL-5) as a key mediator of eosinophilopoiesis led to the use in clinical trials of an anti-IL-5 monoclonal antibody (mepolizumab) for HES. Mepolizumab is an effective corticosteroid sparing agent in patients with HES negative for FIP1L1/PDGFRA.

References

Drug-induced and iatrogenic respiratory disease (DIRD) is a classic, not uncommon and often unpredictable complication of exposure to therapy drugs, including the novel biological kinase inhibitors gefitinib, erlotinib, imatinib, dasatinib and monoclonal antibody therapy, irradiation, abused substances, herbal therapy and vaccines. The diagnosis of DIRD is one of exclusion (table 1), and aetiologies other than the drug or drugs must be ruled out, particularly an infection due to Pneumocystis jiroveci or other opportunistic pathogens. Patients exposed to methotrexate, anti-tumour necrosis factor (TNF) agents, immunosuppressive drugs, chemotherapy agents and rituximab are at risk of developing opportunistic infections, and further tests are required to rule out an infection in such patients.

DIRD is probably under-reported. Incidence is greater with chemotherapy agents (up to 40% depending on which drug regimen is used and which test is used to diagnose the condition) or amiodarone or methotrexate (1–2% per year) compared with other drugs. With most of the other 400 or so drugs known to cause respiratory injury, DIRD is uncommon.

The respiratory system includes the lung, airways, pulmonary circulation, pleura, haemoglobin and neuromuscular system. Each of these can be the target of drug-induced injury, causing varied imaging patterns of involvement (table 2).

Accordingly, DIRD can occur in the form of interstitial lung disease (ILD), where drugs may account for 3% of ILD cases, upper airway obstruction (UAO), bronchospasm or...
bronchiolitis obliterans, pulmonary hypertension, pleural effusion or thickening, impaired oxygen carrying capacity of haemoglobin and reduced inspiratory muscle force. Potentially severe DIRD includes acute angioedema from angiotensin-converting enzyme (ACE) inhibitors, catastrophic bronchospasm from nonsteroidal antiinflammatory drugs (NSAIDs), β-blockers or aspirin, acute methotrexate pneumonitis or minocycline-induced eosinophilic pneumonia, pulmonary oedema from tocolytic agents or chemotherapy drugs, anticoagulant-induced diffuse alveolar haemorrhage, large-volume pleural effusion and acute methaemoglobinemia and drug-induced neuromuscular acute respiratory failure. These drug-induced complications portend immediate severity and may have fatal consequences. In such cases, prompt recognition of the drug aetiology, emergent management of the airway and of respiratory failure and early drug withdrawal are warranted. A maintained list of drugs and patterns of drug-induced respiratory involvement is available on the Pneumotox website at www.pneumotox.com.

Pathophysiology: mechanisms

Drug-induced ILD is characterised by homing, proliferation and persistence of immune-effector cells including eosinophils in lung tissue. This causes pulmonary shadowing, increases in bronchoalveolar lavage (BAL) cells and hindrance to gas exchange. Corticosteroid therapy usually quenches drug-induced pulmonary inflammation and is followed by improvement in symptoms and imaging. Rechallenge with the causal drug often but not always produces relapse of DIRD. The mechanisms for drug-induced cell influx are generally unknown.

Table 1. Checklist for diagnosing drug-induced respiratory disease

| 1. Maintain a high degree of awareness of drug-induced disease vis à vis any new respiratory sign and symptom if not explained otherwise. Use Pneumotox website as needed. |
| 2. Record medical history including history of exposure to drugs, radiation and substances of abuse |
| 3. Evaluate the possibility or likelihood of pulmonary involvement from an underlying condition if present |
| 4. Retrieve pre-therapy imaging and pulmonary function data. Compare with present tests |
| 5. Review timing of exposure to drug versus onset of symptoms (minutes to years, depending on drug and pattern) |
| 6. Try to define pattern of injury in the most conservative way (lung biopsy can be risky; pathology may show nonspecific findings) |
| 7. Evaluate drug causality, taking into account each drug taken in isolation. Correlate with pattern of involvement. |
| 8. Evaluate the likelihood of disease caused by drug versus underlying condition, (an opportunistic infection, other drugs, or incidental disease) using the above and BAL |
| 9. *In vitro* tests of mononuclear cell migration are cumbersome and none has yet proved useful |
| 10. Evaluate literature pertaining to the specific drug or pattern of involvement. |
| 11. Discontinue drug, patient condition permitting. This may not be followed by improvement in patients with acute disease. Check whether the underlying illness needs a substitute drug |
| 12. Evaluate whether corticosteroid therapy is indicated (depending on drug, severity, pattern and effect of drug discontinuance) |
| 13. Organise appropriate follow-up including imaging and pulmonary physiology |
| 14. Discuss rechallenge only if no other drug available to treat the patient’s condition. Otherwise avoid |

BAL: bronchoalveolar lavage; #: match drug and pattern using Pneumotox website.
Table 2. Main imaging pathological patterns of drug-induced infiltrative lung disease

<table>
<thead>
<tr>
<th>Pattern on chest radiograph or CT</th>
<th>Causal drugs</th>
<th>Pathology correlate</th>
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</table>
| Diffuse haze or ground-glass opacity | Drugs that cause interstitial pneumonia<sup>a</sup>  
Chemotherapy agents | Interstitial inflammation, cellular interstitial pneumonia  
Early/mild pulmonary oedema, alveolar haemorrhage or DAD |
| Localised ground-glass opacity | Radiation therapy<sup>a</sup> | Early or mild radiation lung injury (interstitial oedema, cell sloughing, cell debris) |
| Diffuse white-out – white lungs | Drugs that produce acute ILD, pulmonary oedema, DAD, eosinophilic pneumonia or DAH<sup>a</sup> | Dense cellular interstitial pneumonia with or without tissue eosinophilia. Acute pulmonary oedema. DAH |
| Disseminated areas of ground-glass with a mosaic pattern of distribution | Drugs that cause interstitial pneumonia<sup>a</sup> | Cellular interstitial pneumonia. DIP |
| Bilateral perihilar alveolar opacities with a batwing pattern of distribution | Drugs causing pulmonary oedema, DAD or DAH<sup>a</sup> | Pulmonary oedema, DAD, DAH |
| Multiple subpleural areas of condensation | Drugs causing pulmonary eosinophilia or BOOP. Statins<sup>a</sup> | Eosinophilic pneumonia, BOOP |
| Opacities with a recognisable segmental or lobar pattern of distribution | Amiodarone<sup>a</sup>  
Statins<sup>a</sup>  
Paraffin<sup>a</sup> | Phospholipidosis, organising pneumonia  
BOOP  
Exogenous lipoid pneumonia |
| Diffuse miliary pattern | BCG therapy, methotrexate, sirolimus<sup>a</sup> | Granulomatous reaction<sup>a</sup> |
| Area of condensation. A mass | Drugs causing BOOP or eosinophilic pneumonia<sup>a</sup>  
Amiodarone  
Paraffin | BOOP, eosinophilic pneumonia  
Phospholipidosis, APT features, amiodaronoma  
Paraffinoma |
| Wandering opacities | Drugs which cause organising or eosinophilic pneumonia<sup>a</sup>  
Irradiation for breast carcinoma<sup>a</sup> | BOOP, eosinophilic pneumonia  
BOOP |
| Multiple nodular opacities | Amiodarone<sup>a</sup>  
Bleomycin<sup>a</sup> | APT features  
BOOP  
Areas of nodular fibrosis |
| Pulmonary fibrosis. Low lung volumes | Chemotherapy agents. Amiodarone. Nitrofurantoin. Irradiation | Pulmonary fibrosis. UIP pattern |

CT: computed tomography; DAD: diffuse alveolar damage; ILD: interstitial lung disease; DAH: diffuse alveolar haemorrhage; DIP: desquamative interstitial pneumonia pattern; BOOP: bronchiolitis obliterans organising pneumonia; APT: amiodarone pulmonary toxicity; UIP: usual interstitial pneumonia; <sup>a</sup>: see appropriate pattern on Pneumotox website; <sup>b</sup>: interferons and anti-tumour necrosis factor agents may produce a mimic of sarcoidosis.
With some drugs (chemotherapy agents, and drugs that cause pulmonary oedema or bronchospasm), the respiratory reaction is dose dependent. Above a certain drug dosage, most patients exhibit some form of adverse reaction, suggesting a dose-related cytopathic mechanism. Patients on chemotherapy for haematological malignancies or solid tumours may exhibit a time- or dose-related decrease in the diffusing capacity for carbon monoxide, thought to reflect subclinical dose-related pulmonary toxicity, without necessarily exhibiting clinically detectable disease.

However, most drug reactions are idiosyncratic and occur unpredictably in only a few individuals, regardless of dose or time on the drug.

Several drugs in a pharmacological class may cause the same pattern of injury. Examples include the association: of β-blockers or NSAIDs and acute bronchospasm; of chemotherapy agents and pulmonary oedema, acute lung injury (ALI), diffuse alveolar damage (DAD) or pulmonary fibrosis; and of ergots with pleural thickening. This also suggests that a common pathogenetic mechanism caused the injury.

Experimental and clinical evidence suggests that drug disposition in lung is a critical factor for toxicity. For instance, amiodarone and its main metabolite sequester in lung, reaching tissue concentrations that are above the threshold for toxicity to lung cells. This may cause cell toxicity despite serum concentrations being within the therapeutic range. The slow efflux of amiodarone and metabolite from the lung are consistent with for the slow resolution of amiodarone pulmonary toxicity (APT) in the clinic, except when corticosteroid therapy is added.

A few drugs are known to undergo metabolic activation in designated lung cells, leading to the formation of reactive drug species that bind avidly and covalently to cell macromolecules, causing injury or cell loss. Metabolism of nitrofurantoin, cyclophosphamide, mitomycin, bleomycin and the herbicide paraquat can generate reactive oxygen species, which attack cell constituents and deplete reducing equivalents. This may lead to cell death and consequent pulmonary inflammation and/or fibrosis. Of note, the heterogeneous distribution of activating enzymes in the lung may account for the selective alveolar or bronchial injury seen with a specific agent. The delicate and/or unstable architecture of the lung may expose it to potentially severe consequences of even small amounts of tissue damage.

An immunological reaction is thought to cause the adverse reaction to some drugs. For instance, transfusion-related ALI is caused by the binding of human leukocyte antigen antibodies of donor origin to circulating blood cells in the recipient, causing cell activation, endothelial cell injury and an increase in vascular permeability with consequent alveolar oedema. The drug-induced lupus syndrome is characterised by a positive anti-nuclear and sometimes anti-DNA antibody test. The antibody may be at the origin of the adverse pleural reaction that is a hallmark of the drug-induced lupus. Drug-induced asthma is largely non-immunoglobulin E-dependent. Nevertheless, small incremental doses of NSAIDs or aspirin can be given to asthmatics who are intolerant to these drugs and thus a state of tolerance can be induced, should such patients need to be treated with this class of medications.

Alveolar haemorrhage can complicate treatments with variegated anticoagulant drugs, and overdose is thought to account for this complication although not all cases exhibit abnormal coagulation studies. Only a few drugs produce pulmonary capillaritis with consequent alveolar haemorrhage.

Rare cases of drug-induced injury result from deposition of the drug excipient in lung tissue, notably the pulmonary circulation, causing reactive foreign body granulomas around pulmonary arterioles.

**Clinical presentation**

A high degree of suspicion must be maintained at all times, and drugs should be
a diagnostic consideration in any patient with otherwise unexplained respiratory symptoms, abnormal pulmonary physiology or new radiographic findings while being treated with therapy or other drugs. Some adverse reactions to drugs exhibit a short time to onset (e.g. β-blocker-induced bronchospasm, chemotherapy-induced pulmonary oedema), and this readily suggests causality. For most drugs, however, there is a long time delay for DIRD to present and thus, consideration of the drug aetiology is not always raised in due time. Drugs can cause lung injury when administered by the oral, intravenous or intramuscular, inhaled, pleural or intrathecal route or following delivery in a distant organ that is situated upstream of the lung (e.g. bone, brain or liver).

Symptoms of DIRD at presentation may include a nonproductive cough, dyspnoea, wheezing, cyanosis and rigors. Acute bronchospasm, angio-oedema and shock characterise those cases with drug-induced anaphylaxis. Occasional patients present with stridor, hoarseness, wheezing, haemoptysis or acute chest pain. Extrarespiratory signs, symptoms and laboratory features include a cutaneous rash, lymph-node enlargement and hepatitis. Rare patients present with full-blown systemic reactions resembling lupus erythematosus, Churg–Strauss syndrome, Wegener’s granulomatosis or polymyositis.

The severity of DIRD relates to the acuteness, extent, location and reversibility of the adverse reaction. Life-threatening presentations are in patients with acute dense ILD, upper airway oedema, massive pleural effusion or drug-induced systemic involvement.

Drug withdrawal followed by abatement of signs and symptoms is a simple and straightforward test to confirm the drug aetiology. The risk of rechallenge should be balanced against the merit of securing the diagnosis, as fatal reactions may follow rechallenge with the causal agent.

However, many clinical situations are complex. It is possible that patients are exposed to several causal drugs with each drug having differing delay times for DIRD to present, or they have received chest irradiation, or DIRD cannot be confidently separated from pulmonary involvement of the underlying disease for which the drug was given. Examples include patients with thoracic malignancies or rheumatoid arthritis, when they are exposed to corticosteroids and/or novel biological drugs including tyrosine kinase inhibitors or anti-TNF antibody therapy. Similarly, diagnosing DIRD is difficult in patients with autoimmune conditions or recipients of solid organ or bone marrow transplant who are receiving long-term treatments with immunosuppressive drugs, corticosteroids or sirolimus.

**Imaging**

Imaging features of DIRD are diverse, as are their clinical presentations.

Drug-induced bronchospasm may present with hyperinflation concomitant with bronchospasm on imaging.

On CT, airway narrowing can be documented in patients with drug-induced angio-oedema or haematoma and UAO.

Patients with ILD generally present with bilateral lung shadowing (table 2) that may localise in the bases, mid-lung regions or apices or can be diffuse. Both the density and extent of pulmonary involvement correlate with the degree of respiratory impairment. On computed tomography, there is inter- or intralobular septal thickening and lobular or more widespread alveolar filling, depending on patient, drug and pattern of involvement. Pleural effusions may be present in severe ILD presentation. APT may cause electron-dense areas of condensation with, often, pleural effusion. Chemotherapy lung is in the form of basilar opacities or a more diffuse haze or consolidation. In eosinophilic pneumonia, the pulmonary opacities tend to predominate in the lung periphery. Acute nitrofurantoin lung is in the form of diffuse haze. Chronic nitrofurantoin lung is with scattered peribronchovascular areas of consolidation.
Bronchiolitis obliterans organising pneumonia (BOOP) typically presents with migratory alveolar opacities on serial chest films. Mediastinal or hilar lymph node enlargement characterises those cases with a granulomatous pattern of reaction. The pulmonary opacities in exogenous lipoid pneumonia typically have low attenuation numbers. Radiation pneumonia generally develops in the area of the radiation beam. Only in severe cases does the shadowing extend outside the radiation beam. It is very difficult if not impossible to infer pathology from the pattern on imaging.

Drug-induced pleural effusion is indistinguishable from an effusion of other causes, except when APT is present in association. An air-fluid level can be present when the pleural pathology occurs as a complication of chemotherapy in patients with pulmonary metastases adjacent to the pleural surface.

Pathology and other diagnostic tests

BAL is used to rule out an infection, and to evaluate alveolitis by enumerating cell numbers and percentages. Inflammatory cells decrease upon drug withdrawal.

On pathology, drugs can cause virtually any pattern of ILD, including cellular or fibrotic interstitial pneumonia, eosinophilic pneumonia, acute lung injury or diffuse alveolar damage, pulmonary granulomas, DAD, BOOP, desquamative or lymphocytic interstitial pneumonia, a usual interstitial pneumonia pattern or rarely, pulmonary alveolar proteinosis. These patterns are not specific to the drug aetiology and cannot be separated reliably from the idiopathic variant. Thus, while pathology may help eliminate conditions other than drugs, lung biopsy is rarely used to document drug-induced ILD. Notable exceptions include APT and exogenous lipoid pneumonia, which may display characteristic features on pathology.

No in vitro test of monocyte cell migration in the presence of the drug has demonstrated diagnostic utility in DIRD.

Specific reactions

Airways Angio-oedema is a well-demarcated oedema that is classically caused by ACE inhibitors. The condition develops shortly after first exposure to the drug or it occurs later after uneventful weeks or months of treatment in the form of rapidly developing breathing difficulty or asphyxia due to airway narrowing. The condition is more common in elderly African-American women. About 40% of the cases require admission to intensive care. This complication requires emergent identification of the airway, and orotracheal intubation or tracheostomy are indicated in severe cases to stabilise the airway. Even though patients tend to improve quickly upon drug discontinuance, close patient follow-up is required since a rebound can occur after a few hours. Patients should not be rechallenged with any ACE inhibitor, as severe relapse may occur in patients so tested.

Catastrophic bronchospasm may closely follow exposure to as little as one tablet of NSAID, aspirin or a nonselective β-blocker in aspirin-sensitive individuals, atotics, asthmatics or in a patient known to react adversely to these classes of medications. About 15% of acute asthma attack cases admitted to intensive care are thought to be triggered by exposure to drugs. Rechallenge is hazardous and leads to severe relapse with consequent anoxic brain damage and death.

An annoying cough is a frequent complication of treatments with ACE inhibitors. Incidence varies according to the drug used and ethnicity. The condition remits within days or a few weeks with cessation of exposure to the drug.

Parenchymal lung disease Methotrexate pneumonitis is a form of acute, severe and reversible ILD. The condition develops unexpectedly in patients on methotrexate long term – typically rheumatoid arthritis patients. A background of previous ILD is a risk factor for developing methotrexate lung. The disease typically manifests dense diffuse pulmonary shadowing and respiratory failure. Lymphocytes are the predominant cell type in
the BAL. The main differential diagnosis is *Pneumocystis jiroveci* pneumonia or pneumonia due to other opportunistic microorganisms. These need be ruled out confidently using the BAL and molecular diagnostic tools. Mild cases of methotrexate lung exist. In rare cases, pulmonary fibrosis follows an episode of otherwise classic methotrexate pneumonia.

Eosinophilic pneumonia is a common pattern of reaction to drugs. Other causes of pulmonary infiltrates and eosinophilia must be ruled out. The condition shows bilateral shadowing in the context of peripheral and BAL eosinophilia. Acute eosinophilic pneumonia is a severe form of ILD with acute respiratory failure and sometimes, pleural effusion is present. Characteristic causal agents include NSAIDs, antibiotics (e.g. minocycline), abused drugs and exposure to tobacco smoke of recent onset. Rechallenge is contraindicated, as relapse will almost inevitably occur. Severe systemic presentations can occur and are characterised by a cutaneous rash and deep-seated organ involvement. This is called the drug rash with eosinophilia and systemic symptoms (DRESS).

APT is a distinctive condition that develops insidiously after months or years on the drug, in the form of asymmetrical consolidation that may be electron-dense. Pulmonary function is restrictive in nature. Foam cells are present in the BAL and are an aid to diagnosis of APT, although this does not prove toxicity and is a routine finding on the drug. The clinical-imaging-pathological expression of APT is multifaceted and includes ground-glass shadowing, lung nodules, pulmonary fibrosis or, rarely, pleural effusion in isolation. Amiodarone withdrawal may not suffice for APT to clear, due to the high affinity and persistence of amiodarone in lung tissue. Corticosteroid therapy often is required to accelerate recovery. Severe APT may occur in the setting of thoracic surgery and can be in the form of an ARDS picture.

Several drugs can acutely produce lung permeability changes. Pulmonary oedema is mainly observed following exposure to chemotherapy agents including taxanes, gemcitabine, mitomycin and rituximab, blood and blood products. There is a spectrum of severity ranging from transient pulmonary infiltrates following each exposure to the drug to acute pulmonary edema or an acute respiratory distress syndrome (ARDS) picture. Severe cases may develop at once, or after several bouts of pulmonary infiltrates, indicating impending toxicity. Outcome is good in early or mild cases. Severe cases may evolve to refractory respiratory failure.

Chemotherapy agents may cause a peculiar form of acute ILD called chemotherapy lung. The condition is in the form of pulmonary infiltrates during or shortly after completion of treatment with the drug. Bleomycin, cyclophosphamide, gemcitabine, nitrosoureas and taxanes are classic causal drugs, with recent evidence implicating targeted therapies (gefitinib, erlotinib, pemetrexed). On pathology, there is moderate interstitial interstitial inflammation and oedema, along with a reactive epithelium and widespread areas of acute lung injury or alveolar damage. The condition may or may not improve upon drug discontinuance and corticosteroid therapy. In more severe cases an ARDS picture or an accelerated form of pulmonary fibrosis develop.

Drug-induced BOOP resembles BOOP of other causes or which occurs idiomatically. It takes the form of migratory opacities, fixed opacities or masses or diffuse shadowing with respiratory failure. Main causal agents include amiodarone, interferon, methotrexate, minocycline, rituximab, statins and radiation therapy to the breast. Drug withdrawal is indicated in all cases and it is followed by disappearance of signs and symptoms of the condition. Otherwise, sequential relapses may occur. Corticosteroid therapy is reserved for severe cases and in those with equivocal effect of drug withdrawal.

Interferons, anti-TNF agents and a few other drugs may occasion a granulomatous pattern of pulmonary and lymph node reaction that may closely mimic sarcoidosis.

Pulmonary
infiltrates and lymph node enlargement are present on imaging. A confirmatory transbronchial lung biopsy may be required, except if granulomas are present on a readily-accessible tissue such as the dermis.

Drug-induced diffuse alveolar haemorrhage is diagnosed by BAL, which shows a hemorrhagic return. Oral or parenteral anticoagulants, fibrinolytic agents, abciximab, ticlopidine and clopidogrel can cause the syndrome. Rarely, alveolar haemorrhage is a manifestation of drug (mainly propylthiouracil)-induced anti-neutrophil cytoplasmic antibody vasculitis.

Drug-induced pulmonary fibrosis can occur as a complication of treatments with chemotherapy agents, amiodarone and irradiation (fibrosis is localised in the latter). Patients present with dyspnoea. On imaging there are diffuse linear or streaky opacities and volume loss. The condition may stabilise with drug discontinuance. In most patients, however, the disease is progressive and response to corticosteroid therapy is limited.

When drug aetiology is considered likely, corticosteroid therapy is indicated in severe ILD cases and wherever drug withdrawal is not followed by improvement in a few days or weeks.

**Pleuritis** Many drugs can injure the pleura, including the novel targeted agent dasatinib. Involvement is in the form of a pleural exudate with or without pleural eosinophilia or a serosanguineous effusion. Lupus-inducing drugs may cause drug lupus with pleural or pleuroperticardial effusion in the context of positive antinuclear antibodies (ANA). The novel anti-TNF agents infliximab, etanercept and adalimumab may cause a form of lupus syndrome with anti-double-strand DNA in addition to the ANA antibodies, an unusual finding in classic drug-induced lupus.

Ergots are notable for the insidious development of diffuse pleural thickening with or without an effusion causing dyspnoea, chest pain and restrictive lung dysfunction. There is slow improvement with discontinuance of the ergot.

**Pulmonary vasculopathy** This condition mainly is in the form of pulmonary hypertension similar to primary pulmonary hypertension. Anorectic agents, benfluorex and crushed tablets injected intravenously as a form of drug abuse can effectuate the condition.

**Methaemoglobinemia** Methaemoglobinemia is a drug-induced state of oxidation of the iron in haemoglobin, and methaemoglobin is a poor oxygen carrier. The condition is diagnosed by slate-grey cyanosis, a low pulse oxygen saturation, normal arterial oxygen tension and calculated arterial oxygen saturation, and measurement of methaemoglobin in a patient receiving an eligible drug.

**References**

CHAPTER 12:

PULMONARY VASCULAR DISEASES

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Despite the recent advances in prevention and diagnostic imaging, pulmonary embolism (PE) remains a major health problem. The incidence of this pathological condition is as high as one in 1,000 per year in the general population. Early diagnosis is fundamental since early treatment is highly effective. However, due to the low specificity of its clinical presentation, this common disease is still underdiagnosed and it is estimated that in the USA ~50,000 people die each year of PE.

Several points are summarised below concerning the diagnostic strategies to be adopted in patients with clinical suspicion of PE that have been highlighted and brought to the attention of the scientific community by recent scientific publications, expert reviews, and international guidelines.

**General rules for the diagnostic work-up of patients clinically suspected of PE**

- Pre-test clinical probability of PE should be objectively assessed in each patient.
- D-Dimer should be determined if pre-test probability of PE is low or intermediate.
- Diagnostic imaging of the chest should be used to assess post-test probability of PE in most patients. Further testing is necessary when post-test probability of PE is neither sufficiently low nor sufficiently high to permit therapeutic decisions.
- Diagnostic strategies of PE could differ significantly in different clinical contexts and special conditions.

**Key points**

- Although early treatment is highly effective, PE is underdiagnosed and therefore it remains a major health problem.
- Diagnostic strategy should be based on clinical evaluation of the probability of PE.

**Pre-test clinical probability of PE**

A thorough clinical evaluation is the key step in raising the suspicion of the disease and setting up appropriate diagnostic strategies. Although the diagnostic yield of individual clinical symptoms, signs and common laboratory tests is limited, the combination of these variables, either by empirical assessment or by a prediction rule, can be used to stratify patients into an increased risk of PE (low, intermediate or high). The results of two broad prospective studies in the 1990s (Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) and Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED)) indicate that physicians’ estimates of the clinical likelihood of PE, even if based on empirical assessment, do have predictive value.

Three objective scoring systems have been tested prospectively and validated in large-scale clinical trials: Wells score, Geneva score and Pisa score. The three scoring systems perform reasonably well to assess objectively the clinical probability of PE in outpatients or...
emergency room patients. The Pisa score seems to perform better than other scoring systems in hospitalised patients. It appears that fully standardised scoring systems, such as Wells and Geneva scores, with no implicit evaluation of symptoms (e.g. dyspnoea, chest pain) and simple instrumental findings (ECG, chest radiograph) could not perform better than subjective clinical judgment of experienced physicians, as it was obtained in the PIOPED and the PISA-PED studies. Conversely, interpretation of ECG and chest radiograph in these patients, as requested by the Pisa score, necessitates a certain level of clinical experience and is hard to be standardised.

Nevertheless, several prospective studies have shown that, whatever scoring method is used, pre-test clinical probability categorises patients into subgroups with a different prevalence for PE and that the positive and negative predictive value of various objective tests is strongly conditioned by the independently assessed pre-test clinical probability. Accordingly, recent international guidelines recommend that the clinical probability of the disease should be assessed in each patient with suspected PE before any further objective testing occurs. Future research is needed to develop standardised models, of varying degree of complexity, which may find application in different clinical settings to predict the probability of PE.

D-Dimer

D-Dimer plasma levels are elevated in the presence of simultaneous activation of coagulation and fibrinolysis. A normal D-dimer level has, consequently, a high negative predictive value for PE or deep vein thrombosis (DVT). However, fibrin endogenous production may be increased in a wide variety of conditions including, among others, cancer, inflammation, infection, pregnancy, chronic disease. Elevated plasma D-dimer levels have, for this reason, a low positive predictive value for PE and DVT.

The value of D-dimer measurement in the diagnostic workup of each patient must be considered according to the determined PE clinical probability and the sensitivity of the particular D-dimer method of measurement employed. A negative D-dimer test result, measured by any method, in combination with a low probability clinical assessment, excludes PE with accuracy. An intermediate clinical probability also would exclude PE with reasonable certainty if D-dimer was measured by a high sensitivity ELISA method. It has been shown that the 3-month risk of PE or DVT in untreated patients with a negative D-dimer and a low or intermediate clinical probability is <1%. Conversely, if clinical assessment results in high probability for PE, a concomitant negative D-dimer test does not exclude PE.

The number of patients with suspected PE in whom D-Dimer must be measured to exclude one PE episode ranges between three in the emergency dept and ∼10 in hospitalised patients. It then appears recommendable to consider D-Dimer measurement in the diagnostic work-up of PE only in outpatients or in patients of the emergency dept with low or intermediate levels of clinical probability.

The sensitivity of D-Dimer testing for pulmonary embolism increases with the extent of PE. D-Dimer concentrations are the highest in patients with PE involving the pulmonary trunk and lobar arteries and with perfusion scan defects involving >50% of the pulmonary circulation.

Diagnostic imaging of the chest (post-test probability of PE)

The contribution of computed tomography angiography (CTA) in the diagnosis of PE has in recent years greatly increased as a consequence of the extraordinary advancement in CTA technology. Multidetector CTA has become the most widely used technique for the diagnosis or exclusion of PE and has almost replaced lung scanning as a screening test and conventional pulmonary angiography as the reference standard for the diagnosis of acute pulmonary embolism. CTA, however, does not escape the simple rule that the combined use of the
estimated clinical probability and the results of one noninvasive test substantially increases the accuracy in confirming or ruling out a disease, as compared with either assessment alone. As shown by the PIOPED II trial, the predictive value of CTA is high with a concordant clinical assessment, but additional testing is necessary when clinical probability is inconsistent with the imaging results.

Perfusion (Q′) lung scan was introduced 40 yrs ago as the first chest imaging method for the diagnosis of PE. A normal Q′ scan excludes PE (high sensitivity and high negative predictive value), whatever the pre-test clinical probability. However, Q′ scanning was thought to be poorly specific (low positive predictive value) for PE because all common pulmonary diseases (infections, neoplasms, chronic obstructive pulmonary disease) can produce decreased blood flow to the affected regions. Ventilation (V′) scan was added to Q′ scan to increase the specificity of scintigraphy. This diagnostic approach is based on the flawed expectation that regions of the lung excluded from perfusion by emboli maintain normal ventilation, thus giving rise to V′/Q′ mismatch. This criterion to diagnose PE is at variance with the notion that ventilation is shifted away from embolised lung regions. The concept that dead space ventilation is not significantly increased in the course of PE was widely held in respiratory pathophysiology before the V′/Q′ scanning approach was developed as it was asserted by COMROE (1966), who foresaw that “decrease in wasted ventilation (ventilation to unperfused or poorly perfused lung) helps the patient but hinders the physician in diagnosis.” This is in keeping with the results of the PIOPED trial, in which it was shown that the high probability V′/Q′ scan (Q′ defects without matching V′ abnormalities) lacks sensitivity in diagnosing PE since it fails to identify 59% of PE patients (sensitivity 41%, specificity 97%). The combination of clinical probability and V′/Q′ scan results either confirms or excludes PE in <30% of patients. The diagnostic value of the Q′ scan (without V′ imaging) was reappraised in the PISA-PED study, in which Q′ scans were read either as compatible with PE when featuring wedge-shaped (segmental) perfusion defects or not compatible with PE when featuring defects other than wedge-shaped or normal perfusion. When compared with the original PIOPED protocol, the PISA-PED approach has several advantages, as follows: 1) Q′ scan either confirms or excludes the clinical suspicion of PE (thus virtually eliminating nondiagnostic examinations); 2) the sensitivity of lung scintigraphy is greatly increased (86% versus 41%), yet with minor reduction of specificity (from 97% to 93%); 3) the combination of clinical probability and Q′ scan results confirms or excludes PE in ~80% of patients. More recently the diagnostic performance of Q′ scan for PE was confirmed by examining 889 scans from the PIOPED II. PIOPED II data were used to test the hypothesis that reading Q′ scans without V′ scans, and categorising the Q′ scan as “PE present”, “PE absent”, or “nondiagnostic” can result in clinically useful sensitivity and specificity in a high proportion of patients. The study has confirmed that Q′ scan and CTA have comparable positive and negative predictive values, with no nondiagnostic readings for the Q′ scan (table 1).

Diagnostic strategies in different clinical contexts and special conditions

Most clinicians and diagnostic radiologists feel, however, more comfortable with an anatomical demonstration of whether a clot is present or not as compared to assess a PE probability by looking at V′/Q′ mismatches (PIOPED) or to evaluate the shape of a perfusion defect (PISA-PED). Furthermore, contrary to scintigraphy, in most hospitals, CTA is available 24 h/7 days a week. However, CTA cannot be performed in the whole population of patients suspected of PE. As shown in the PIOPED II trial, ~50% of the recruited patients did not undergo CTA for documented contraindications, such as renal failure, abnormal creatinine levels, allergy to contrast agent, possible pregnancy, critical illness, requirement of ventilator support, or recent myocardial infarction. In all these conditions, Q′ scan could be the preferred alternative approach to the diagnosis of PE.
This approach is particularly important for reproductive-age female patients in whom the breast irradiation dose from CT angiography can be minimised by using the Q’ scan as the first imaging test.

Under circumstances in which clinical probability and imaging test (CTA or scintigraphy) results are discordant and further testing, such as lower limb compression ultrasonography, is required to either confirm or exclude the diagnosis. Another practical approach could be to image the pulmonary circulation with CTA if Q’ scan was the first imaging test used or vice versa.

Summary and conclusions

The choice of a diagnostic strategy for pulmonary embolism depends on the pre-test clinical probability of PE, the condition of the patient, the availability of the necessary test, the risks of testing, the risk of an inaccurate positive or negative diagnosis, and the cost. Clinical evaluation makes it possible to classify patients into probability categories corresponding to an increasing prevalence of PE, whether assessed by implicit clinical judgment or by a validated prediction rule. Structured models to assess clinical probability so far developed have different performances in patients of the emergency department and those who are hospitalised. Exclusion of PE by clinical probability assessment and d-dimer spares the cost and radiation of an imaging evaluation. CTA has become the method of choice for imaging the pulmonary vasculature when PE is suspected in routine clinical practice. Scintigraphy can be considered as the preferred alternative chest imaging technique for patients with contraindication to CTA. If scintigraphy is used, eliminating the ventilation scan can reduce cost and radiation load with gain in diagnostic yield.

References


<table>
<thead>
<tr>
<th>Imaging test</th>
<th>Positive predictive value %</th>
<th>Negative predictive value %</th>
<th>Nondiagnostic %</th>
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<tbody>
<tr>
<td>Q’ scan</td>
<td>85</td>
<td>96</td>
<td>0</td>
</tr>
<tr>
<td>CTA</td>
<td>86</td>
<td>95</td>
<td>6</td>
</tr>
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Table 1. Predictive value of multidetector computed tomography angiography (CTA) and perfusion scintigraphy (Q’) scan from retrospective evaluation of PIOPED II data
The principles of diagnosis and management are broadly similar across the individual pulmonary vasculitides, sub-divided into primary systemic and secondary disorders (table 1). The main challenges for the clinician are to recognise that vasculitis is a possible diagnosis, to make the diagnosis in nonclassical disease and to select a level of treatment appropriate to disease severity. Wegener’s granulomatosis (WG) and Churg–Strauss syndrome (CSS) are the most frequent examples of life-threatening disease.

**Epidemiology and pathogenesis**

WG is the third most prevalent systemic vasculitis (after giant cell arteritis and vasculitis in rheumatoid arthritis), with an annual incidence of 3–11 per million, largely affecting adults aged 30–50 yrs. CSS has an annual incidence of ~3 per million and mainly affects adults aged 30–50 yrs. In neither disorder is there a strong sex predilection.

Antineutrophil cytoplasmic antibodies (ANCA) are often present in systemic vasculitides involving the small- and medium-sized vessels, including CSS, WG and microscopic polyangitis. ANCA are subcategorised as cytoplasmic, perinuclear or atypical and are directed primarily against proteinase 3 in WG (cytoplasmic) and against myeloperoxidase in CSS (perinuclear), although all ANCA patterns have been reported in both disorders. *In vitro* and animal data suggest that ANCA interact with primed neutrophils, leading to endothelial damage and further neutrophil recruitment. Both diseases are generally considered to be triggered by foreign agents, including drugs and infections, with the most suggestive data relating to chronic nasal carriage of *Staphylococcus aureus* in WG.

**Clinical presentation**

Vasculitis should be suspected in diffuse alveolar haemorrhage, which may be difficult to diagnose as haemoptysis is often absent or scanty. Diffuse alveolar haemorrhage should be suspected when unexplained infiltrates on chest imaging are associated with a fall in haemoglobin over a day or two or, in chronic low-grade haemorrhage, with an iron-deficiency anaemia. Bronchoalveolar lavage is usually diagnostic of haemorrhage. Vasculitis should also be suspected: 1) in patients presenting with breathlessness on exertion and an unexplained isolated or disproportionate reduction in carbon monoxide diffusing capacity; and 2) in patients with features of an underlying systemic vasculitis, such as WG, CSS or a pulmonary-renal syndrome (of which Goodpasture’s disease is the best-known example).

Investigations that tend to be useful in suspected vasculitis are shown in table 2.

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**Key points**

- Haemoptysis is often scanty or absent in diffuse alveolar haemorrhage.
- Vasculitis must often be treated empirically, in the absence of full diagnostic clinical criteria or a histological diagnosis.
- Initial treatment should be definitive, even when the diagnosis is tentative.
- Chronic infection and malignancy are the most frequent differential diagnosis.
Churg–Strauss Syndrome

The American College of Rheumatology definition of CSS requires the satisfaction of at least four of six criteria (table 3). There is typically a prodrome of rhinitis with nasal polyps and the eventual development of late-onset asthma, followed by eosinophilia in tissue or peripheral blood and, ultimately, systemic vasculitis. Other frequent sites of involvement include the central nervous system (especially mononeuritis multiplex in 75%), skin (60%), heart (50%), joints and, less frequently, the kidneys and gastrointestinal tract. The classical triad at lung biopsy is necrotising angiitis, granulomas and tissue eosinophilia. Pulmonary infiltrates on chest imaging are more common than pulmonary nodules (which very seldom cavitate). Pleural disease is present in 50% of cases. The diagnostic role of ANCA continues to be debated. ANCA, usually p-ANCA, are present in up to two-thirds of patients, but also occur in many other nonvasculitic autoimmune and infectious conditions. Thus, neither the presence nor the absence of p-ANCA is diagnostically definitive, and is no more than a useful ancillary finding, increasing or decreasing the diagnostic likelihood.

Wegener’s granulomatosis

The classic historical WG triad consists of renal, lower respiratory tract and upper respiratory tract involvement. Most often, chronic rhinitis, sinusitis or mastoiditis progresses to generalised disease over months to years with lower respiratory tract involvement in 65–85%, including diffuse alveolar haemorrhage, which may be life-threatening. Fever and weight loss are frequent. There is a wide range of extrapulmonary organ involvement. Lung involvement is asymptomatic in a third of cases. The cardinal histological features are granulomatous inflammation and necrotising vasculitis, affecting small- to medium-sized vessels. Chest imaging may show one or more nodules which can cavitate, localised or diffuse infiltrates (which may represent alveolar haemorrhage), or evidence of large and small airway disease. As in CSS, the diagnosis should never be dependent upon ANCA positivity.
c-ANCA are not present in all cases and are also found in other vasculitides, chronic bacterial infections and cryoglobulinaemia.

Among vasculitides, microscopic polyangiitis, a necrotising vasculitis affecting small to medium-sized vessels, is the main clinical mimic of WG. This disorder also often presents with diffuse alveolar haemorrhage, which can have a poor prognosis. Necrotising glomerulonephritis, mononeuritis multiplex, and skin lesions are variably present. The cardinal histological distinction is the absence of granulomas, which are characteristically present in WG.

Diagnosis of vasculitis

A confident diagnosis requires histological confirmation or satisfaction of the requisite number of clinical criteria. However, many patients with vasculitis have features overlapping between diagnostic entities with transient or nonfulfilment of diagnostic criteria. Thus, a versatile diagnostic approach is required. When vasculitis is suspected but full clinical criteria are not satisfied, a histological diagnosis should be made, if possible. However, a negative biopsy does not exclude vasculitis, which may be patchy or give rise to nonspecific inflammatory change (as in upper airway biopsies in WG patients).

Thus, the diagnosis of a vasculitic syndrome is sometimes necessarily empirical, with chronic infection and malignancy the most frequent differential diagnoses. In such cases, initial treatment and monitoring should be as for the vasculitic syndrome most closely corresponding to the clinical presentation in that patient. Initial treatment should be definitive, as a clear response provides important support for the diagnosis, whereas a tentative therapeutic approach often prolongs diagnostic uncertainty.

Prognosis

The poor historical outcome of the vasculitic syndromes has been transformed by more aggressive therapy, but also by the increasing detection of milder disease, including patients

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Table 2. Useful investigations for suspected pulmonary vasculitis

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Chest radiography, high-resolution computed tomography</th>
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<tr>
<td>Lung function tests</td>
<td>Pulmonary function tests, arterial gases</td>
</tr>
<tr>
<td>Renal function</td>
<td>Urine dipstick testing and microscopy for proteinuria, haematuria and cellular casts; estimation of renal function; consider renal biopsy (if evidence of nephritis)</td>
</tr>
<tr>
<td>Immunology</td>
<td>Antineutrophil cytoplasmic antibodies (ANCA), antiglomerular basement membrane (anti-GBM), immune complexes, rheumatoid factor, antinuclear antibodies (ANA), antiphospholipid antibodies</td>
</tr>
<tr>
<td>Bronchoalveolar lavage</td>
<td>Iron-laden macrophages</td>
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<tr>
<td>Biopsy</td>
<td>Renal</td>
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<tr>
<td></td>
<td>Skin</td>
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<tr>
<td></td>
<td>Lung (surgical)</td>
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</table>

Table 3. ACR diagnostic criteria for CSS (four out of six are required)

1. Presence of asthma
2. Peripheral blood eosinophilia (>10%)
3. Evidence of a neuropathy in a vasculitic pattern (e.g. mononeuritis multiplex)
4. Transient pulmonary infiltrates
5. A history of sinus disease
6. Evidence of extra-vascular eosinophilia on biopsy
with limited involvement. In localised pulmonary WG and CSS alike, the outcome is much better than with multi-organ involvement. In CSS, the prognosis worsens strikingly with two or more extrapulmonary complications (5-yr survival 54%). Mortality is largely ascribable to sepsis (as a complication of treatment) or disease progression. Death from progressive disease is most commonly due to renal failure or lung involvement in WG, and to renal failure, cerebrovascular involvement and gastrointestinal disease in CSS (with 10% of deaths accounted for by lung disease).

Treatment

In most patients with WG, and in severe vasculitis in general, intense immunosuppression to induce remission is usual. In WG, oral cyclophosphamide (2.0 mg·kg⁻¹·day⁻¹) and intravenous cyclophosphamide (600 mg·m⁻² at 3–4 weekly intervals, depending on disease severity) are equally successful in inducing remission. Intravenous therapy is associated with a slightly higher relapse rate, but is much less toxic in the short-term and is much less likely to provoke haemorrhagic cystitis and subsequent malignancy, based on long-term systemic lupus erythematosus data. In life-threatening disease, cyclophosphamide and intravenous methyl prednisolone should be administered concurrently. Prophylactic co-trimoxazole (trimethoprim 160 mg/sulfamethoxazole 800 mg three times a week) is often used with prolonged intense immunosuppression, to reduce the risk of Pneumocystis carinii opportunistic infection.

In less severe vasculitis, a less aggressive initial approach is justified. In isolated pulmonary CSS, a good response is usual with oral prednisolone (1 mg·kg⁻¹·day⁻¹, up to 60 mg·day⁻¹) or, in more severe disease, intravenous methylprednisolone (up to 1 g daily on three successive days). In WG without major organ involvement, methotrexate (0.3 mg·kg⁻¹·week⁻¹) is as effective as daily oral cyclophosphamide in the induction of remission, although relapse is more likely with cessation of treatment at 12 months.

Following initial treatment, less intense long-term therapy is almost invariably required. In WG, standard maintenance treatment has consisted of azathioprine (2.0 mg·kg⁻¹·day⁻¹), usually with low-dose corticosteroid therapy, although no comparison with other agents (such as methotrexate and mycophenolate mofetil) has been undertaken, either in WG or other vasculitides. In WG, co-trimoxazole therapy has been efficacious in localised respiratory tract disease and may have an ancillary role in maintaining remission.

Intravenous immunoglobulin and anti-thymocyte globulin have been variably efficacious in resistant WG. Rituximab therapy is more promising, based on striking responses recently reported in patients refractory to standard treatments.

References

Pulmonary hypertension (PH) is defined as an increase in mean pulmonary arterial pressure $P_{pa} \geq 25$ mmHg at rest as assessed by right heart catheterisation.

**Classification**

According to values of pulmonary wedge pressure ($P_{pw}$), PH can be pre-capillary ($P_{pw} \leq 15$ mmHg) or post-capillary ($P_{pw} > 15$ mmHg).

PH can be classified into five groups according to pathological, pathophysiological and therapeutic characteristics. Despite comparable elevations of $P_{pa}$ in the different clinical groups, the underlying mechanisms, diagnostic approaches, and prognostic and therapeutic implications are completely different.

The new clinical classification is shown in Table 1. Group 1 relates to pulmonary arterial hypertension (PAH), corresponding to idiopathic, heritable and associated pre-capillary pulmonary hypertension. The term familial PAH has been replaced by heritable PAH because specific gene mutations have been identified in sporadic cases with no family history. Heritable forms of PAH include clinically sporadic idiopathic PAH with germline mutations (mainly bone morphogenetic protein receptor 2 gene as well as activin receptor-like kinase type-1 gene or endoglin gene) and clinical familial cases with or without identified mutation. Associated PAH includes conditions that can have a similar clinical presentation to that seen in idiopathic PAH with comparable histological findings. Associated PAH account for approximately half of the patients followed at specialised centres. Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary haemangiomatosis remain difficult disorders to classify since they share some

**Key points**

- PAH is a rare condition characterised by elevated pulmonary arterial resistance leading to right heart failure and death.
- PAH can be sporadic (idiopathic PAH), heritable, induced by drugs or toxins, or associated with other conditions such as connective tissue diseases.
- Doppler echocardiography is the investigation of choice for noninvasive screening but measurement of haemodynamic parameters during right heart catheterisation is mandatory to confirm the diagnosis (mean pulmonary artery pressure $\geq 25$ mmHg and pulmonary artery wedge pressure $\leq 15$ mmHg).
- Recent advances in the management of PAH include prostaglandins, endothelin receptor antagonists and type 5 phosphodiesterase inhibitors.
- Lung transplantation is an option for severe patients deteriorating despite medical treatment.
characteristics with PAH but also demonstrate a number of differences. Given the current evidence, these conditions have been individualised as a distinct category but not completely separated from PAH and have been designated as clinical group 1. Chronic thromboembolic pulmonary hypertension (CTEPH) is an important subcategory of PH, which may be cured by surgical pulmonary endarterectomy. It was decided to maintain only a single category of CTEPH without attempting to distinguish between proximal and distal forms. The most frequent causes of PH are those complicating left heart diseases (group 2) and pulmonary diseases (group 3).

All forms of PH have some common pathologic features regardless of their aetiology: medial hypertrophy of muscular and elastic arteries; dilation and intimal atheromas of elastic pulmonary arteries; and right ventricular hypertrophy. In addition to

<table>
<thead>
<tr>
<th>Table 1. Updated clinical classification of pulmonary hypertension (PH)</th>
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<tbody>
<tr>
<td><strong>1 PAH</strong></td>
</tr>
<tr>
<td>1.1 Idiopathic PAH</td>
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<tr>
<td>1.2 Heritable</td>
</tr>
<tr>
<td>1.2.1 BMPR2</td>
</tr>
<tr>
<td>1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)</td>
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<tr>
<td>1.2.3 Unknown.</td>
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<tr>
<td>1.3 Drugs and toxins induced</td>
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<td>1.4 APAH:</td>
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<tr>
<td>1.4.1 Connective tissue diseases</td>
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<td>1.4.2 HIV infection</td>
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<tr>
<td>1.4.3 Portal hypertension</td>
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<tr>
<td>1.4.4 Congenital heart disease</td>
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<tr>
<td>1.4.5 Schistosomiasis</td>
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<td>1.4.6 Chronic haemolytic anaemia</td>
</tr>
<tr>
<td>1.5 Persistent PH of the newborn</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>1 Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2 PH due to left heart disease</strong></td>
</tr>
<tr>
<td>2.1 Systolic dysfunction</td>
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<tr>
<td>2.2 Diastolic dysfunction</td>
</tr>
<tr>
<td>2.3 Valvular disease</td>
</tr>
</tbody>
</table>

| **3 PH due to lung diseases and/or hypoxia**                                                 |
| 3.1 Chronic obstructive pulmonary disease                                                   |
| 3.2 Interstitial lung disease                                                                |
| 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern                |
| 3.4 Sleep-disordered breathing                                                               |
| 3.5 Alveolar hypoventilation disorders                                                       |
| 3.6 Chronic exposure to high altitude                                                       |
| 3.7 Developmental abnormalities                                                              |

| **4 Chronic thromboembolic PH**                                                              |
| 4.1 Haematological disorders: myeloproliferative disorders, splenectomy.                    |
| 4.2 Systemic disorders, sarcoidosis, pulmonary Langerhans’ cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis |
| 4.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders       |
| 4.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis |

PAH: pulmonary arterial hypertension; BMPR2: Bone morphogenetic protein receptor, type II; ALK1: Activin receptor-like kinase 1 gene; APAH: associated PAH. Reproduced from SIMONNEAU et al. (2009), with permission from the publisher.
the aforementioned pathologic changes common to all forms of PH, PAH is characterised by constrictive and complex arterial lesions involving to varying degrees the pre- and intra-acinar pulmonary arteries. The plexiform lesion is a focal proliferation of endothelial channels lined by myofibroblasts, smooth muscle cells, and connective tissue matrix. The lesion is located within pre- and intra-acinar pulmonary arteries, and is associated with expansion and partial destruction of the arterial wall with extension of the plexiform lesion into the perivascular connective tissue. The plexiform lesion is often located at an arterial branching point (fig. 1).

**Epidemiology and survival**

PAH is a rare condition with a prevalence ranging 15–50 per million in western Europe. The prevalence of idiopathic PAH was about 6 per million in the French Registry and its incidence was 2 per million per yr. Median survival of idiopathic PAH was 2.8 yrs in the National Institutes of Health Registry before the recent development of PAH-specific therapies. Despite improvements in recent years, idiopathic, familial, and anorexigen-associated PAH remains a progressive, fatal disease in the modern management era. Mortality is most closely associated with male sex, right ventricular haemodynamic function and exercise limitation.

**Diagnosis**

The diagnostic process starts with the identification of the more common clinical groups of PH (group 2 – left heart diseases and group 3 – pulmonary diseases), to distinguish group 4 – CTEPH and finally to make the diagnosis and recognise the different types of group 1 – PAH and the rarer conditions of group 5.

PAH should be considered in the differential diagnosis of exertional dyspnoea, syncope, angina and/or progressive limitation of exercise capacity, particularly in patients without apparent risk factors, symptoms or signs of common cardiovascular and respiratory disorders. Special awareness should be directed towards patients with associated conditions and/or risk factors for development of PAH such as family history, connective tissue diseases, congenital heart diseases, HIV infection, portal hypertension, haemolytic anaemia, or a history of drug and toxin intake known to induce PAH. In everyday clinical practice, such awareness may be low. More often, PH is found unexpectedly on transthoracic echocardiography requested for another indication.

If noninvasive assessment is compatible with PH, clinical history, symptoms, signs, ECG, chest radiograph, transthoracic echocardiogram, pulmonary function tests (including nocturnal oximetry if required) and high-resolution computed tomography (HRCT) of the chest are requested to identify the presence of group 2 – left heart diseases or group 3 – pulmonary diseases. If these are not found or if PH seems “out of proportion” to their severity, less common causes of PH should be sought. Ventilation/perfusion lung scan should be considered. If ventilation/perfusion scan shows multiple segmental perfusion defects, a diagnosis of group 4 – CTEPH should be suspected. The final diagnosis of CTEPH (and the assessment of suitability for pulmonary endarterectomy) will require helical computed tomography of the chest, right heart catheterisation and selective pulmonary angiography. HRCT of the chest may also show signs suggestive of...
### Pulmonary Hypertension

**Avoid excessive physical activity (I-C)**
- Physiological support (Ila-C)
- Influenza and pneumococcal infection vaccination (IIIC)

**Initial therapy**
- **General measures and supportive therapy**
  - Expert referral (I-C)
  - Acute vasoreactivity test (I-C for IPAH) (IIb-C for APAH)

**Vasoreactive**
- Ambrisentan, Bosentan
- Sitaxsentan
- Sildenafil
- Tadalafil
- Treprostinil s.c., inhaled

**Non vasoreactive**
- Ambrisentan, Bosentan
- Sitaxentan
- Sildenafil, Tadalafil
- Iloprost inhaled and i.v.
- Treprostinil s.c., i.v.

**Inadequate clinical response**
- Vasoreactive (Ila-C)
  - Sustained response (WHO-FC III)
  - Worksheet (I-C)
  - Continue CCB

- Non vasoreactive (IIb-C)
  - Inadequate clinical response
  - Baseline (I-C) and/or Lung transplantation (I-C)
  - Sequential combination therapy (IIa-B+)
    - ERA
    - PDE-5 I

---

**Figure 2**: Evidence-based treatment algorithm for pulmonary arterial hypertension (PAH) patients (for group 1 patients only). Level of recommendation and evidence have been evaluated in the ESC/ERS European Guidelines. IPAH: idiopathic pulmonary arterial hypertension; APAH: associated pulmonary arterial hypertension; WHO-FC: World Health Organization functional class; CCB: calcium channel blockers; i.v.: intravenous; s.c.: subcutaneous; BAS: balloon atrial septostomy; ERA: endothelin receptor antagonist; PDE5 I: phosphodiesterase type-5 inhibitor. #: to maintain arterial blood O2 pressure > 8 kPa (60 mmHg); †: under regulatory review; ‡: Ila-C for WHO-FC II.
group 1’ – PVOD. If a ventilation/perfusion scan is normal or shows only subsegmental “patchy” perfusion defects, a tentative diagnosis of group 1 - PAH or the rarer conditions of group 5 is made. Performing a right heart catheterisation will be necessary to confirm the diagnosis and assess hemodynamic severity. Additional specific diagnostic tests, including haematology, biochemistry, immunology, serology and ultrasonography, will allow the final diagnosis to be refined. 6-min walk distance is an important marker of exercise limitation with prognostic value in PAH.

**Treatment**

A treatment algorithm for PAH patients is shown in figure 2. The grades of recommendation and levels of evidence for the PAH treatments are derived from European Guidelines published jointly by the European Respiratory Society and the European Society of Cardiology in 2010. Drug classes are listed by alphabetical order (ERA: endothelin receptor antagonists; PDE5 I: phosphodiesterase type-5 inhibitors; prostanoids) and single compounds are listed by alphabetical order within each class. The treatment algorithm does not apply to patients in other clinical groups, and in particular not to patients with PH associated with group 2 - left heart disease or with group 3 - pulmonary diseases. In addition, the different treatments have been evaluated by randomised control trials mainly in idiopathic PAH, heritable PAH, PAH due to anorexigen drugs and in PAH associated with connective tissue diseases or with congenital heart diseases (surgically corrected or not). The grades of recommendation and levels of evidence for the other PAH subgroups are lower.

The suggested initial approach, after the diagnosis of PAH, is the adoption of general measures, the initiation of supportive therapy and referral to an expert centre. Acute vasoreactivity testing with inhaled nitric oxide or intravenous prostacyclin or adenosine should be performed in all patients with group 1 – PAH, although patients with idiopathic PAH, heritable PAH, and PAH associated with anorexigen use are the most likely to exhibit an acute positive response and to profit from high-dose calcium-channel blocker therapy. Vasoreactive patients should be treated with optimally tolerated doses of calcium channel blockers; adequate response should be confirmed after 3–4 months of treatment. Nonresponders to acute vasoreactivity testing who are in New York Heart Association (NYHA) functional class II should be treated with an ERA or a PDE5 I. Nonresponders to acute vasoreactivity testing, or responders who remain in (or progress to) NYHA functional class III should be considered candidates for treatment with either an ERA or a PDE5 I or a prostanoid. As head-to-head comparisons among different compounds are not available, no evidence-based first-line treatment can be proposed. In this case, the choice of drug is dependent on a variety of factors, including the approval status, the route of administration, the side-effect profile, patients' preferences and physicians' experience. Some experts still use first-line *i.v.* epoprostenol in NYHA functional class III patients, because of its survival benefits. Continuous *i.v.* epoprostenol may be considered as first-line therapy for NYHA functional class IV PAH patients because of the survival benefit in this subset.

In case of inadequate clinical response, sequential combination therapy should be considered. Combination therapy can either include an ERA plus a PDE5 I or a prostanoid plus an ERA or a prostanoid plus a PDE5 I. Appropriate protocols for timing and dosing to limit possible side-effects of the combination have still to be defined.

Balloon atrioseptostomy and/or lung transplantation are indicated for PAH with inadequate clinical response despite optimal medical therapy or where medical treatments are unavailable. These procedures should be performed only in experienced centres.

**References**


CHAPTER 13:

PLEURAL, MEDIASTINAL AND CHEST WALL DISEASES

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Pleural effusion is defined as accumulation of fluid in the pleural space that exceeds the physiological amounts of 10–20 mL. Pleural effusion develops either when the formation of pleural fluid is excessive or when fluid resorption is disturbed. Pleural effusions may represent a primary manifestation of many diseases, but most often they are observed as secondary manifestations or complications of other diseases.

Pleural effusion is found in almost 10% of patients who have internal diseases and the main cause in 30–40% of these is cardiac failure. Among the noncardiac effusions, parapneumonic effusions are the most common at 48%, of which 75% are of bacterial and 25% of viral origin. Malignant pleural effusions follow in 24% of cases, half of which are caused by lung or breast cancer. Pleural effusion is secondary to pulmonary embolism in 18% of cases, to liver cirrhosis in 6%, and to gastrointestinal diseases, mainly pancreatitis, in 3% of cases. Many other possible causes, albeit extremely rare, play an important role in differential diagnosis.

Pleural effusion may result from a number of pathophysiological mechanisms, all of which disturb the physiological balance between the formation and removal of pleural fluid. Most effusions develop from both an increase in the entry rate of liquid into the pleural space and a decrease in the maximal exit rate of liquid from the pleural space. Transudative effusions are caused either by increased hydrostatic pressure (e.g. in cardiac failure), or by reduced plasma oncotic pressure because of protein deficiency (e.g. liver cirrhosis, nephrotic syndrome).
syndrome). The pleura itself remains intact. Rarely, transudates may arise from the entry of liquids with low protein concentrations (e.g. urine, cerebrospinal fluid or iatrogenic intrapleural infusion of fluids). In contrast, pathological changes in the pleura result in exudation caused by diffuse increase of capillary permeability, due to localised ruptures (e.g. blood vessels, lymphatic vessels, lung abscess, oesophagus) or to disturbed absorption (e.g. lymphatic blockage).

Pleural effusion may present at all ages, but is mainly found in adults. Malignant pleural effusions are observed mainly in patients aged >60 yrs; the most common presentations are dyspnoea and chest pain, and those of the individual underlying diseases. Physical examination reveals dullness on percussion, usually at the base of the thorax, and decreased breath sounds.

Pleural effusion may be demonstrated by a number of techniques with different sensitivities. The demonstration by percussion requires at least 300–400 mL of fluid, whereas at least 200–300 mL is necessary for standard chest radiography. Smaller amounts can be recognised by lateral decubitus radiography, which also demonstrates whether the fluid is moving freely. Ultrasound is able to demonstrate small effusions, and the sensitivity is almost 100% for volumes of ≥100 mL. Computed tomography and magnetic resonance imaging have very similar sensitivities, but require a more advanced technology and are therefore much more expensive.

In the majority of cases, the aetiology is based on the case history, clinical presentation, imaging techniques and examination of the pleural fluid.

The presence of a pleural effusion is established only by thoracentesis. The site should be selected according to the results of the diagnostic procedures. If the effusion is small, thoracentesis can be performed under ultrasound guidance. Thoracentesis is indicated in all cases of pleural effusion of unknown origin and in effusions that do not resolve after appropriate treatment.

Additional biopsy procedures, such as closed needle biopsy or medical thoracoscopy/pleuroscopy, may be necessary to confirm or exclude malignant or tuberculous causes. These are performed in a stepwise diagnostic approach (fig. 1).

In many cases, evaluation of the pleural fluid yields valuable diagnostic information or even permits a clear diagnosis. The most important criteria are appearance, protein content and cellular components. In case of more specific diagnostic questions, routine measurement of the glucose content is supplemented by determination of further laboratory.
parameters and search for infecting organisms (table 1).

The most important laboratory parameter is total protein content in the effusion, for which a threshold value of 30 g·L⁻¹ separates a transudate from an exudate. However, this value is not exclusive, and additional parameters such as lactate dehydrogenase (LDH > 200 U·L⁻¹) or cholesterol (>0.55 mmol·L⁻¹) may be helpful (table 2). The simultaneous determination of serum values is important, because these may strongly influence the values in the pleura. Low glucose values may indicate rheumatoid pleuritis, lupus pleuritis, empyema, tuberculous or malignant effusion or oesophageal perforation.

Markedly elevated amylase values are observed in acute pancreatitis and pancreatic pseudocysts, oesophageal perforation and occasionally in malignant effusions.

Haemorrhage is characterised by purely bloody effusions and haematocrit values that exceed those in peripheral blood by >50%. Increased triglycerides distinguish chylous from pseudochylous effusions. Although nonspecific, adenosine deaminase and T-cell-based interferon-γ release assays may allow the diagnosis of tuberculosis as cause of pleural effusion with high sensitivity and specificity.

Diagnostic testing for the infecting organisms that cause pleural effusion is indicated in empyemas with aerobic and anaerobic cultures and in suspected tuberculous, fungal or parasitic effusions.

Therapeutic aims in patients with pleural effusion are palliation of symptoms (pain, dyspnoea), treatment of underlying diseases, prevention of pleural fibrosis with reduction of pulmonary function, and prevention of recurrences. The therapeutic approach depends on the availability of options for causal or only symptomatic treatments.

Empyema usually requires, besides antibiotic treatment, additional pleural drainage. Resolution may be further facilitated by instillation of a fibrinolytic agent. In malignant pleural effusions, therapeutic thoracentesis or chest-tube drainage combined with chemical pleurodesis or medical thoracoscopy with talc poudrage are the preferred options for local treatment. In those resulting from tumours likely to respond to chemotherapy or hormonal treatment, systemic treatment should be started and may be combined with therapeutic thoracentesis or pleurodesis.

<table>
<thead>
<tr>
<th>Table 1. Investigative parameters of pleural effusion</th>
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</thead>
<tbody>
<tr>
<td><strong>Obligatory</strong></td>
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<tr>
<td>Appearance</td>
</tr>
<tr>
<td>Total protein</td>
</tr>
<tr>
<td>Cell differentiation (cytology)</td>
</tr>
<tr>
<td><strong>Optional</strong></td>
</tr>
<tr>
<td>Glucose (pH)</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
</tr>
<tr>
<td>Cholesterol</td>
</tr>
<tr>
<td>NT-proBNP</td>
</tr>
<tr>
<td>Triglycerides</td>
</tr>
<tr>
<td>Amylase</td>
</tr>
<tr>
<td>Bilirubin</td>
</tr>
<tr>
<td>Creatinine</td>
</tr>
<tr>
<td>Haematocrit</td>
</tr>
<tr>
<td>Immunocytology</td>
</tr>
<tr>
<td>Tumour markers</td>
</tr>
<tr>
<td>Adenosine deaminase</td>
</tr>
<tr>
<td>Interferon-γ release assay</td>
</tr>
<tr>
<td>Antinuclear factor, rheumatoid factors, etc.</td>
</tr>
<tr>
<td>Search for infecting organisms</td>
</tr>
<tr>
<td>Tubercle bacilli</td>
</tr>
<tr>
<td>Gram staining</td>
</tr>
<tr>
<td>Anaerobic, aerobic bacteria</td>
</tr>
<tr>
<td>Fungi, parasites</td>
</tr>
</tbody>
</table>

NT-proBNP: N-terminal pro-B-type natriuretic peptide.

<table>
<thead>
<tr>
<th>Table 2. Light’s criteria for exudates</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP &gt; 3 g·dL⁻¹ TP - pleura/TP - serum &gt; 0.5</td>
</tr>
<tr>
<td>LDH &gt; 200 U·L⁻¹ LDH - pleura/LDH - serum &gt; 0.6</td>
</tr>
</tbody>
</table>

TP: total protein; LDH: lactate dehydrogenase. Sensitivity of ratios 89.5/91.4, accuracy 95.4/94.7.
References

PNEUMOTHORAX AND PNEUMOMEDIASTINUM

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Introduction and classification
Pneumothorax is defined as an accumulation of air in the pleural space with secondary lung collapse. This accumulation is of diverse derivation, but visceral pleural rupture with air leakage is the most common cause. An original possible ruptured oesophagus with diminished chest wall integrity can cause free air in the pleural space, and more rarely a gas-forming organism.

In most instances the pneumothorax presents with minor symptoms without any physiological changes. Rarely, a simple pneumothorax progresses and develops with significant haemodynamic and respiratory instability, hypoxia and shock. This clinical presentation is accompanied by a tension pneumothorax and demands emergency treatment.

The pneumothorax can be classified according to cause or clinical presentation; or of spontaneous, traumatic or iatrogenic aetiology (table 1). The first category includes primary and secondary causes. A primary spontaneous pneumothorax occurs in individuals with no known pulmonary disease. A secondary pneumothorax occurs in patients with clinical or radiographic evidence of underlying lung disease. Traumatic pneumothorax occurs as a result of penetrating or blunt trauma with disruption of the bronchus, the lung, or the oesophagus. A traumatic pneumothorax is defined as "open" with an associated disruption of the chest wall. Iatrogenic pneumothorax includes the diagnostic and therapeutic pneumothorax, which are relatively common in the hospital environment but will not be considered in this discussion.

Primary spontaneous pneumothorax
Clinical features The most likely cause of a primary spontaneous pneumothorax is the rupture of small subpleural bulla (fig. 1), occurring at rest or during exercise. It is seen most often in young, tall male patients with admitted cigarette or cannabis smoking habits. Hereditary aspects have been described.

Key points
- The most likely cause of a primary spontaneous pneumothorax is the rupture of small subpleural bulla.
- Pneumothorax usually present with acute chest pain and dyspnoea.
- Pneumothorax can be complicated by persistent air leak >3 days, pneumomediastinum and haemopneumothorax.
- Recurrence is the most common indication for surgery in patients with a primary spontaneous pneumothorax.
- Surgery is accomplished by a video-assisted thoracoscopy mechanical abrasion, or by parietal apical pleurectomy in association with resection of the lung.
- In secondary pneumothorax the mortality rate for surgery may reach 10 percent and the morbidity is significant.
In the North American population, incidence varies from 6–7 per 100,000 men to 1–2 per 100,000 women. Bilateral pneumothoraces occur in <10% of patients. Recurrences are observed in 42% of patients, usually within 2 yrs. After the second pneumothorax, the chances of having a third episode increase to >50%.

The clinical presentation usually relates to the degree of pulmonary collapse. Although some patients have an asymptomatic pneumothorax, more often they present with acute chest pain and dyspnoea.

Physical findings may be totally absent if the collapse is minimal, while substantial collapse is defined in decreased chest wall movement on the affected side. Percussion of the chest cavity is hyperresonant and tympanic, and on auscultation breath sounds are decreased or absent. A pleural friction rub can sometimes be heard. Tachycardia is found in most patients.

**Diagnosis**
The clinical diagnosis of a pneumothorax is best confirmed by erect posteroanterior and lateral chest radiographs. Expiration posteroanterior chest radiography may be useful to demonstrate a small pneumothorax not seen on standard film.

Computed tomography scanning is generally not necessary unless abnormalities are noted on the plain chest radiograph or for further evaluation (e.g. suspected secondary pneumothorax), or if an aberrant chest drain emplacement is suspected.

**Complications**
Air leakage may persist for >48 h after the treatment of a pneumothorax. Often the air leak is seen in patients with a secondary pneumothorax, but occasionally patients with a primary spontaneous pneumothorax develop this complication. In this instance, surgery must be considered.

Pneumomediastinum (fig. 2) is secondary to the dissection of air along the bronchial and pulmonary vessel sheets or as a complication of a spontaneous pneumothorax. It is generally of no clinical consequence, but other causes of pneumomediastinum, such as injury to major airways or oesophagus perforation, may be needed to be excluded! Pneumoperitoneum secondary to a pneumothorax is rare, and it must be differentiated from a pneumoperitoneum associated with a perforated abdominal organ. Interstitial and subcutaneous emphysema are usually of no consequence.

Haemothorax (fig. 3) is a rare complication of a pneumothorax and results more often from the rupture of a small vessel located in adhesions between the visceral and the parietal pleura. Often re-expansion of the lung with a chest drain helps to tamponade the bleeding point.

---

**Table 1. Classification of pneumothorax**

<table>
<thead>
<tr>
<th>Spontaneous</th>
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<tbody>
<tr>
<td>Primary (healthy individuals)</td>
</tr>
<tr>
<td>Secondary (underlying pulmonary disease)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Neoplasm</td>
</tr>
<tr>
<td>Catamenial</td>
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<tr>
<td>Miscellaneous</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Traumatic</th>
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<tbody>
<tr>
<td>Blunt</td>
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<tr>
<td>Penetrating</td>
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<table>
<thead>
<tr>
<th>Iatrogenic</th>
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<tbody>
<tr>
<td>Inadvertent</td>
</tr>
<tr>
<td>Diagnostic</td>
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<tr>
<td>Therapeutic</td>
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**Figure 1. Bulla on the apex.**
Occasionally the patient becomes hypotensive and requires emergency surgery.

Bilateral pneumothorax happens in <1% of cases and can be simultaneous or, more commonly, sequential.

**Management** The different clinical situations in spontaneous pneumothorax require different therapeutic approaches. The nonoperative approach includes observation, simple aspiration, and thoracostomy with ambulatory chest drainage. Chemical pleurodesis with tetracycline or talc are options that can be used to reduce the risk of recurrence. Surgical intervention entails apical bullectomy with or without pleurodesis by pleurectomy or gauze abrasion.

**Observation** Asymptomatic patients in good health (<20%) with a small pneumothorax and no evidence of radiographic progression may be treated per observation. To ensure no complications develop, it is recommended that these patients be observed in hospital for 24-48 h. Before discharge, patients must be warned of a potential tension pneumothorax development. A weekly follow-up with clinical examination and chest radiograph is to be carried out until the pneumothorax has been completely resolved. The main inconvenience in this form of therapy is the duration, which far exceeds what is seen with conventional pleural drainage plus the added risk of a tension pneumothorax development. Therefore observation only is inappropriate in most cases.

**Aspiration and small chest tube drainage** Simple aspiration of air with a 16-gauge intravenous cannula connected to a three-way stopcock and a 60-mL syringe is an option. Small 9-Fr. chest tubes with or without flutter valves have also been used as an alternative to larger and more conventional thoracostomy tubes. The success rate is high, but problems associated with kinking and occlusion of the drains have been described. Treatment is still controversial. Simple aspiration is recommended by the British Thoracic Society – but not by the American College of Chest Physicians – as first-line treatment for the primary pneumothorax requiring intervention. Acceptance by medical staff is seemingly modest.

**Conventional tube thoracostomy** Conventional tube thoracostomy remains the procedure of choice for the management of moderate-to-large pneumothoraces. The drain allows for rapid and complete evacuation of air from the pleural space. Although underwater-seal drainage is sufficient for most cases of...
pneumothorax, the current author prefers the use of negative intrapleural pressure to maintain lung re-expansion over a period of 5 days.

**Nonsurgical therapy of recurrences** Most surgeons are concerned about the routine use of chemopleurodesis in the treatment of spontaneous pneumothorax. Being a benign disease occurring in young people who may require surgery in later life (for other disease development) the important symphysis which follows chemopleurodesis complicates and multiplies the risk in association with high morbidity rates, especially if lung resection or transplantation is considered. Chemical pleurodesis should therefore be used only in selected cases.

**Indications for surgery** Surgery may be indicated in the first instance, if the pneumothorax is complicated by a persisting air leak over 3 days. Furthermore, haemothorax development, failure to re-expand the lung, bilateral involvement and tension hazard are indications. Patients with an occupational risk hazard are a classic indication. Some authors have proposed that all young patients with a diagnosed spontaneous pneumothorax should be spared a drain thoracostomy and proceed directly to surgical intervention. This approach is not standard treatment, though many patients are operated on as a result of complication or disease recurrence. See table 2 for indications for surgery in primary spontaneous pneumothorax.

**Surgical therapy** The principles of surgical intervention for spontaneous pneumothorax consist of bulla or bleb resection (fig. 4) and obliteration of the pleural space to prevent recurrence.

Recurrence is the most common indication for surgery in patients with a primary spontaneous pneumothorax.

Multiple wedge resections may also be required when the disease is present at several sites. Segmentectomy and lobectomy are usually unnecessary and are contraindicated.

Obliteration of the pleural space is thought to be necessary to prevent recurrences. It is accomplished by mechanical abrasion, or by parietal apical pleurectomy (fig. 5), which is performed in association with resection of the lung during a video-assisted thoracoscopy.

This operation is carried out under general anaesthesia with a dual-lumen endotracheal tube. Only two thoracic incisions are made for the thoracoscope and dissecting or stapling instruments.

Apical parietal pleurectomy can be performed easily using this technique with modern endoscissors and forceps.

Video-assisted surgery is recommended as the first-line surgical treatment for patients with recurrent primary spontaneous pneumothorax. This recommendation is based on its favourable early postoperative course without major complication and the long-term outcome with 3% recurrence and patient satisfaction.

**Secondary pneumothorax**

Spontaneous pneumothorax can be secondary to a variety of pulmonary and nonpulmonary disorders.

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**Table 2. Indications for surgery in primary spontaneous pneumothorax**

<table>
<thead>
<tr>
<th>First episode</th>
<th>Second episode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged air leak</td>
<td>Ipsilateral recurrence</td>
</tr>
<tr>
<td>Non re-expansion of the lung</td>
<td>Contralateral recurrence after a first pneumothorax</td>
</tr>
<tr>
<td>Bilateral pneumothoraces</td>
<td></td>
</tr>
<tr>
<td>Haemopneumothorax</td>
<td></td>
</tr>
<tr>
<td>Occupational hazard (flight personnel, divers)</td>
<td></td>
</tr>
<tr>
<td>Absence of medical facilities in isolated area</td>
<td></td>
</tr>
<tr>
<td>Tension pneumothorax</td>
<td></td>
</tr>
<tr>
<td>Associated single large bulla</td>
<td></td>
</tr>
<tr>
<td>Individual indication</td>
<td></td>
</tr>
</tbody>
</table>

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Pneumothorax and pneumomediastinum
Chronic obstructive pulmonary disease (COPD) is the most common cause of secondary pneumothorax (fig. 6, table 3). It occurs typically in patients aged >50 yrs and is the result of a bulla rupture into the pleural space. Most patients with COPD and pneumothorax present with chest pain and acute sudden respiratory distress. These patients show little tolerance to even a small pneumothorax because of their limited pulmonary function. The diagnosis is difficult due to physical findings associated with COPD.

(e.g. hyperresonance on percussion and diminished breath sounds at auscultation). In most cases, the diagnosis is made by chest radiographs, which are also difficult to interpret because of the increased radiolucency of the diseased lung. For these difficult cases, computed tomography may be necessary to confirm the diagnosis, localise the pneumothorax and facilitate distinction between a large bulla and a pneumothorax.

The emergency treatment of patients with a secondary pneumothorax is similar to that described for primary spontaneous pneumothorax, except that observation alone is seldom justified. If the pleural space is adequately drained and the lung maintains a re-expanded state, the air leak eventually closes. In some patients, however, a bronchopleural fistula persists for 10–15 days, and surgical repair must be considered.

When surgery is required, the procedure must be individualised and based on the extent and disease infiltration, as well as the air leak location.

Staple resection of the bullae should be carried out, followed by a subtotal parietal pleurectomy or pleural abrasion.

The mortality rate for this surgery may reach 10% and morbidity is significant in those individuals with a poor overall physical condition. Other options, such as chemical...
pleurodesis, autologous blood injection and permanent fistula drainage can be considered in individual cases.

**Summary**

Primary spontaneous pneumothorax occurs in young patients with no evidence of coexisting lung disease while secondary pneumothorax is mostly seen in emphysema patients. Unless there is a complication, most surgeons will manage the first episode by conventional tube drainage. Recurrences are treated by bulla or bleb resection with apical parietal pleurectomy. Video-assisted surgery is the safest approach with excellent long-term results.

**References**


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**Table 3. Causes of secondary pneumothorax**

<table>
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<tr>
<th>Airway and pulmonary disease</th>
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<tbody>
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<td>Collagen disease</td>
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**Figure 7. Severe pulmonary fibrosis with pneumothorax on the left side.**
MEDIASTINITIS

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The majority of acute mediastinal infections results from oesophageal perforation or infection following a trans-sternal cardiac procedure. Occasionally, acute mediastinitis results from oropharyngeal abscesses with severe cervical infection spreading along the fascial planes into the mediastinum. This particularly virulent form of mediastinal infection is described as descending necrotising mediastinitis (DNM).

DNM is a potentially lethal condition especially if diagnosis or treatment is delayed or inappropriate. Despite the introduction of modern antimicrobial therapy and computed tomographic (CT) imaging, DNM has continued to produce high mortality rates (reported between 25% and 40%).

Criteria for diagnosis of DNM

Criteria for diagnosis of DNM have been accurately defined as follows:

- Clinical manifestations of a severe infection.
- Establishment of a relationship between an oropharyngeal or cervical infection and subsequent mediastinitis.
- Demonstration of radiographic features characteristic of DNM.
- Documentation of a necrotising mediastinal infection at the time of operative debridement or necropsy.

Epidemiology

Primary sites of infection are peridontal abscess, retropharyngeal abscess, and peritonsillar abscess. According to Wheatley et al. (1990), the most common primary oropharyngeal infection is odontogenic (25 of 43 cases) with mandibular second or third molar abscess.

Route of diffusion

Familiarity with the cervical fascial planes is essential in understanding the propagation pathways, symptoms and thoracic complications of cervical infections. The infection from neck to mediastinum spreads along three primary routes: via the retropharyngeal space, the perivascular space and the pretracheal space. The retropharyngeal space has been thought to be the most important route by which a cervical infectious disease spreads to the mediastinum (70% of cases in the series of Moncada et al. (1978)). Rapid spread of infection is facilitated by tissue necrosis (loose of anatomical structure), gravity and negative intrathoracic pressure.

Key points

- DNM is a particularly virulent and potentially lethal mediastinal infection.
- Initial presentation is toxic shock and respiratory difficulty, sometimes with other signs such as erythema and oedema of the neck and upper chest.
- DNM is an emergency, and should be treated with broad-spectrum i.v. antibiotics as well as early and aggressive surgical drainage.
**Pathogens involved**

DNM is a polymicrobial process with anaerobic organisms being the most predominant. Freeman et al. (2000) reviewed the English literature and found 96 patients with DNM between 1990 and 1999. All but four (4%) had mixed aerobic and anaerobic infection, with those pathogens acting often synergistically; in the four exceptions, the sole pathogen was β-haemolytic Streptococcus. Chow et al. (1978) reported that anaerobes had been recovered from 94% of patients with DNM; 52% had mixed infections and 88% had polymicrobial infections.

**Clinical and radiological signs**

Anamnesis:

- **Phase I**: periodontal or peritonsillar abscess treated by simple antibiotherapy.
- **Phase II**: erythema and oedema of the neck associated with subcutaneous emphysema.
- **Phase III**: acute aggravation of the infectious syndrome; onset of cough, dyspnoea, sternal pain and painful dysphagia.

Patients with DNM usually present with toxic shock and respiratory difficulty. Other presenting signs may include erythema and oedema of the neck and upper chest. In severe infections, frank necrosis of skin, fascia and muscle may be present. In the chest, DNM may produce abscesses and empyemas, pleural and pericardial effusions, intrathoracic haemorrhage and cardiac tamponade, and frequently results in the death of the patient.

Delay of diagnosis is one of the primary reasons for high mortality in DNM. Diagnosis of DNM from conventional radiographic studies may be difficult, principally because the signs appear late in the course of the disease. Cervicothoracic CT imaging is currently considered as the diagnostic study of choice for patients in whom DNM is suspected. Indeed, CT scan findings have been proven to confirmed the diagnosis of DNM with high accuracy in these patients who often have a nonspecific constellation of symptoms. Various CT imaging findings are increased attenuation of mediastinal fat, air fluid levels, pleural and pericardial effusions, oesophageal thickening and enlarged lymph nodes. Brunelli et al. (1996) found cervicothoracic CT imaging to be immediately diagnostic in all patients in whom it was used.

**Treatment**

Principles of treatment are:

- **Emergency**.
- Intravenous broad-spectrum antibiotic therapy: probabilistic and secondarily adapted to the pathogen(s).
- Early and aggressive surgical drainage: extensive debridement, excision of necrotic tissue, bacteriological sampling, mediastinal and pleural irrigation, feeding jejunostomy.

The decision on the type of surgical drainage to be employed is a crucial one. Four approaches have been classically reported: transcervical, standard posterolateral thoracotomy, median sternotomy and transthoracic via subxyphoid or clamshell incision. Thoracoscopic approach and video-assisted mediastinoscopic drainage can also be found. Although each of these techniques offers potential advantages and disadvantages, the posterolateral thoracotomy incision (sometimes bilateral) remains the standard by which other transthoracic approaches should be measured.

The optimal surgical approach for mediastinal drainage is theoretically dependent on the level of diffusion of necrotising process. Several studies have reported that mediastinal drainage is best accomplished through a transthoracic approach when the necrotising process extends below the level of the fourth thoracic vertebra posteriorly or the tracheal bifurcation anteriorly. However, because of the rapid spread of this type of infection, other investigators have advocated mandatory transthoracic mediastinal exploration regardless of the level of infection. This latter...
point was confirmed in a meta-analysis, where a statistically significant difference (p<0.05) in survival was found between patients undergoing transcervical mediastinal drainage (53%) versus those receiving transthoracic mediastinal drainage (81%).

**Close-watch care** Recurrent abscesses and collections are common after first operative drainage (50%) and they should be drained promptly. CT scan (at best) or ultrasound-guided percutaneous drainage (for lack) of recurrent abscesses and collections may decrease the need for recurrent surgical procedures in these critically ill patients. Surveillance should be continued until no evidence of progressive infection is found on CT imaging and the patient displays no clinical signs of infection. Hyperbaric oxygen therapy has not shown any real proof of effectiveness in this particular framework, when looking at evidence-based medicine. It should not take the place or delay surgical treatment.

**Mediastinal fibrosis** Fibrosing mediastinitis is an uncommon chronic sequela of prior infectious mediastinal involvement. A chronic, noninfectious inflammatory process results in progressive mediastinal fibrosis. The fibrosis may constrict or obstruct virtually any of the mediastinal organs (in particular, superior vena cava, oesophagus, pulmonary vein or artery). CT scans demonstrate a localised (or less frequently diffuse) mass infiltrating the mediastinum and constricting the structure; extensive calcification is associated with the fibrotic mass in a vast majority of the cases. This appearance is pathognomonic of the disorder.

**Conclusions**

DNM is caused by downward spread of neck infections and constitutes a highly fatal complication of oropharyngeal lesions. CT imaging should be performed in all patients with persistent symptoms of septicaemia after being treated for oropharyngeal infections. Prompt surgical drainage of the mediastinum should be performed. Optimal mediastinal drainage method should be tailored to each patient’s condition and extension of the mediastinitis (posterolateral thoracotomy is frequently required). In the postoperative period, progression of the disease and effectiveness of surgical therapy should be monitored by CT scanning. Further drainage should be carried out if necessary either surgically or by percutaneous drainage.

**References**

Various neuromuscular diseases (NMD) can progress to the point where they cause pulmonary complications (table 1); a careful respiratory follow-up adapted to the variable time course of each disease is therefore mandatory. Although the diseases have different causes and clinical courses, common principles apply in their management.

Evaluation of patients with suspected respiratory impairment

Clinical evaluation As the first step, a systematic clinical evaluation is essential to detect the subtle respiratory symptoms and signs related to respiratory muscle failure. Symptoms are frequently nonspecific, including fatigue, lethargy, or difficulty in concentrating. Dyspnoea and orthopnoea are often late findings in patients with usually severe functional impairment due to peripheral muscle weakness. Patients with sleep-disordered breathing (SDB) often seem to have symptoms such as an unrefreshed feeling upon awakening, morning headaches, disappearance of snoring, daytime tiredness, and irritability as a result of repeated arousals and carbon dioxide retention. Physical evaluation is essential and may reveal an increase in respiratory rate, followed by alternating abdominal and rib cage breathing (respiratory alternans), the absence of outward excursion of the abdomen during inspiration or even paradoxical inward inspiratory movement due to diaphragm weakness (abdominal paradox), accessory muscle recruitment, and mucous encumbrance of upper or lower airways.

Indicators of bulbar muscle involvement include dysarthria, trouble swallowing liquids, aspiration manifesting as a new-onset cough, or frank choking.

Pulmonary function testing Pulmonary function tests (PFT) should be routinely performed during the evaluation of patients with NMD. Because of the inadequacy of inspiratory muscle function, PFT generally reveals a pattern of restrictive ventilatory defect, with the following characteristics:

- preserved total lung capacity until a far-advanced stage of the disease
- elevated residual volume
- reduced vital capacity (VC)
- preserved functional residual capacity

When VC falls below 55% of predicted values, the onset of insidiously progressive hypercapnia is likely. A significant difference between upright and recumbent lung volumes has been reported frequently for patients with
NMD; in particular, a fall in VC of \( \geq 25\% \) has been considered a sensitive indicator of diaphragmatic weakness. A specific evaluation of respiratory muscle strength is mandatory as these tests are both sensitive and highly prognostic. A high-negative maximal inspiratory pressure (MIP) result (\(<-80\) cm H\(_2\)O) or a high positive maximal expiratory pressure result (\(>+90\) cmH\(_2\)O) excludes clinically relevant inspiratory or expiratory muscle weakness. Cough peak expiratory flow (CPEF) is the single most important factor in determining whether the ability to eliminate bronchial secretions is well preserved. Patients who either alone or with assistance are able to generate a CPEF \(>260\) L·min\(^{-1}\) can effectively remove bronchial secretions, whereas those with a CPEF \(<160\) L·min\(^{-1}\) usually require tracheal suctioning at the onset of respiratory infections. The frequency of pulmonary function monitoring depends on the rapidity of progression of the neuromuscular syndrome and may range from every 1–2 months to yearly. Once the VC drops below 40–50\% predicted, or MIP below 30\% predicted, daytime arterial blood gases should be performed.

**Sleep study** All patients with NMD should be monitored carefully for the presence of SDB. Nocturnal oximetry alone is inadequate at detecting sleep apnoea and hypoventilation. In addition, criteria defining significant desaturations remain controversial. Overnight polysomnography (PLSG) or respiratory polygraphy (RP) is advisable for patients who develop symptoms and signs of

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<tr>
<th><strong>Site of lesion</strong></th>
<th><strong>Specific disorders</strong></th>
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| Anterior horn cell | Amyotrophic lateral sclerosis  
|  | Poliomyelitis  
|  | Type I SMA, intermediate SMA  |
| Peripheral nerve and/or nerve roots | Guillain–Barré Syndrome  
|  | Charcot-Marie-Tooth disease  |
| Neuromuscular junction | Congenital myasthenia  |
| Muscle | Duchenne/Becker muscular dystrophy  
|  | Limb-girdle muscular dystrophy (especially types 2C-2F-2I)  
|  | Facio-scapulo-humeral muscular dystrophy  
|  | Congenital muscular dystrophy  
|  | Congenital myotonic dystrophy  
|  | Acid maltase deficiency  
|  | Congenital myopathy  
|  | Mitochondrial myopathy  
|  | Bethlem myopathy  |

SMA: spinal muscular atrophy.
sleep-wake abnormality or nocturnal respiratory failure (RF). It has been suggested that PLSG or RP should be performed in all NMD patients as early as possible to take a baseline recording. It should be repeated according to the course of the disease to detect abnormalities during sleep and subsequent indication to long-term ventilatory treatment.

**Management**

**Noninvasive positive pressure ventilation (NPPV)** In recent years, the approach of care in neuromuscular RF has been revised, due to two new critical developments: 1) technology has advanced and several new types of ventilatory aids have been introduced, which deliver effective mechanical ventilation (MV), even noninvasively. 2) the majority of severely disabled ventilator users have expressed satisfaction with their lives, even though they are usually unable to achieve some of the goals associated with acceptable quality of life in the "normal" population.

As a consequence, increasing numbers of NMD patients with advanced respiratory impairment are now being successfully treated by long-term NPPV usually in the home setting. The non-invasive administration of positive pressure ventilation requires a positive pressure ventilator delivering pressurised gas to the lungs through an interface with the nose or mouth, or both. In recent years, manufacturers have developed a new generation of microprocessor-controlled ventilators that supply both volume- and pressure-limited modes. Also, special features have been incorporated that are designed to facilitate the application of noninvasive techniques and are simple, reliable and easy for the patient to use.

Long-term NPPV is required when spontaneous respiratory muscle efforts are unable to sustain adequate alveolar ventilation, causing chronic-stable, or slowly progressive RF.

Indications for NPPV therapy in chronic NMD are:

1. Symptoms (such as fatigue, dyspnoea, morning headache) and one of the following:
2. Physiological criteria:
   - Significant daytime CO₂ retention (arterial CO₂ tension > 50 mmHg).
   - Nocturnal oxygen desaturation (arterial oxygen saturation <88% for at least five consecutive minutes).
   - Forced VC <50% predicted or MIP <60 cmH₂O, only for rapidly progressive disease.

The following complications are considered to be contraindications for the noninvasive ventilatory approach:

- Severely impaired swallowing, leading to chronic aspiration and repeated pneumonia.
- Ineffective clearing of tracheobronchial secretions, despite the use of noninvasive manual or mechanical expiratory aids.
- The need for around-the-clock (>20 h) ventilatory support.

These conditions usually require an invasive application of MV via tracheostomy. There is no consensus on the optimal interface to use in delivering NPPV: nasal masks are usually preferable for nocturnal ventilation, due to the fact that they are more comfortable and permit better speech; conversely, oronasal interfaces may be a suitable alternative for subjects who have excessive air leaking through the mouth or nose. Mouthpiece interfaces have also been successfully used to deliver NPPV for up to 24 h-day¹. Finally, the choice of ventilator and interface in most cases is individualised according to patients' preference and physicians' intuition and experience, rather than based on standardised evidence-based guidelines. Administration of NPPV to NMD patients with chronic RF may be expected to allow some individuals with nonprogressive pathology to live to nearly normal life expectancy, extend survival by
many years in patients with other conditions, improve physiological lung function and quality of life (QoL), as well as decrease the frequency of exacerbations requiring acute care facilities. Although ineffective for prolonging survival in patients with rapidly progressive conditions and advanced bulbar muscle involvement, such as amyotrophic lateral sclerosis/motor neurone disease, NPPV may be added with the aim of improving some aspects of the QoL, in particular energy, vitality and symptoms related to SDB, being considered as an important part of the total palliative care plan for terminally ill cases.

**Assisted coughing techniques** The onset of acute RF in patients with advanced stage NMD may be caused by airway encumbrance with mucous as a result of weakened respiratory muscles and an inability to cough effectively. A noninvasive approach to the management of tracheobronchial secretions, based on the combination of expiratory muscle aid and NPPV, has been proposed. This treatment strategy may result in a reduced need for nasal suctioning and conventional intubation, and/or tracheostomy. Among noninvasive expiratory aids, manually assisted coughing (MAC) techniques have been demonstrated to be effective in facilitating the elimination of airway secretions. Additionally, mechanical insufflation-exsufflation (MI-E) has been shown to effectively mobilise mucous secretions and has been proposed as a complement to MAC techniques in the prevention of pulmonary morbidity during respiratory tract infections (fig. 1). MI-E can be administered by a device consisting of a two-stage axial compressor that provides positive pressure to the airway, then rapidly shifts to negative pressure, thereby generating a forced expiration.

**Conclusion**

It is now clear that life can be greatly prolonged for most individuals with NMD by the availability of noninvasive aids and that the great majority of severely disabled patients submitted to ventilatory assistance are satisfied with their lives. Clinicians with a special competence in the management of such patients have the responsibility of offering these treatment options, encouraging the patients to decide in advance whether or not these measures would be acceptable.

**References**


CHEST WALL DISORDERS

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There is a large and diverse group of congenital abnormalities of the thorax that manifest as deformities and/or defect of the anterior chest wall. Depending on the severity of the case, the cardiopulmonary sphere (tolerance to exercise) as well as the psychological area may be implicated.

This diverse group includes pectus excavatum (PE), pectus carinatum (PC), Poland syndrome and cleft sternum. Among them, the two most common chest wall abnormalities are PE ("funnel chest") and PC ("keel chest").

Pathogenesis

Over the years, the theories concerning the pathogenesis of pectus deformities evolved from substernal ligament traction to overgrowth of the rib cartilage and later to a stress-strain imbalance. The genetic aspects of pectus deformities have just started to emerge and hopefully will answer many questions unanswered so far.

PE

PE is a recessively inherited chest wall deformities with an occurrence of 0.3% of all births (9:1 predominance in males). In patients with PE, the normal moderately convex contour of the anterior chest wall is replaced by precordial depression. Depending on the severity of the anomaly, the sternovertebral space is narrowed, there is a shift of the heart into the left hemithorax and pulmonary expansion is confined.

The PE indications for surgery may be summarised as follows:

- Aesthetic (psychological repercussion)
- Symptom
- Exercise intolerance; decreased endurance; exercise-induced asthma
- Body images issues (computed tomography (CT) scan)
- Pain
- Abnormal/low forced vital capacity, forced expiratory volume in 1 s, maximum voluntary ventilation
- Decreased oxygen pulse, oxygen uptake, minute ventilation
- Echocardiogram: compression of right atrium/right ventricle (rare)
- CT Haller index > 3.0
- Calliper measurement depth > 2.5

Key points

- The two most common chest wall abnormalities are pectus excavatum and pectus carinatum.
- The two most common surgical procedures for pectus excavatum repair are the modified Ravitch technique and the Nuss technique.
- Careful pre-operative evaluation on the basis of clinical but also psychological symptoms is required to select potential candidates for surgical remodelling.
- The optimal timing of surgical repair would be after the main growth has stopped (late teens or early 20s).
**PC**

In PC, the clinical aspect includes a variety of protrusion deformities of the anterior chest wall. The most common variety consists of anterior displacement of the sternal gladiolus with the appropriate cartilages in tow. In severe forms, there is also a narrowing of the transverse diameter of the chest, which seems to further exaggerate the anomaly.

The PC indications for surgery may be summarised as follows:

- Aesthetic (psychological repercussion)
- Pain
- Frequent injury
- Body image issues
- Abnormal pulmonary function testing

**Surgical treatment**

**PE** Although there are a number of different techniques utilised by surgeons, most repairs performed today will be either the modified Ravitch technique or the Nuss procedure (note that the "Wada" procedure of sternal turnover is no longer realised).

The Ravitch technique requires the exposition of the thorax's anterior region (horizontal inframammary fold incision preferred) with resection of costal cartilages affected bilaterally, the performance of a cross-sternal osteotomy with the placing of a temporary stabiliser (support bar anterior to the sternum), and the development of a muscular flap.

The Nuss technique is an alternative and new technique done by means of minimally invasive surgery and based on the skeleton's malleability and the remodelling capacity of the thorax. The technique consists in the implantation of a retrosternal steel bar that would modify the concavity of the sternum while maintaining the contour of the reformed thorax, all done by means of two small incisions on each side of the thorax.

**PC** The repair of PC, including exposure, detachment of the pectoralis muscles, transverse osteotomy and resection of the deformed cartilages, is largely identical to that described in PE. Operative correction required double bilateral chondrotomy parasternally and at points of transition to normal ribs, followed by detorsion of the sternum, retrosternal mobilisation and correction of the everted sternum, as well as of the everted and inverted ribs. After incomplete wedge osteotomy the mobilised sternum is finally stabilised by a temporary support bar anterior to the sternum and cartilages (in place for at least 6 months).

**Controversies**

Some controversies do need to be mentioned:

First, concerning PE, there has never been a randomised controlled trial comparing the results of the two most common surgical procedures (there is currently an ongoing evaluation from a multi-centre study).

Secondly, concerning the optimal timing of surgical repair, it seems that the best time for repair would be after the main growth has stopped (i.e. after adolescence in the late teens or early 20s), as opposed to an early repair. Although the operation is more traumatic after adolescence, the results are far better with minimal recurrence. Thirdly, the goal of such an approach remains elusive. Not only are we unable to reach an agreement on such simple issues as how to measure the clinical or even the anatomical severity of pectus deformities, but we are still engaged in a seemingly endless debate with the insurance companies as to whether these often physiologically and psychologically crippling abnormalities should be even considered a “disease” at all.

**Conclusions**

Chest wall abnormalities, PE and PC, are a relatively rare problem, but are commonly seen in the practice of general thoracic surgery. Careful pre-operative evaluation on the basis of clinical but also psychological

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Chest wall disorders
symptoms is required to select potential candidates for surgical remodelling. Surgical procedures, based on the surgeon’s personal expertise, are currently relatively well codified and provide satisfactory results with a low rate of complications.

References

CHAPTER 14:

THORACIC TUMOURS

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Lung cancer is the most common cause of cancer-related mortality worldwide for both males and females, with an incidence of about 1.3 million cases per year. The term lung cancer, or bronchogenic carcinoma, refers to malignancies that originate in the airways or pulmonary parenchyma.

**Epidemiology**

Lung cancer occurs through a complex multistage process that results from the combination of carcinogen exposure and genetic susceptibility (fig. 1).

A number of lifestyle and environmental factors have been associated with the development of lung cancer, of which cigarette smoking is the most important. Cigarette smoking accounts for ~80–90% of all lung cancers. Compared with nonsmokers, smokers have an ~20-fold increase in lung cancer risk, depending on the duration of smoking and the number of cigarettes smoked per day. Cigarette smokers can benefit at any age from smoking cessation: as the period of abstinence from smoking increases, the risk of lung cancer decreases, although it remains elevated compared with never-smokers. In recent years, an increasing number of never-smoker patients present with a lung cancer, often of adenocarcinoma histology. A number of other factors may also affect the risk of developing lung cancer, such as underlying acquired lung diseases (chronic obstructive pulmonary disease and pulmonary fibrosis) and environmental exposures, often synergistically with smoking (asbestos, radon, metals, ionising radiation including previous radiotherapy and polycyclic aromatic hydrocarbons).

Several molecular genetic abnormalities have been described in lung cancer, including chromosomal aberrations (*e.g.* chromosome 3p or 8p deletions), overexpression of oncogenes (*K*-ras, c-MET, Bcl-2, *etc.*), deletions and/or mutations in tumour suppressor genes (p53, retinoblastoma gene, genes on chromosome 3p) or altered telomerase activity.

**Classification of malignant lung tumours**

The World Health Organization (WHO) classification of lung tumours is based on histological characteristics in surgical samples or biopsies and is primarily based on light-optic microscopy. The following major subcategories can be distinguished:

- **Pre-invasive lesions**: mild, moderate, severe squamous dysplasia and carcinoma *in situ* are precursors of squamous cell carcinoma, atypical adenomatous hyperplasia of adenocarcinoma; and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia of neuroendocrine tumours.

- **Small cell lung cancer (SCLC)**: carcinoma with typical small cells, closely linked to smoking. A

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**Key points**

- Combined modality treatment has improved cure rates for nonmetastatic patients.
- Systemic therapy has improved quantity and quality of life for metastatic patients.
variant 'combined' type harbours >10% nonsmall cell components.

**Nonsmall cell lung cancer (NSCLC):** carcinoma with larger cells and a varying degree of squamous epithelial or glandular differentiation. *Squamous cell carcinoma* is a typically centrally located tumour in smokers. *Adenocarcinoma* is the predominant histological subtype and the most prevalent form of lung cancer in younger males (<50 yrs old) and in females of all ages, in never- and former-smokers. *Large cell carcinoma* and large cell neuroendocrine carcinoma (LCNEC); the latter is also described in the spectrum of neuroendocrine tumours extending from the low-grade typical carcinoid over the intermediate-grade atypical carcinoid to high-grade neuroendocrine tumours (LCNEC and SCLC).

Immunohistochemistry (and electron microscopy) are valuable adjuncts for differential diagnosis, e.g. the subclassification of NSCLC, the distinction between pleural metastatic adenocarcinoma and mesothelioma (calretinin and cytokeratin). They are required for diagnosis of LCNEC (chromogranin, synaptophysin, neural cell adhesion molecule).

**Clinical manifestations**

The majority of patients with lung cancer have advanced disease at clinical presentation, which reflects the frequent asymptomatic course of early stage lung cancer.

Symptoms due to the intrathoracic effects of the tumour are cough (central airway or pleural involvement), haemoptysis, chest pain, dyspnoea, hoarseness (laryngeal nerve involvement), superior vena cava syndrome (dilated neck veins, facial oedema), Pancoast's syndrome (pain, Horner sign, hand muscle atrophy).

In addition, paraneoplastic effects of lung cancer are common: hypercalcaemia (nausea, lethargy, dehydration), syndrome of inappropriate antidiuretic hormone (hyponatraemia), hypertrophic osteoarthropathy (clubbing, periostal proliferation of tubular bones), dermatomyositis, haematological manifestations (anaemia, leukocytosis, thrombocytosis), hypercoagulability, Cushing's syndrome, neurological syndromes (Lambert–Eaton). It is important to distinguish paraneoplastic effects from symptoms due to metastasis, as only the latter impede a radical approach.

As for extrathoracic disease, the most frequent sites of distant metastasis are the liver (pain, constitutional symptoms), adrenal glands, bones (pain) and brain (headache, paresis, seizures). General symptoms such as anorexia, weight loss and asthenia are often also present.

**Diagnosis**

Bronchoscopy is the appropriate test for centrally located tumours, where a pathological diagnosis will be obtained in ~90% of cases, by means of forceps biopsy, bronchial brushing or washing.

Peripheral lesions, especially solitary pulmonary nodules, can be a diagnostic
challenge. Noninvasive techniques are positron emission tomography with $^{18}$F-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET: enhanced uptake of FDG in tumours) or contrast enhanced computed tomography (CT). For most lesions, pathological documentation is needed: peripheral sampling of tissue by bronchoscopy (nowadays with help of endobronchial ultrasound), fine needle aspiration by CT guidance, sometimes surgical sampling by video-assisted thoracoscopy.

**Staging**

A proposal for revision of the Tumour-Node-Metastasis (TNM) classification of lung tumours was officially adopted for NSCLC, SCLC and carcinoid tumours in 2010. The combination of T, N, and M descriptors determines the overall disease stage: stage I (localised tumour, no lymph node spread), stage II (spread to hilar nodes), stage III (more advanced tumour and/or mediastinal lymph node spread) and stage IV (distant metastasis). The stage defines the prognosis and guides management.

A detailed medical history, physical examination, blood testing and contrast-enhanced CT from the adrenal gland to the lung apex should be performed. According to symptoms and locoregional spread, a CT or magnetic resonance image of the brain, a bone scintigraphy or other tests may be appropriate. Patients without evident metastatic disease benefit from FDG-PET or fusion FDG-PET-CT, which improve staging of locoregional lymph node and distant spread. The role of PET for SCLC is less well defined.

**Functional assessment**

In patients scheduled for radical treatment (surgical or nonsurgical combined modality treatment), an appropriate functional evaluation is needed. This can be simple (ECG and basic pulmonary function tests) in fit individuals, but is often more complex because of co-existing smoking-related cardiopulmonary disease. Diffusion capacity, cardiopulmonary exercise testing, measurement of left/right distribution of pulmonary function by, for example, scintigraphy, echocardiography, and other tests may be appropriate.

Performance status (PS), measured by, for example, the Karnofsky or WHO scale, is very important in patients with advanced disease, where it is strongly related to prognosis and treatment choices.

**Treatment of NSCLC (table 1)**

For fit patients with stage I and II, upfront surgical resection is indicated, followed by adjuvant cisplatin-based chemotherapy in case of lymph node spread or largersized (>4–5 cm) primary tumour. Curative conformal radiotherapy is to be considered in medically inoperable patients.

Stage III is subdivided into stage IIIA (ipsilateral mediastinal lymph node spread) or stage IIIB (contralateral). In stage IIIA patients, assessment of resectability in a multidisciplinary group is essential. Patients with resectable stage IIIA benefit from surgical combined modality treatment (induction therapy followed by complete resection), as this approach improves local control, progression-free survival and overall survival if pneumonectomy can be avoided. For patients with unresectable stage IIIA or stage IIIB, nonsurgical combined modality treatment is preferred (chemotherapy plus radiotherapy). For fit patients, concurrent administration is preferred; for others, a sequential approach.

In patients with advanced NSCLC and good PS (Karnofsky >80%), two-drug platinum-based chemotherapy is indicated because of modest gain in survival and improved symptom control and quality-of-life. Recent data point at the importance of histology for treatment: patients with adenocarcinoma have a superior outcome with cisplatin-pemetrexed chemotherapy, while the opposite is true for squamous cell carcinoma, where gemcitabine, vinorelbine, or a taxane can be added to platinum. Moreover, some
adenocarcinomas harbour activating mutations in the epidermal growth factor receptor (EGFR) gene, which predicts a sustained tumour control in case of therapy with EGFR tyrosine kinase inhibitors. Second-line systemic treatment (docetaxel, pemetrexed, erlotinib) also improves disease-related symptoms and survival. Nevertheless, quite some patients have a lower PS. They may be treated with single-agent chemotherapy or best supportive care.

### Treatment of SCLC

Patients with stages I–III should be treated with four to six cycles of cisplatin-etoposide chemotherapy in combination with thoracic radiotherapy. Concurrent administration is preferred if the patient is fit enough and if the tumour volume is not too bulky. Prophylactic cranial irradiation (PCI) should be offered to patients with response following chemoradiotherapy, as it reduces the risk of cerebral metastases and improves survival. Patients with stage IV should be treated with platinum (cisplatin or carboplatin) in combination with etoposide for four to six cycles. PCI is added in case of major response after chemotherapy. Patients with good performance status relapsing after response to first-line chemotherapy should be considered for retreatment, either with repeat platinum-etoposide or with topotecan.

### General treatment measures

Radiotherapy plays an important role in palliation of local problems such as vena cava superior syndrome, haemoptysis, postobstructive pneumonia, bone pain and brain metastasis. Endobronchial treatment (cryotherapy, laser resection, endobronchial stenting) may relieve symptoms in patients with major airway obstruction. Overall supportive measures, such as analgesics, corticosteroids, biphosphonates in the case of bone disease, etc., should accompany the primary tumour treatment, or may be the only option in patients with very poor performance status. A multidisciplinary team including doctors, nurses, psychologists, social workers and others will have a major role in the latter situation. Smoking cessation should be advised to all patients in remission after treatment.

### References


### Table 1. Major staging groups, preferred treatment patterns, and expected 5yr survival rates for nonsmall cell lung cancer

<table>
<thead>
<tr>
<th>Group</th>
<th>Stage</th>
<th>Treatment</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early stages</td>
<td>Stage I</td>
<td>Surgical resection (adjuvant chemotherapy for large tumours)</td>
<td>58-73%</td>
</tr>
<tr>
<td></td>
<td>Stage II</td>
<td>Radiotherapy if medically inoperable</td>
<td></td>
</tr>
<tr>
<td>Locally advanced stages</td>
<td>Stage IIIA</td>
<td>Surgical or nonsurgical combined modality treatment</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>Stage IIIB</td>
<td>Nonsurgical combined modality treatment</td>
<td>9%</td>
</tr>
<tr>
<td>Advanced stage</td>
<td>Stage IV</td>
<td>Chemotherapy and/or targeted agents</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

Data from Goldstraw et al. (2007).
In oncology, chemotherapy involves the use of substances with nonspecific cytotoxic and anti-proliferative properties to control tumour spread and symptoms, improve quality of life and lengthen survival.

Depending on the clinical situation, either a single chemotherapeutic agent or a doublet may be given. In metastatic lung cancer, chemotherapy is palliative; however, in earlier stages of disease it can be curative when combined with local irradiation (radiochemotherapy) or surgery. Chemotherapy given after surgery is known as adjuvant chemotherapy; that administered before surgery is neoadjuvant or induction chemotherapy. Generally, chemotherapy is administered intravenously, although some agents may be given orally. There are also circumstances in which chemotherapeutic agents may be administered locally (intrathecally or in the pleural space). Although most modern chemotherapeutic agents have milder side-effects than the older agents, side-effects remain problematic and include neutropenia, neuropathy, nephropathy, fatigue, hair loss and nausea and vomiting (table 1).

The decision how to treat a patient is dependant not only on the diagnosis itself, but on the patient’s comorbidities and overall medical condition, as well as on the overall prognosis and goal of treatment (table 2). Performance status scales attempt to standardise the assessment of a patient’s
general state of health; the Karnofsky scale and the World Health Organization/Eastern Cooperative Oncology Group (WHO/ECOG) scale are commonly used (table 3).

In most cases the overall management of lung cancer involves a combination of chemotherapy, radiation, bronchoscopic intervention and surgery. For this reason, interdisciplinary tumour boards are an important forum for discussion and decision making in the care of lung cancer patients.

**Chemotherapy in small cell lung cancer**

**First line** Small cell lung cancer (SCLC) is almost always a systemic disease and in most cases the initial response to chemotherapy is quite good.

Cisplatin plus etoposide is a frequently used first-line combination, although carboplatin can be used instead of cisplatin in patients with poor prognosis/performance status or contraindications to cisplatin. Another commonly used but less effective regimen is adriamycin, cyclophosphamid, vincristin. In small cell lung cancer, chemotherapy offers a clear survival benefit, from 4–6-week survival in untreated patients with extensive disease, to 12-month survival in extensive disease with chemotherapy.

**Second line** The second-line treatment of SCLC has been shown to increase survival and quality of life compared with best supportive care alone. Here the choice of medications depends on the length of time since the initial remission. For patients whose tumours initially respond well to chemotherapy and then go on to recur or progress >3–6 months later, the medications used in first-line treatment can be given again. Tumours that progress <3 months after the end of first-line therapy should be treated with different agents: in this setting, topotecan monotherapy is a common choice and can be given intravenously or orally. If the tumour does not respond to first-line therapies or progresses quickly after chemotherapy, second-line treatment is

### Table 1. The major side-effects of chemotherapeutic agents

<table>
<thead>
<tr>
<th>Side-effect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>Cisplatin is highly emetogenic. Prophylactic anti-emetics should be given to all patients receiving chemotherapy. Delayed nausea and vomiting may occur days after administration. Commonly used anti-emetics include dexamethasone, serotonin antagonists and neurokinin-1 inhibition.</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Severe neutropenia refers to peripheral neutrophil counts &lt;500 cells·µL⁻¹. Reverse isolation in hospitalised patients with severe neutropenia may reduce the risk of nosocomial infections. Febrile neutropenia refers to elevated oral or axillary temperature (&gt;38°C for &gt;1 h, or &gt;38.2°C one-time measurement) in the setting of severe neutropenia, and should be treated with intravenous antibiotics. The prophylactic use of granulocyte colony-stimulating factors can be considered in those at increased risk of developing febrile neutropenia.</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Consider transfusion in symptomatic patients or those with very low haemoglobin. The use of erythrocyte-stimulating factors (e.g. erythropoietin) is generally not recommended; however, it can reduce the number of transfusions and improves fatigue.</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Most commonly caused by the taxanes and vinorelbine.</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Multifactorial. Malnutrition, anaemia and depression commonly play a role.</td>
</tr>
</tbody>
</table>
usually recommended. Inclusion in clinical trials or best supportive care alone also are also reasonable options.

**Multimodal therapy** Studies have shown that adjuvant chemotherapy improves survival in SCLC patients with completely resected very limited disease. In patients with limited disease, local radiation is generally combined with chemotherapy. Concurrent chemoradiation regimens including cisplatin are the most effective. In extensive disease SCLC, thoracic radiation may be considered in patients who have responded well to chemotherapy. Prophylactic cranial irradiation has been shown to improve survival in SCLC patients who reach good remission after chemotherapy, including those with extensive disease at the time of diagnosis.

**Nonsmall cell lung cancer**

Chemotherapy is the treatment of choice for nonsmall cell lung cancer (NSCLC) patients with distant metastases or malignant pleural

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**Table 2. Considerations for individual chemotherapeutic agents**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Highly emetogenic (appropriate use of anti-emetics is essential)</td>
</tr>
<tr>
<td></td>
<td>Nephrotoxic. Avoid in patients with reduced GFR</td>
</tr>
<tr>
<td></td>
<td>Prehydration (≥ 500 mL NaCl 0.9% per 50 mg cisplatin) reduces the risk of</td>
</tr>
<tr>
<td></td>
<td>nephrotoxicity</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Consider as alternative to cisplatin in elderly patients or those with</td>
</tr>
<tr>
<td></td>
<td>contraindications to cisplatin, dosed at AUC</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>May cause neuropathy or neutropenia</td>
</tr>
<tr>
<td></td>
<td>Available in pill form for oral administration</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>30-min infusion time (more toxicity with slower infusion), avoid combination</td>
</tr>
<tr>
<td></td>
<td>with radiotherapy due to increased side-effects</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>Short (10-min) infusion time</td>
</tr>
<tr>
<td></td>
<td>Effective in patients with nonsquamous cell NSCLC and mesothelioma</td>
</tr>
<tr>
<td></td>
<td>The risk of myelosuppression can be significantly reduced by vitamin B12 (1,000 IU</td>
</tr>
<tr>
<td></td>
<td>i.m. every 9 weeks) and folate (0.35–1 mg-day)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Premedication to prevent allergic reaction is required (dexamethasone and</td>
</tr>
<tr>
<td></td>
<td>antihistamine)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Premedication to prevent allergic reaction is required (dexamethasone)</td>
</tr>
</tbody>
</table>

| GFR: glomerular filtration rate; AUC: area under the curve; NSCLC: nonsmall cell lung cancer; i.m.: intramuscular. |

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**Table 3. The World Health Organization/Eastern Cooperative Oncology Group (WHO/ECOG) scale**

<table>
<thead>
<tr>
<th>WHO/ECOG Performance status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Patient is fully active and unrestricted in daily activities</td>
</tr>
<tr>
<td>1</td>
<td>Patient cannot carry out physically strenuous activities, but is able to care for self and carry out light work</td>
</tr>
<tr>
<td>2</td>
<td>Patient is ambulatory and can care for self but is unable to work. Up and about for &gt;50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Patient is limited in self care activities and confined to bed or chair for &gt;50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot care for self. Totally confined to bed or chair</td>
</tr>
</tbody>
</table>
effusion, although its efficacy is limited. In fit patients, first-line treatment should consist of cisplatin or carboplatin paired with one of gemcitabine, docetaxel, paclitaxel, pemetrexed or vinorelbine, administered over 4–6 cycles. The increase in survival offered by platinum-based chemotherapy is in the range of several months, although some patients experience durable remissions, and there is evidence that chemotherapy improves patients' quality of life and performance status. Unfortunately, ~40% of NSCLC tumours do not respond to chemotherapy and only 20% of NSCLC patients experience significant regression of their tumours. In earlier randomised trials with platinum-based chemotherapy doublets (cisplatin/paclitaxel, cisplatin/gemcitabine, cisplatin/docetaxel, vinorelbine/cisplatin or carboplatin/paclitaxel), there were no significant differences in response rate or overall survival. More recent studies show that histology plays a role in the response of NSCLC to various chemotherapeutic medications. In particular, nonsquamous histology (adenocarcinomas and large cell NSCLC) is predictive for better activity of pemetrexed.

Patients with poor performance status may not tolerate platinum-based doublet chemotherapy, but can often be treated with a single chemotherapeutic agent, for instance gemcitabine or paclitaxel, or in some cases with a carboplatin-based doublet.

Second-/third-line chemotherapy Second/third-line chemotherapy in NSCLC generally involves monotherapy with a chemotherapeutic agent (docetaxel and pemetrexed are licensed in this setting) or, in selected patients, erlotinib. Participation in phase II or III clinical trials with newer targeted agents may offer patients the option of treatment with medications not yet available on the market. There is some recent evidence that early second-line or maintenance therapy may be beneficial, especially for patients who did not respond particularly well to firstline chemotherapy (stable disease patients compared to partial/complete responders).

Targeted therapies The role of targeted therapies in NSCLC is growing rapidly. Unlike traditional chemotherapeutics, which interfere with cell division in all rapidly dividing cells, targeted therapies attempt to inhibit cell activity more selectively at the level of growth factor receptors and intracellular signalling cascades.

The epidermal growth factor receptor (EGFR) is involved in signalling cascades leading to cell division and proliferation. In tumour cells, mutations and overexpression in EGFR or in downstream components of the EGFR pathway increase proliferation, survival and metastasis. Several targeted therapies attempt to interfere with this abnormal EGFR activity: erlotinib and gefitinib are both tyrosine kinase inhibitors (TKIs) which inactivate the intracellular portion or EGFR, whereas cetuximab, as an antibody, binds to the extracellular domain of the receptor. EGFR inhibitors do not cause typical chemotherapy side-effects, but commonly cause clinically significant rash, diarrhoea and liver enzyme elevation.

There is evidence that EGFR mutations in exon 19 and 21 (“activating mutations”) predict a good response to EGFR TKIs, whereas other mutations such as T790M predict resistance. Response to EGFR inhibitors is also associated with certain clinical characteristics (female patients, nonsmokers, adenocarcinoma, Asian ethnicity). Erlotinib is approved as a second- or third-line therapy in NSCLC. Gefitinib is only approved for use in patients with a documented activating mutation in EGFR.

Because tumours are dependent on the growth of new blood vessels, inhibition of angiogenesis is of major therapeutic interest. Bevacizumab is a monoclonal antibody against the vascular endothelial growth factor. In stage IIIB and IV NSCLC patients, there is evidence that the addition of bevacizumab to platinum-based doublets is beneficial. The combination of bevacizumab with carboplatin + paclitaxel was shown to provide a survival benefit, whereas the combination of bevacizumab with cisplatin + gemcitabine
only showed a benefit in progression-free survival.

Bevacizumab can cause severe haemoptysis, seen in the randomised phase II trial mostly in patients with squamous cell histology. Thereafter, most studies have excluded patients with brain metastases, previous haemoptysis, cavitary lung lesions or concurrent anticoagulation.

**Malignant mesothelioma**

If systemic treatment is applied, usually cisplatin plus pemetrexed are given. Often more than 6 cycles are used. In patients with contraindications to cisplatin, the off-label use of carboplatin can be considered. There is evidence supporting off-label second-line treatment with vinorelbine, gemcitabine or in some cases with pemetrexed.

**Palliative treatments**

In advanced lung cancer, progressive tumour growth in the central airways can produce haemoptysis, cough, and airway obstruction leading to shortness of breath or pneumonia. In these situations quality of life may primarily be improved through the palliative use of endoscopic tumour debulking techniques or prosthetic measures. Brachytherapy is also an effective option for the local treatment of tumour growth in or around the central airways, and stents may be used to maintain airway patency in patients with compression due to tumour.

Palliative radiation provides symptomatic relief in patients with brain and bone metastases. Pleurodesis is an option for patients with recurrent malignant pleural effusions.

**References**


**Weblinks**

PRINCIPLES OF SURGICAL TREATMENT FOR EARLY-STAGE NONSMALL CELL LUNG CANCER

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Despite the progress made in thoracic oncology over the past 30 yrs, surgical resection remains the mainstay of curative treatment for nonsmall cell lung cancer (NSCLC). Although combined modality treatments based on neoadjuvant or adjuvant chemotherapy are credited with a slight advantage in survival, the area under the survival curve proves that the most substantial part of cure is owed to surgery. Contemporary alternatives to surgery for small tumours are stereotactic radiotherapy and radiofrequency ablation; these treatments are not yet scientifically validated and ignore lymphatic spread (see below). In the N2 category, surgery has been challenged by exclusive radiochemotherapy in a recent multicentre trial by VAN MEERBEECK et al. (2007), whose conclusions are not acceptable: the surgical arm comprised an incomplete resection rate of nearly 50%. Most patients nowadays are subjected to combined treatments, but the scientific evidence remains ambiguous and controversial. It is unclear whether neoadjuvant therapies are more beneficial to the N2 population, or to those with incipient disease. Meta-analysis demonstrated a benefit for patients undergoing adjuvant therapy; the latter is of weak clinical relevance for the individual patient, knowing that treatment of 20 patients is needed to save one at 2 yrs. The result deteriorates in the long term, and long-term complications of chemotherapy appear in survivors.

Workup of the patient should include a check-up of fitness according to European Respiratory Society/European Society of Thoracic Surgeons guidelines.

Key points
The following recommendations are evidence-based:

- Optimal results are obtained by specialised surgeons working in large-volume units.
- Anatomical resection combined with a complete lymph node dissection is the gold standard.
- Bronchoplastic and angioplastic lobectomies are viable alternatives to pneumonectomy, provided that a complete resection may be achieved.
- Segmentectomies could be applied to high-risk patients with tumours <2 cm in diameter; wedge excisions may be recommended for very small bronchoalveolar carcinoma (ground-glass opacity).
The aim of this article is to describe the quality requirements of contemporary oncologic thoracic surgery, based on recommendations issued by a working group of the French Society for Thoracic and Cardiovascular Surgery.

**How can we define early-stage lung cancer?**

Although there is no clear definition, it seems adequate to restrict this label to patients with reasonable chances for survival. Since lymph node invasion at the N2 level is a marker of poor prognosis, the medical oncologist would certainly restrict the definition to stages N0 and N1.

For the surgeon, resectable disease offers an advantage over nonresectable disease. Minimal N2, defined as microscopic metastasis to a single N2 node, is credited with a survival rate of 30-35% at 5 yrs, which is comparable to the worst N1. Further, resectable T4N0 disease, such as selected cases of Pancoast tumors or main carinal invasion, may achieve a 5-yr survival of >40%.

Any marginal situation needs to be discussed with a qualified thoracic surgeon, and any decision not to operate should be validated by a qualified thoracic surgeon in a multidisciplinary discussion.

**What are the usual survival figures?**

The following figures drawn from the classic surgical literature apply to surgical treatment, regardless of any neoadjuvant or adjuvant treatment.

For stage I, the usual figures vary from 55-75% with a substantial difference between T1 and T2. Survival is further influenced by the type of resection (lobectomy versus pneumonectomy) and the comorbidity, which accounts for half of late deaths (table 1).

For stage II, reported 5-yr survival rates vary between 35-50%. Besides a difference between T1N1 and T2N1, there is a very dissimilar survival pattern according to the intralobar or extralobar location of the N1 node. Intralobar N1 is credited with 5-yr survival close to 55%, whereas in extralobar N1 it reaches only 35% (table 2).

For stage IIIA-N2, survival rates at 5 yrs are considerably lower and range from 15-25%. However, minimal N2 is a subgroup with a possible survival rate of 35% at 5 yrs. There is a small subset of completely resectable IIIA-T4N0 disease (Pancoast tumors, main carina involvement) that can achieve a survival of close to 50% at 5 yrs.

The large majority of patients with stage IIIB are inoperable, and global survival at 5 yrs is <5%.

**Quality requirements: what depends on the surgeon and his institution!**

Thoracic oncologic surgery is a specialised medical activity. The best results are obtained by well-trained specialised thoracic surgeons, working in high-volume units.

1. **Qualification of the individual surgeon**
   A comparison of the results of lung resections performed by either general or well-trained thoracic surgeons in a cohort of 1,583 cases of resection for lung cancer performed between 1991 and 1995 showed that operative mortality was twice as high when resection was performed by general surgeons. It is remarkable that 75% of general surgeons performed fewer than 10 resections during the observation period.

2. **Hospital volume and its impact on post-operative mortality**
   A review of data from the Medicare registry between 1994 and 1999 revealed that operative mortality following lobectomy varied from 6.4% in a low-activity centre (<9 cases per year) to 4.2% in a high-activity centre (>46 cases per year); following pneumonectomy, the range extended from 17% to 10.6%.

We may conclude that a high hospital volume warrants the necessary routine not only of the operating surgeon, but also of the surrounding team.
3. Hospital volume and its impact on long-term survival

It has been confirmed that hospital volume affects not only early outcome, but also long-term survival, in a study that included 2,118 patients operated upon in one of 76 hospitals over a 10-yr period, divided into quintiles according to hospital volume. Operative mortality ranged from 3% at high-volume units to 6% at low-volume units; operative morbidity ranged 20–44%. The 5-yr survival decreased from 44% at high-volume units to 33% at low-volume centres.

This study suggests that appropriate decision making is enhanced by routine.

Basic principles of surgical treatment: complete anatomic resection and complete lymph node dissection.

The basic principles described here are based on recommendations issued by a working group of the French Society for Thoracic and Cardiovascular Surgery. A complete cancer operation requires anatomic resection of the primary lesion and complete homolateral lymph-node dissection.

1. Complete anatomic resection

Anatomic resection means either lobectomy or pneumonectomy with precise hilar dissection, according to the loco-regional extent of the tumour. The rule is to privilege lobectomy whenever it enables a complete resection. Standard lobectomy is not possible if the tumour extends across the fissure, invades the main pulmonary artery or involves the bronchial tree proximal to the lobar take-off; a double location in different lobes is also an indication for pneumonectomy.

Lobectomy is preferred to pneumonectomy because of a substantially lower operative risk. Operative mortality is ~2% following lobectomy, and ranges from 6–10% following pneumonectomy. Mortality after pneumonectomy may be >10% in patients aged >70 yrs, or in case of extended resection. There is an ongoing debate whether mortality of pneumonectomy is increased after induction chemotherapy, especially on the right side. We have recently demonstrated a similar risk when compared to standard operations, and a survival advantage even if the patient remains stage N2. Other disadvantages of pneumonectomy are decreased quality of life owing to loss of respiratory function, and decreased possibilities of repeated curative resection, should a metachronous primary cancer occur (~10% of stages I and II).

To resect less than a pulmonary lobe is not recommended as a routine. The Lung Cancer

<table>
<thead>
<tr>
<th>First author</th>
<th>Patients n</th>
<th>Intralobar N1</th>
<th>Extralobar N1</th>
</tr>
</thead>
<tbody>
<tr>
<td>YANO</td>
<td>78</td>
<td>64</td>
<td>39</td>
</tr>
<tr>
<td>VAN VELZEN</td>
<td>391</td>
<td>57</td>
<td>30</td>
</tr>
<tr>
<td>RIQUET</td>
<td>256</td>
<td>53</td>
<td>38</td>
</tr>
</tbody>
</table>

Table 1. Survival following stage I disease: independent factors of prognosis

<table>
<thead>
<tr>
<th></th>
<th>Yes %</th>
<th>No %</th>
<th>p-value</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonectomy</td>
<td>53</td>
<td>62.7</td>
<td>0.031</td>
<td>1.55</td>
</tr>
<tr>
<td>Angio-invasion</td>
<td>54.5</td>
<td>61.9</td>
<td>0.029</td>
<td>1.85</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>46.3</td>
<td>64.3</td>
<td>0.017</td>
<td>1.55</td>
</tr>
</tbody>
</table>

Adapted from THOMAS et al. (2002).
Study Group (Ginsberg et al. (1995)) compared lobectomy and segmentectomy (or wedge excision) for T1N0 cancer in a randomised trial. There was a drop of 20% in 5-yr survival for patients subjected to segmentectomy, and a 3-fold increase of local recurrence following segmentectomy or wedge excision. More recent investigations from Japan conclude that wedge excisions are valuable in small bronchoalveolar carcinoma; similarly, segmentectomies could be applied to stage I tumours <2 cm.

When the tumour is invading surrounding anatomical structures, an enlarged en bloc R-0 resection may achieve satisfactory long-term results; this should be carried out in specialised institutions so that an excessive operative mortality does not erase the survival benefit of resection.

2. Complete homolateral lymph node dissection The goals of lymph node dissection are: 1) to ascertain staging; and 2) to ensure complete resection of the disease.

Staging is important on the individual level to set prognosis and to define the most appropriate treatment strategy. On the collective level, adequate staging facilitates comparison of different treatment modalities, or results from different institutions.

Leaving unrecognised lymph node metastases obviously leads to “local recurrence”. Medical imaging has serious pitfalls. Computed tomography underestimates N2 stage in one patient out of five, and overestimates in one patient out of two. A negative positron emission tomography (PET) scan matches with mediastinoscopy, but the latter is subject to 10–15% failures; a positive PET requires histologic assessment because the false-positive rate is >40%. Furthermore, >30% of patients with N2 disease have no apparent disease at the N1 level (so called skip metastases). Even among patients with T1 disease, 22% have mediastinal lymph node involvement.

As such, intraoperative exploration of the mediastinum is mandatory, and can be achieved by two different procedures: either random sampling of nodes, or complete node dissection. Obviously, only complete dissection appears to be serious and reliable. The arguments are as follows.

In patients with pathological stage I-N0 disease, survival increases with the number of dissected nodes. This demonstrates that the more lymph nodes are harvested, the lower the risk of ignoring an invaded node, and the more reliable the staging.

In a cross-sectional analysis, we have compared sampling and dissection in each single case of 248 resections. Sampling identified 52% of N2; multilevel N2 was identified in 42% of events only. Resection based on sampling alone would have been complete in only 12%.

The standard lymph node dissection is defined as an en bloc dissection of all lymphatic tissue along its anatomical borders (tracheobronchial tree, sheets of major vessels, oesophagus). On the right side, it includes lower oesophageal nodes within the

<table>
<thead>
<tr>
<th>Stage</th>
<th>268 dissections</th>
<th>264 samplings</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>82.2</td>
<td>57.5</td>
</tr>
<tr>
<td>II</td>
<td>50.4</td>
<td>34.0</td>
</tr>
<tr>
<td>III</td>
<td>27.0</td>
<td>6.2</td>
</tr>
<tr>
<td>Global</td>
<td>48.4</td>
<td>36.9</td>
</tr>
</tbody>
</table>

Reproduced from Wu et al. (2002), with permission from the publisher.
pulmonary ligament, subcarinal space and paratracheal space. On the left side, it includes pulmonary ligament, subcarinal space, aorto–pulmonary window, phrenic nodes and subaortic nodes up to the left tracheo-bronchial angle.

Formal lymph node dissection does not increase the postoperative complication rate. There is increasing evidence for a positive effect on survival. A first, nonrandomised study compared sampling to dissection in stage II and III and concluded that there is a survival advantage following dissection.

A randomised study including >500 patients demonstrated a survival advantage of node dissection without relation to a stage migration effect: it was observed not only stage by stage, but also when comparing the two investigated groups as a whole (table 3).

A meta-analysis concluded that 4-yr survival was increased in patients having undergone node dissection, with a hazard ratio of 0.78.

**Are there alternatives to pneumonectomy?**

Given the high operative mortality rate of pneumonectomy, it is meaningful to look for alternatives. Bronchoplastic operations (sleeve lobectomy) are indicated: 1) when the tumour involves the lobar take-off on the endobronchial side; and 2) when positive N1 nodes with capsular disruption are identified at the origin of the lobar bronchus. Angioplastic lobectomies are indicated when the lobar branches destined to the upper lobe cannot be divided safely with tumour-free margins; this situation is much more frequent on the left side for anatomical reasons.

The operative risk of bronchoplastic lobectomy is comparable to standard lobectomy, with a mortality of ≤2%. Long-term survival and rate of local recurrence match with reported data per stage (table 4). A meta-analysis published by Ma et al. (2007) showed that mortality was almost half that after pneumonectomy in experienced teams; 1-year survival was improved after bronchoplastic resection.

**References**


**Table 4. Survival following bronchoplastic lobectomy**

<table>
<thead>
<tr>
<th>First author</th>
<th>Stage I %</th>
<th>Stage II %</th>
<th>Stage III %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tedder</td>
<td>63</td>
<td>37</td>
<td>21</td>
</tr>
<tr>
<td>Mehran</td>
<td>57</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td>Van Schil</td>
<td>62</td>
<td>31</td>
<td>31</td>
</tr>
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<td>Massard</td>
<td>70</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>Icardi</td>
<td>60</td>
<td>30</td>
<td>27</td>
</tr>
<tr>
<td>Tronc</td>
<td>63</td>
<td>48</td>
<td>8</td>
</tr>
</tbody>
</table>

ERS Handbook: Respiratory Medicine


The thorax is a common site of metastasis from various cancers, which may affect the hilar or mediastinal lymph nodes, bone (chest wall and vertebrae), lung, pleura, muscle or heart, and pericardium. These metastases may induce mediastinal compression syndromes (Pancoast, superior vena cava syndrome, dysphagia etc., just like locoregional extension of a primary lung cancer).

**Pleural metastases**

Pleural metastasis occur commonly in patients with haematological or solid tumours. In an already old series of 133 patients, the most common primary sites appear to be breast carcinoma (35 patients), lung cancer (32), lymphomas (20), Hodgkin’s disease (12), ovary carcinoma (9), adenocarcinoma of unknown primary tumour (6) and melanoma (4). In women specifically, 37% of malignant pleural effusions were due to breast cancer, 20% to gynaecological cancers and 15% to lung cancer. Probably, with the increase of the frequency of lung cancer in women, there will be a higher percentage of malignant pleural effusions secondary to lung cancer in the forthcoming years.

**Pericardial effusions**

Out of 55 patients admitted to an intensive care unit with malignant pericardial effusion, 30 had a lung carcinoma as a primary tumour, nine breast cancer, five haematological malignancies and 11 other solid tumours. Figure 1 shows a neoplastic pericardial effusion in a patient with lung cancer.

**Pulmonary metastases**

Endothoracic metastases of breast cancer are essentially pleuropulmonary (figs 2a and b, and 3). In a review of 660 cases of breast cancers followed during a period of 5 yrs between 1975 and 1979, 119 endothoracic metastases were recorded. Among them, 79 were pleural or pleuroparietal, 80 were pulmonary (lymphangitis 41, multiple nodules 34, solitary nodules nine, endobronchial seven, tumoral emboli two, alveolar metastasis one), 46 hilar or mediastinal, and two myocardial metastases Chatkin et al. (2007).
Pulmonary metastases were also frequent in lung cancer and their prognosis appeared to be of intermediate value if there is no other site involved. In fact, they will be classified as M1a in the new staging classification. Sometimes, pulmonary metastases may be excavated (fig. 4).

Endobronchial metastasis is an infrequent feature (table 1), the most frequent primary site being head and neck (although, it might be difficult to distinguish them from a primary lung cancer) followed by breast and kidney.

It may be quite difficult, if not impossible, to distinguish a primary lung cancer from endobronchial metastasis on a computed tomography (CT) scan. Endobronchial metastases from melanoma are often black. Endobronchial metastases of a kidney cancer display strong enhancement on the contrast-enhanced CT images. Whenever a bronchofibroscopy is performed, there may be quite severe bleeding at biopsy attempt. In fact, cough with haemoptysis is the most frequent symptom.

Tumoral emboli may provide similar clinical and radiological features as cruroic emboli; however, peripheral tumoral micro-emboli are characterised by respiratory failure despite normal imaging. Diagnosis may be obtained by transbronchial biopsy or by video-thoracoscopy with, at histology, multiple carcinomatous emboli in distal pulmonary arteries, veins and lymphatics.

### Hilar and mediastinal metastatic lymph nodes

Of course, metastatic hilar and mediastinal lymph nodes are usually linked to an intrathoracic carcinoma. Among 565 patients, only 37 had a history of extrathoracic...
cancer in a surgical series. Primary cancer was most frequently breast but also kidney, testis, prostate, thyroid and other. Metastasis of breast cancer to intrathoracic nodes seems to occur quite frequently. In an autopsy series of women who had died of disseminated breast cancer, metastatic involvement of intrathoracic lymph nodes was found in 71% of cases. Lymph node involvement was more extensive in the mediastinum ipsilateral to the primary breast cancer than in the contralateral mediastinum.

Bone metastases in the chest

Bone metastases in the chest are common sites of secondary lesions of lung, prostate and breast cancer in which bone is the most common metastatic site. Bone metastases affect 8% of patients with breast cancer. Bone scans remain the primary means for detection of bone metastases. In a meta-analysis of six studies comparing bone scan and positron-emission tomography (PET) scan without CT, a pooled lesion-based sensitivity of 88% and specificity of 87% in breast cancer was found for bone scan and a pooled lesion-based sensitivity of 69% and a specificity of 98% was found for PET scan. With regard to lung cancer, bone is also a frequent metastatic site (fig. 4). In a recent study of 1,000 patients, 105 (10.5%) had bone metastases at diagnosis. Sensitivity of PET scan and CT was 94.3% compared with 78.1% with bone scan and specificity was 98.8% and 97.4%, respectively. Among the 346 bone metastases detected by PET scan and CT, 55 were in the thoracic spine, 28 in the scapula or clavicles (fig. 4), 12 in the sternum and 56 in the ribs (fig. 5); i.e. 44% of the foci were in the chest. The main problem of PET scan is poor anatomical resolution (fig. 6).

Table 1. Endobronchial metastases: frequency by primary site

<table>
<thead>
<tr>
<th>Primary tumour</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck</td>
<td>71 (31)</td>
</tr>
<tr>
<td>Breast</td>
<td>32 (14)</td>
</tr>
<tr>
<td>Kidney</td>
<td>31 (13)</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>25 (11)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>18 (8)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Bladder</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Prostate</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Testis</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Stomach</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

Modified from Sorensen (2004).

pooled lesion-based sensitivity of 88% and specificity of 87% in breast cancer was found for bone scan and a pooled lesion-based sensitivity of 69% and a specificity of 98% was found for PET scan. With regard to lung cancer, bone is also a frequent metastatic site (fig. 4). In a recent study of 1,000 patients, 105 (10.5%) had bone metastases at diagnosis. Sensitivity of PET scan and CT was 94.3% compared with 78.1% with bone scan and specificity was 98.8% and 97.4%, respectively. Among the 346 bone metastases detected by PET scan and CT, 55 were in the thoracic spine, 28 in the scapula or clavicles (fig. 4), 12 in the sternum and 56 in the ribs (fig. 5); i.e. 44% of the foci were in the chest. The main problem of PET scan is poor anatomical resolution (fig. 6).
Magnetic resonance imaging is the best imaging procedure whenever spinal cord compression is suspected.

Conclusions

The chest is a frequent site of metastasis especially for lung, breast, kidney, prostate, colon and ovary carcinomas. The prognosis of these metastases is more related to the possibilities of control of the underlying neoplasm than to their possible immediate complications, such as tamponade. However, some of the metastases may especially alter quality of life, such as bone metastases with a special attention to be paid to the spine because of the risk of cord compression.

References

PLEURAL AND CHEST WALL TUMOURS

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Pleural and chest wall malignancies are quite common diseases in our practice. Malignant pleural effusions (MPEs) and pleural metastases are much more frequent than primary tumours of these tissues (mesothelioma, sarcoma, lymphoma, etc.). Primary chest wall tumours are a heterogeneous group of rare tumours (<2% of all primary tumours; 60% of them are malignant) developing in the bones and soft tissues of the thoracic cage, but have similar diagnostic and therapeutic issues.

Epidemiology and pathogenesis

Malignant pleural mesothelioma (MPM) Malignant mesothelioma, a highly aggressive tumour involving the pleura in 90% of cases, is a rare tumour but with increasing incidence. MPM may occur in subjects up to 40 yrs after occupational asbestos exposure (found in >80% of male cases but <40% in female), the main factor involved in MPM pathogenesis.

Pleural metastases and MPEs Pleural tumour involvement may result from a direct invasion from adjacent structures (lung, chest wall, etc.), blood dissemination or more often from tumour emboli to the visceral pleura with secondary seeding to the parietal pleura (lung cancer). Effusion may be due to the pleural tumour lesions or to a lymphatic blockade at the mediastinal level. MPEs also depend on interactions between tumour cells and mesothelial cells through growth factors such as vascular endothelial growth factor that increase vascular permeability and angiogenesis.

Key points

- MPEs are much more frequent than primary pleural or chest wall tumours.
- Diagnostic strategy includes pleural cytology, but a firm and reliable diagnosis of cancer is based on histology usually best obtained by biopsies during thoracoscopy.
- Talc pleurodesis by thoracoscopy is the best local treatment of recurrent or massive MPE, but indwelling pleural catheter represents an interesting alternative.
- Figures 1 and 2 summarise a proposal for MPE and MPM management.

An MPE is found in up to 6% of patients with malignancy. In half of these cases, MPE may reveal the cancer. Neoplasias responsible for pleural metastases and/or MPE are mostly lung cancer (approximately one-third of cases) or breast cancer (10–15%), but other cancers include carcinomas (ovary, stomach, etc.) or noncarcinoma proliferations such as lymphoma, sarcoma, melanoma, seminoma or thymoma.

Pleural effusion is the main clinical element but it is not found in all pleural malignancies. Moreover, pleurisy is not systematically
synonymous with MPE in cancer patients because it may be induced by other mechanisms such as pneumonia and/or atelectasis due to bronchial obstruction, transudate induced by severe denutrition or cardiac failure, or even drug- or radiotherapy-induced effusion. Therefore the diagnostic strategy may differ whether the patient has a cancer background or not, but should always rely on cytology or, better still, on histology.

**Lymphoma and chest wall sarcoma** Initial thoracic involvement of lymphoma is common but mostly involves the mediastinum. Lung parenchyma and/or pleural localisations are less frequent and need to be histologically proven because they modify the staging and prognosis of the tumour. Primary softtissue sarcoma of the chest wall is a rare disease (<10% of the 8,000 new cases per year of soft-tissue sarcomas in the USA).

**Prognosis**

The prognosis of patients with pleural metastases or MPM is poor (median 1-yr survival 13%, and median survival <12 months, respectively). However survival may vary according to the primary cancer: from a few months usually for lung cancer to a potential much longer survival in breast cancer or lymphoma. In fact, lymphoma is characterised by a good outcome (cure rate >80%). Sarcomas have a variable prognosis, with a reported 5-yr survival from 15% up to 90%, depending mostly of the localisation, the grade and the differentiation the tumour and the possibility to achieve an early wide resection of the sarcoma.

**Diagnosis**

**Clinical signs** Dyspnoea on exertion and dry cough are the most common signs of MPE. Dyspnoea is usually progressive and more marked as the effusion becomes larger, but it may be also modulated by other factors: bronchus obstruction, carcinomatous lymphangitis or associated (pulmonary, cardiac) comorbidities. Chest pain suggests chest wall involvement. Other signs may include weight loss, anorexia, asthenia, haemoptysis (lung cancer), adenopathy, peritoneal effusion, etc. However, MPE or MPM may be diagnosed in asymptomatic patients by routine chest imaging. A diagnosis of MPM should not be based on unspecific and usually late clinical signs. However, the association of chest pain, thoracic "shrinkage", and/or a unilateral pleural effusion or thoracic mass in asbestos-exposed patients may suggest this diagnosis.

There are no reliable clinical features for distinguishing benign from malignant chest wall tumours. A palpable mass and pain are common in both groups of tumours. The final diagnosis is often obtained only after surgery.

**Imaging** Pleural metastases usually exhibit a moderate-to-large, nonloculated and unilateral pleural effusion. MPE may be associated with an irregular pleural thickening. Typically this large pleural effusion induces a contralateral mediastinal shift. If not, one should suspect an obstruction of a main bronchus by lung cancer or metastasis, a fixed mediastinum caused by the cancer and/or lymph nodes, an extensive tumour infiltration of the ipsilatary lung mimicking a large effusion, or MPM.

Chest radiograph or, better, computed tomography (CT) scan shows typically an unspecific, unilateral (95% of cases) pleural effusion ± mediastinal shift in MPM patients. More rarely, pleural thickening or mass, without pleuresy, may be observed. Pleural plugs are very common (70% of cases); about 20% of patients exhibit the association of asbestos-induced pulmonary interstitial fibrosis. Definitive diagnosis of MPM is not possible by CT scan, but is recommended for diagnosis and staging (after removal of pleural effusion if applicable). Magnetic resonance imaging is mostly useful to assess the tumour extent into the diaphragm and chest wall.

18-Fluorodeoxyglucose-positron emission tomography ([18F]FDG-PET) usually shows
hypermetabolism of pleural mesothelioma, metastatic adenopathy and metastasis, but should not currently be performed for the diagnosis of MPM. Pleural hypermetabolism is also found after talc pleurodesis. PET may be helpful for the staging of pleural malignancies, or in the search of primary cancer.

**Pathology and diagnostic procedures** In patients suspected of malignancy with pleural effusion, a thoracocentesis is the first diagnostic step (American Thoracic Society/ European Respiratory Society (ERS) guidelines). Pleural fluid analysis finds usually an exudate according to Light’s criteria, but a
transudate due to major hypoprotidaemia with cachexia or to malignant pericardial effusion does not eliminate the diagnosis of MPE. Assessment of the adenosine deaminase (ADA) pleural level can bring false-positive results in some cases of MPM or lymphoma, but may be helpful in countries with medium-to-high prevalence of tuberculosis. The diagnostic sensitivity of pleural cytology in MPE may vary, depending on the extension of the pleural lesions and the primary cancer, from 62–90% in series. Thus in a patient with a history of cancer, cytology may be enough for the diagnosis of pleural metastases. A diagnosis of MPM should not be based on cytology alone because of its poor sensitivity (30%) and specificity (potential confusion with reactive mesothelial cells or adenocarcinoma cells).

Closed, percutaneous needle (e.g. Abrams) pleural biopsies are quite easy to perform with local anaesthesia on an outpatient basis. However, due to the potentially scarce and irregular distribution of the tumour lesions in the pleural cavity, a positive yield of blind biopsies is low (30–40%), adding little to a negative cytology.

Figure 2. Proposed management for malignant pleural mesothelioma (MPM). US: ultrasound; CT: computed tomography.
Guided biopsies did better than blind biopsies in series of MPEs (70–80% sensitivity), but did worse than thoracoscopy, and are not recommended for the diagnosis of MPM except in patients for whom thoracoscopy (or mini-thoracotomy if pleural symphysis) is contra-indicated or rejected by the patient. If MPM is not clearly suspected, closed needle biopsies may be first proposed in young patients with pleural lesions and exudative, cytology-negative pleural effusion from countries with a relatively high prevalence of tuberculosis.

Medical (pleuroscopy) or surgical (video-assisted thoracoscopic surgery (VATS)) thoracoscopy with multiple pleural biopsies is the "gold standard" to obtain the diagnosis of MPM or pleural metastasis. Diagnostic accuracy is >90% and complications occur in <10% of cases. MPM or pleural metastasis will usually appear as nodules or masses of various diameters. Thoracoscopy is also useful for the staging of MPM and may permit talc pleurodesis in case of massive and/or recurrent pleural effusion.

Immunohistochemistry is helpful in the search of primary cancer for pleural metastases or to obtain an accurate diagnosis of mesothelioma, referring to the international classification of pleural tumours (World Health Organization (WHO) 2004). Epithelioid subtype is the most frequent mesothelioma subtype.

Soluble biomarkers have been searched to obtain an early and reliable diagnosis of pleural malignancies but none was considered as valuable in routine. Soluble mesothelin (or soluble mesothelin-related peptides (SMRPs)) levels were increased in serum and pleural fluid of patients with MPM compared with healthy asbestos-exposed subjects or patients with benign pleural lesions or pleural metastasis. SMRPs showed interesting sensitivity (70–80%) and specificity (80–100%) as diagnostic markers for MPM. However, SMRPs do not capture sarcomatoid (and some mixed) mesothelioma subtypes, and should not be used for MPM screening.

Staging and pre-therapeutic assessment of MPM

It is recommended to use the Union Internationale Contre le Cancer/International Mesothelioma Interest Group 1995 TNM staging system, even if it is inaccurate in describing T and N extent by current imaging procedures. Only a patient's performance status (PS) and histological subtype are recognised as prognostic factors for the management of MPM in routine.

To identify candidates for proper treatment, the 2008 ERS/European Society of Thoracic Surgeons (ESTS) experts on MPM proposed a simple and sequential three-step pre-treatment assessment (see references for full details).

Treatment

It includes palliative local therapies, mostly to improve the patient’s symptoms, and a treatment of primary cancer depending of the nature of the malignancy, the clinical status and the wishes of the patient.

Treatment of primary cancer MPM treatment relies mostly on best supportive care (BSC: oxygen, pain relief, nutrition, etc.) associated with chemotherapy, and has been summarised by the 2008 ERS/ESTS guidelines, as follows.

Surgery has very little indication in MPM. Debulking surgery (pleurectomy/decortication) should not be proposed with a curative intent, but can be considered to obtain symptom control, especially in symptomatic patients with entrapped lung syndrome who cannot benefit from chemical pleurodesis. There is limited evidence for the efficacy of radical surgery for mesothelioma, except parietal pleurectomy in very early and rare stage Ia disease. Extrapleural pneumonectomy (EPP), as well as post-operative irradiation, should be performed only in clinical trials, in specialised centres, as a part of multimodal treatment.

Palliative radiotherapy aimed at pain relief may be considered in case of painful chest wall infiltration or nodules. The value of
prophylactic radiotherapy to prevent subcutaneous metastasis developing along drainage channels or thoracocentesis tracts is questionable after recent studies and did not permit any recommendation.

When a decision is made to treat patients with chemotherapy, subjects with a good PS should be treated with first-line chemotherapy combining of platinum and anti-metabolite (pemetrexed), or could be included in clinical trials. No drug has been validated in second-line chemotherapy, and patients with a good PS should rather be proposed to enter into clinical trials. Patients demonstrating prolonged symptomatic and objective response with first-line chemotherapy may be treated again with the same regimen in the event of recurrence or relapse. For assessment and follow-up of MPM, only chest CT scan is recommended. PET scan and biological markers are still under investigation. The modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria are the preferred method of measuring response to treatment.

**Pleural metastases** Because of the systemic dissemination of the cancer, it relies on chemotherapy and/or hormone therapy, associated with BSC. The choice of cytotoxic drugs depends on the nature of the primary cancer. Mediastinal and/or abdominal radiotherapy may be combined with chemotherapy for lymphoma.

**Chest wall sarcomas** The treatment of choice is an early adequate and wide resection of the sarcoma. Adjuvant radio- and/or chemotherapy are considered for high/grade sarcomas.

**Local treatment** Pleurodesis is useful in treating a patient’s symptoms and in preventing recurrent effusions. Sterile talc is preferred to other agents and may be administered in the pleural space through a chest drain (“talc slurry”, TS) or better during medical (pleuroscopy) or surgical thoracoscopy (VATS) (“talc poudrage”, TP). Pleurodesis is most effective when performed early in the disease process before effusions have become loculated and/or the lung has become fixed and is unable to expand fully, but it should not be performed before sufficient tissue for diagnosis has been obtained. Criteria for talc pleurodesis are a sufficient WHO PS < 2, an estimated survival > 3 months, an established diagnosis of the tumour, and no arguments for either a trapped lung (suspected if a pneumothorax persists after thoracocentesis) or an endobronchial tumour (massive pleural effusion without a contralateral mediastinal shift). This may justify a bronchoscopy or a pleural manometry before the pleurodesis. To decrease the risk of pleurodesis failure in MPE, it is recommended to use 4 g of talc after complete aspiration of pleural effusion. In a phase III multicentric randomised study, success rates in TP versus TS in patients with MPE were respectively 67% versus 56% (p=0.045), and 82% versus 67% in the subgroup of lung or breast cancers (p=0.022). Benign usual side-effects of talc (fever, chest pain) were observed with both methods, but no acute respiratory distress syndrome and death.

Alternatives to talc pleurodesis are repeated pleural punctures or indwelling pleural catheters. This last ambulatory procedure has to be proposed rather than a second talc pleurodesis in the case of trapped lung, a pleuro-peritoneal shunt with a high risk of complications, or a parietal pleurectomy in frail patients. Spontaneous pleurodesis may be obtained by indwelling pleural catheter without mortality or major morbidity in nearly half of the cases when pleural drainage is done via the catheter every other day, or even up to 70% in MPE patients fit for pleurodesis.

**References**


MEDIASTINAL TUMOURS

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The mediastinum, which is defined as the anatomical compartment between both lungs, is a fascinating region due to its surprising complexity and variety.

Variety of compartments and organs

Although no universal agreement exists, the mediastinum is commonly divided into a superior compartment above a straight line from the sternal angle of Louis to the vertebral column, and an inferior part below this imaginary line. The latter is composed of an anterior compartment in front of the heart, a middle compartment at the level of the heart, and a posterior part lying behind the heart. Each compartment contains different organs and structures, varying from heart and great vessels to lymphatic tissue and pluripotent cells.

Variety of histological types and tumours

In both young and old patients, a range of primary tumours and cysts is encountered in the mediastinum; these are summarised in table 1. Metastases may also occur in the mediastinum.

Variety of symptoms

Mediastinal tumours can grow to a large size before symptoms appear. Pressure on surrounding structures may result in hoarseness, dyspnoea, dysphagia and superior vena cava syndrome. Various paraneoplastic syndromes have been described, such as myasthenia gravis and pure red cell aplasia in case of thymoma (fig. 1).

Variety of diagnostic means

Chest computed tomography (CT), magnetic resonance imaging and positron emission tomography provide exact anatomical delineation of a tumour and may suggest a specific entity. To obtain a precise histological diagnosis, CT-guided puncture, endoscopic or endobronchial ultrasound, mediastinoscopy, mediastinotomy and video-assisted thoracic surgery are utilised. In the case of suspicion of lymphoma, germ cell tumour or thymoma,

Key points

- Mediastinal tumours are characterised by a wide variation in clinical presentation, histological features and treatment options.
- A multidisciplinary approach is necessary to determine optimal treatment.
- Surgical treatment should aim at complete resection.

Figure 1. A large thymoma in the right hemithorax presenting with myasthenia gravis. The tumour was resected by a bilateral anterior thoracotomy (clam-shell incision).
large biopsies are required. Well-circumscribed tumours in young patients should be excised at once so as not to breach the surrounding capsule.

**Variety of therapeutic strategies**

Operable lesions are treated by surgical excision. Minimally invasive and even robotic techniques can be applied if a complete resection can be obtained by this approach. In the case of incomplete resection or capsular invasion, adjuvant radio- or chemotherapy may be indicated. Inoperable lesions and lymphomas are treated by a combination of chemo- and radiotherapy. In selected cases, induction therapy may be a valid approach to downstage a locally aggressive tumour. Salvage surgery may be attempted in tumours that are no longer responsive to chemo- or radiotherapy. Long-term survival depends on histological type and completeness of resection.

**References**

OBSTRUCTIVE SLEEP APNOEA/HYPOPNOEA SYNDROME

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Obstructive sleep apnoea/hypopnoea syndrome (OSAHS) is characterised by recurrent episodes of partial or complete upper airway collapse during sleep. The collapse is highlighted by a reduction in, or complete cessation of, airflow despite ongoing inspiratory efforts. Due to the lack of adequate alveolar ventilation that results from the upper airway narrowing, oxygen saturation may drop and partial pressure of CO$_2$ may occasionally increase. The events are mostly terminated by arousals. Clinical consequences are excessive daytime sleepiness related to the sleep disruption. Minimal diagnostic criteria have been defined for OSAHS. Patients should have excessive daytime sleepiness that cannot be better explained by other factors, or experience two or more of the following symptoms, again that are not better explained by other factors: choking or gasping during sleep; recurrent awakenings from sleep; unrefreshing sleep; daytime fatigue; and impaired concentration.

All patients should have more than five obstructed breathing events per hour during sleep. An obstructive apnoea or hypopnoea can be defined as an event that lasts for $\geq$ 10 s and is characterised by an absence or a decrease from baseline in the amplitude of a valid measure of breathing during sleep that either reaches $\geq$ 50% with an oxygen desaturation of 3% or an arousal (alternatively a 30% reduction with 4% desaturation). These definitions are recommended by the American Academy of Sleep Medicine (AASM). The Task Force of the AASM also states that there are common pathogenic mechanisms for obstructive apnoea syndrome, central apnoea syndrome, sleep hypoventilation syndrome and Cheyne–Stokes breathing. It was more preferable to discuss each of these separately; although, they could be placed under the common denominator of “sleep-disordered breathing syndrome”. The definition of OSAHS using two components, daytime symptoms and breathing pattern disturbances during sleep, may suggest that there is a tight correlation between the two. However, unfortunately this is not the case. The breathing pattern abnormalities, mostly described by an apnoea/hypopnoea index (AHI), only weakly correlate with quantified measures of sleepiness, such as the Epworth Sleepiness Scale (ESS). This probably means that inter-individual sensitivity, with some individuals coping better with sleep fragmentation than others, does compromise the relationship between the AHI and daytime sleepiness.

Key points

- OSAHS is characterised by recurrent episodes or partial or complete upper airway collapse during sleep.
- Minimal diagnostic criteria exist for OSAHS.
- Overnight polysomnography is the gold standard for OSAHS diagnosis.
scores. In addition, epidemiological studies show a broad range of sleepiness in the general population. Obviously, epidemiological studies investigating the prevalence of OSAHS are all biased by the lack of a uniform definition. The prevalence of an AHI of $>5$ events h$^{-1}$ in a general population (without taking into account symptoms of sleepiness) has previously been estimated to be $24\%$ in a male population. When symptoms of sleepiness were also taken into account, the prevalence decreased to $4\%$ in males and $2\%$ in females.

**Assessment of OSAHS**

The most widely used gold standard for diagnosis is overnight polysomnography including nasal and/or oral airflow, thoraco-abdominal movement, snoring, EEG, EOG, EMG and oxygen saturation. Cardiorespiratory monitoring alone can be considered as highly sensitive ($78\textendash100\%$) and specific ($67\textendash100\%$). Sleepiness is often evaluated using the ESS, which assesses global level of sleepiness and is independent of shortterm variations in sleepiness. The ESS discriminates between normal and pathological sleepiness.

**Pathophysiology**

Structural narrowing of the upper airway at one specific location is unlikely to be a major cause. Studies have shown that the upper airway collapse is not restricted to one place but is rather a dynamic phenomenon starting at a certain level and spreading caudally. Upper airway obstruction involves more than one specific site of the upper airway in the majority of sleep apnoea patients. The upper airway can collapse when insufficient load compensation is generated when an imbalance between the activation of the upper airway dilator muscles and the diaphragm occurs. When this occurs, the airway will collapse during inspiration or at least narrow with the development of flow limitation. However, there is increasing evidence that the collapse of the upper airway occurs during expiration. Furthermore, it has been convincingly shown that the upper airway behaves like a Starling resistor, making the collapse independent of the suction force brought about by the diaphragm, but rather dependent on the balance between the upper airway pressure and the tissue pressure at the collapsible site. The airway remains patent, regardless of the excessive pressure applied as long as the critical pressure of positive end-expiratory pressure ($P\text{crit}$) remains low relative to $P_u$ (pressure upstream to the collapsible segment). Closure of the upper airway occurs when $P_u$ falls below the surrounding tissue pressure ($P\text{crit}$). In the model of the Starling resistor, maximal flow ($V_{\text{max}}$) becomes a function of the pressure gradient and the resistance in the segment upstream to the collapsible segment $R_u$: $V_{\text{max}} = (P_u - P\text{crit})/R_u$. The collapse of the upper airway then finally occurs during expiration when, due to the absence of dilator muscle, $P\text{crit}$ exceeds the upstream pressures. Prolonged expiratory time, as occurs during central apnoeas, therefore predisposes to collapse, but other factors may contribute and can be considered as risk factors (table 1).

Central and obstructive events are closely linked. Sometimes a central event with already partially collapsed upper airway can transit towards an obstructive event with ongoing occlusion of the upper airway despite the resumption of effort. Often, however, with resumption of effort at the end of the central apnoea, the obstruction of the upper airway disappears, presumably due to reactivation of the upper airway dilator muscles. However, the mechanisms remain unclear and more research is needed to understand why central apnoeas are sometimes followed by obstructive apnoeas and in some cases followed by reopening of the airways. In any case, since central apnoeas can trigger classical obstructive apnoeas, the mechanisms leading to unstable breathing (and thus central apnoeas) are also important in the genesis of obstructive apnoeas.

**Consequences**

**Cardiovascular consequences** Obstructed airways may generate negative intrathoracic pressure that increases left ventricular
transmural pressure and left ventricular afterload. The negative pressure also draws more blood into the thorax and increases right ventricular preload. Intermittent hypoxia related to obstructive sleep apnoea (OSA) will also impair cardiac contractility and diastolic relaxation (fig. 1).

OSA patients also have attenuated endothelium-dependent vasodilation and decreased circulating markers of nitric oxide. These effects, together with increased sympathetic vasoconstrictor activity and inflammation, will predispose to hypertension and atherosclerosis. In addition, platelet activation and aggregability are increased and predispose to thrombotic disease. Epidemiological studies indicate that OSA can initiate or promote cardiovascular disease, such as hypertension, coronary heart disease, heart failure, cardiac arrhythmias (bradyarrhythmias, atrial fibrillation and ventricular ectopy) and cerebrovascular disease.

Metabolic consequences OSA is associated with several components of the metabolic syndrome (MetS), mainly insulin resistance (IR) and abnormal lipid metabolism. Sleep restriction causes IR by inducing a pro-inflammatory state (increased release of interleukin-6 and tumour necrosis factor-α). Epidemiological studies have shown that sleep-related hypoxaemia is associated with glucose intolerance independent of age, sex, body mass index and waist circumference. MetS can be triggered by both intermittent hypoxia and sleep fragmentation/deprivation. The mechanisms are shown in figure 2.

MetS can be due to the release of free fatty acids, agiotensin II and adipokines by adipose tissue, which may damage the pancreas, leading to insufficient insulin release and apparent IR.

Mean and nadir arterial oxygen saturation during sleep is an independent predictor of MetS in overweight children and adolescents.
**CPAP treatment**

**Therapy with nasal continuous positive pressure: mode of action** Treatment with nasal continuous positive pressure (nCPAP) is perceived by most physicians as a very effective treatment for sleep apnoea and has been shown to be effective in controlled studies. nCPAP results in better sleep quality with lower arousal index: less stage 1 and more stage 3 and 4 sleep in a placebo-controlled (using placebo capsules) study. In addition, in milder forms of sleep apnoea nCPAP improved self-reported symptoms of...
OSA, including snoring, restless sleep, daytime sleepiness and irritability. Neuropsychological tests also improved after nCPAP compared with ineffective nCPAP. Blood pressure can also be reduced with nCPAP when compared to oral placebo, especially in patients using nCPAP for \( \geq 3.5 \) h-night\(^1\) and in those with >20 desaturations of 4% per hour.

**nCPAP and the upper airway** Occlusion of the upper airway can be prevented when either the resistance of the upper airway upstream, \( R_u \) or \( P_{crit} \) can be lowered. Regardless of the severity of the changes in \( P_{crit} \) and \( R_u \), nCPAP can effectively increase (or restore) flow, largely through its effect on \( R_u \) \( (V_{max} = (P_u - P_{crit})/R_u) \). Appropriate titration of the CPAP restores flow. nCPAP can increase \( P_u \) much more than local interventions, such as uvulopalatopharyngoplasty, can. Therefore, it also explains that overall nCPAP is much more clinically effective than was shown in previous controlled studies.

**nCPAP and control of breathing** As mentioned previously, some clinical observations initially indicated that unstable breathing is part of OSA syndrome, while more recent systematic analysis confirmed the increased loop gain and instability in the breathing pattern in OSA patients. It can be questioned, therefore, whether nCPAP can influence control of breathing in (obstructive) sleep apnoea patients. One could demonstrate that prolonged treatment with nCPAP significantly decreases the slope of the hypercapnic ventilatory response curve when measured during wakefulness, together with an increase in arterial oxygen tension and a decrease in the arterial–alveolar oxygen tension difference. It is clear that all of these changes may contribute to lowering of the gain in the system and promote a more stable breathing pattern. Changes in lung volume, although mostly small, can also be observed during nCPAP therapy.

nCPAP has also been demonstrated to be effective in central sleep apnoea. nCPAP can increase carbon dioxide tension above the apnoeic threshold and, therefore, eliminate central apnoeas. However, central apnoeas are often also characterised by (near) occlusion of the upper airway; as highlighted earlier, nCPAP can also presumably be effective in preventing this collapse and its associated local reflexes.

**nCPAP and the heart** nCPAP can effectively be used to treat acute cardiogenic pulmonary oedema with shifting volume from intra- to extrathoracic compartments.

nCPAP may relieve CSA in chronic heart failure patients by increasing the arterial carbon dioxide tension above the apnoeic threshold. nCPAP may reduce ventilation by redistributing excess lung water to extrathoracic compartments thereby reducing stimulation of pulmonary vagal irritant receptors. nCPAP may also unload the inspiratory muscles by increasing lung compliance, again due to extrathoracic redistribution of lung water.

nCPAP may significantly reduce left ventricular afterload by lowering the transmural pressure in patients with compromised cardiac function. In the normal heart, where cardiac output is largely preload dependent, CPAP decreases cardiac output by reducing left ventricular preload. In contrast, the failing heart is relatively insensitive to changes in preload but very sensitive to reductions in afterload. CPAP induced reductions in left ventricular transmural pressure (and afterload) can augment cardiac output.

nCPAP may also attenuate sympathetic nervous activity and increase cardiac vagal modulation of the heart with favourable effects on blood pressure regulation.

In a large prospective study severe untreated OSA patients had more fatal and non-fatal cardiovascular events, this difference disappeared with nCPAP treatment.

**nCPAP and metabolic/systemic effects of OSA** nCPAP may improve MetS although it is not always certain that nCPAP has an independent effect. nCPAP also lowers tumour necrosis factor-\( \alpha \), interleukin-6 and C-reactive protein.
Non-CPAP treatment

Mandibular advancement device
Mandibular advancement devices (MAD) are the most common oral appliances used for the treatment of OSA and/or snoring. They have either a one-piece (monobloc) or two-piece (duobloc) configuration while customised devices have a better retention, tolerance and efficacy. MAD are effective if they increase the volume of the upper airway, which may enlarge at some sites and also narrow at other sites. Therefore, the overall efficacy is sometimes suboptimal; 65% of patients achieve a 50% reduction in AHI. Also snoring, excessive daytime sleepiness, neuropsychological function and cardiovascular risk may decrease. It is important to try to predict the outcome. Imaging and modelling studies can be of help for this purpose.

Surgical treatment Several techniques have been performed, all with the aim of enlarging the volume of the upper airway and reducing the closing pressure. Uvulopalatopharyngoplasty reduces upper airway obstruction by shortening the uvula, trimming the soft plate and suturing back the anterior and posterior pharyngeal pillars. Tonsillectomy is performed at the same time if tonsils are found to be enlarged. Maxillomandibular advancement osteotomy advances the maxilla and mandible to enlarge the retrolingual and retropalatal spaces. Adenotonsillectomy is first-line treatment in children. Electrical stimulation of the genioglossus with an implanted pacemaker has recently been tested and found to be efficient in selected patients, although more clinical studies are needed in order to learn which patients will benefit most.

References
CENTRAL SLEEP APNOEA

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Central sleep apnoea/hypopnoea (CSA) refers to the cessation or reduction of ventilation lasting for ≥10 s (in adults) due to transient loss of neural output to the respiratory muscles. Many patients with CSA have mild hypocapnia or normocapnia, but rarely are hypercapnia and hypoventilation also observed. A periodic pattern of waxing and waning of ventilation with periods of hyperventilation alternating with central apnoea/hypopnoea is termed Cheyne–Stokes respiration (CSR).

Prevalence, aetiology and pathophysiology

The prevalence of CSA in the general population is not known. However, it seems to be significantly less common than obstructive sleep apnoea (OSA), as <5% of patients referred to a sleep laboratory revealed predominant CSA. In contrast, a relatively high prevalence of CSA is observed in association with various conditions including congestive heart failure, pulmonary hypertension, ischaemic stroke, neuromuscular disease, obesity hypoventilation syndrome and narcotic use, or during initiation of continuous positive airway pressure (CPAP) therapy in patients with OSA. In healthy subjects, CSA may occur during hypoxia at altitude. In addition, idiopathic CSA is not associated with any comorbid condition.

Pathophysiological mechanisms underlying CSA include: respiratory control instability, due to an increased chemical drive that moves the prevailing arterial carbon dioxide tension closer to the apnoea threshold; a prolonged circulation time; and altered respiratory mechanics. Subsequently, different forms of CSA will be discussed.

CSR/CSA syndrome in heart failure patients

The prevalence of CSR/CSA with an apnoea/hypopnoea index of >15 events·h⁻¹ has been found to be very high (15–37%) and OSA is even common (10–26%) among patients with severe heart failure (left ventricular ejection fraction ≤45%) irrespective of a suspicion of sleep apnoea. In some patients CSR/CSA and OSA may coexist and alternate over the course of a night. Symptoms attributable to CSR/CSA are not well defined and may

Key points

- CSA is the loss or reduction in ventilation due to transient loss of neural output to the respiratory muscles.
- A high prevalence of CSA is observed in association with other conditions, such as congestive heart failure, pulmonary hypertension, ischaemic stroke, neuromuscular disease, obesity hypoventilation syndrome and narcotic use.
- Risk factors for CSA/CSR are age >60 yrs, male sex, severe heart failure, hypocapnia and atrial fibrillation.
- Treatment includes oxygen, acetazolamide and positive pressure ventilation, in particular adaptive servo-ventilation.
include paroxysmal nocturnal dyspnoea, poor sleep quality, excessive daytime sleepiness, fatigue and poor exercise tolerance.

CSR/CSA in heart failure patients is associated with poor prognosis. Several studies have found an increased mortality in patients with CSR/CSA even after controlling for the severity of heart failure, age, sex and other potential confounders. Mortality was particularly high in patients presenting with CSR during physical activity during the day (fig. 1).

Sleep-related breathing disturbances should be suspected in all patients with heart failure who suffer from nocturnal dyspnoea, unrefreshing sleep or daytime sleepiness. Particular risk factors for CSA/CSR include: severe heart failure, older age (≥ 60 yrs), male sex, hypocapnia, atrial fibrillation and CSR observed during the day. The diagnosis should be evaluated by polysomnography or a cardiorespiratory sleep study, since pulse oximetry can not make the important distinction between CSA and OSA.

Optimised medical therapy of heart failure is the first step in the treatment of CSR/CSA. Cardiac resynchronisation by biventricular pacing and heart transplantation may also alleviate CSR/CSA. If medical therapy is ineffective, noninvasive ventilation may additionally be required. Nocturnal CPAP has been shown to improve nocturnal CSR/CSA, oxygen saturation, left ventricular ejection fraction, sympathetic nervous system activity and the 6-min walking distance. However, CPAP did not prolong survival without heart transplantation during a 2-yr follow-up in a large trial (CANPAP), although a post hoc analysis suggested a survival benefit if CPAP sufficiently suppressed CSR/CSA. Adaptive servo-ventilation is a mode of bi-level positive airway pressure ventilation that continuously adjusts pressure support according to the breathing pattern of the patient in order to stabilise periodic breathing. It is a promising treatment option for CSR/CSA as it has been shown to improve nocturnal breathing pattern, daytime vigilance and quality of life after treatment for several weeks. Studies in larger patient cohorts over longer time periods are needed to confirm these effects and to evaluate a potentially improved

Figure 1. Cheyne-Stokes breathing in a patient with congestive heart failure. Inductive plethysmographic signals from rib cage and abdominal sensors showing regular waxing and waning of ventilation with central hypopnoea and corresponding oscillations of oxygen saturation. The upper panel represents a 58-min daytime recording, the lower panels show enlarged portions obtained while standing (left) and in the supine position (right). $S_{p, O_2}$: arterial oxygen saturation measured by pulse oximetry. Modified from Brack et al. (2007).
survival. Supplemental oxygen and acetazolamide have also been shown to alleviate CSR/CSA. Further studies are required to better define the role of these adjuncts for the treatment of heart failure in patients with CSR/CSA.

**Complex sleep apnoea syndrome**

In some patients diagnosed with OSA a CSR/CSA breathing pattern may emerge during initial CPAP therapy. The clinical relevance of this phenomenon, referred to as complex sleep apnoea, is still a matter of debate since studies suggest that CSA disappears in the majority of OSA patients during prolonged CPAP therapy. However, persistent residual CSA may disturb sleep quality, prevent complete symptomatic improvement and may lead to CPAP intolerance in OSA patients. In this setting adaptive servo-ventilation has been successfully used to normalise the breathing pattern and improve sleep quality.

**Idiopathic CSA apnoea syndrome**

Idiopathic CSA syndrome (fig. 2) is, by definition, not associated with any underlying disease. CSA causes sleep fragmentation which may be perceived as unrefreshing sleep and may result in daytime sleepiness. Idiopathic CSA is thought to be much less common than OSA, although no systematic epidemiological studies have been performed. Treatment options include acetazolamide, theophylline, CPAP and adaptive servo-ventilation.

**CSA in various conditions**

CSA and ataxic breathing have been observed in patients on chronic opioid medication and can be successfully treated with adaptive servo-ventilation, although the relevance of the breathing disturbances requires further study. Patients with stroke and neuromuscular disease, such as post-polio syndrome, motor neuron disease, multiple system atrophy or with idiopathic central hypoventilation, may

![Figure 2. Idiopathic central sleep apnoea in a 56-yr-old male suffering from unrefreshing sleep. The 5-min recording shows repetitive central apnoeas of variable duration (20–90 s) associated with severe oxygen desaturation (minimal value of 66%). The absence of excursions in the inductive plethysmographic rib cage and abdominal signals during cessation of airflow indicates that apnoeas are due to intermittent loss of neuromuscular drive.](image-url)
exhibit CSA with or without associated OSA and/or hypoventilation. Depending on the prevailing breathing disturbance, bi-level positive pressure ventilation, CPAP or adaptive servo-ventilation may improve breathing and alleviate symptoms.

**High-altitude periodic breathing**

In healthy subjects, hypobaric hypoxia at altitudes of >2,000 m may induce periodic breathing with central apnoea/hypopnoea. Breathing instability is related to an enhanced chemosensitivity (high controller gain) causing a tendency for a ventilatory overshoot and hyperventilation with a reduced CO₂ reserve, ie. the eupneic carbon dioxide tension approaches the apnoeic threshold which promotes apnoea during minor ventilatory alterations. Symptoms may include paroxysmal dyspnoea and poor sleep quality. In some subjects, high-altitude periodic breathing is associated with acute mountain sickness; a syndrome characterised by headaches, insomnia, poor appetite, fatigue and, in more severe forms, ataxia and altered consciousness. The diagnosis of high-altitude periodic breathing is based on clinical observations in the appropriate context combined with pulse oximetry or more sophisticated sleep studies if feasible. Treatment is often not required but can be performed by altitude descent or the administration of supplemental oxygen or acetazolamide, which is also effective against acute mountain sickness.

**Conclusions**

In conclusion, CSA/CSR is less common than OSA. However, in certain conditions, including congestive heart failure, neuromuscular disorders, during opioid use and at high altitude, the prevalence of CSA is high. Treatment for CSA is not as well established as that for OSA, and may include oxygen, acetazolamide and positive pressure ventilation, in particular adaptive servo-ventilation.

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HYPOVENTILATION SYNDROMES

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Sleep-related hypoventilation syndromes, together with central and obstructive sleep apnoea syndromes, are sleep-related breathing disorders (table 1).

Sleep-induced hypoventilation is characterised by elevated levels of arterial carbon dioxide tension \( (P_{a,CO_2}) \) of \( >45 \) mmHg while asleep or disproportionately increased relative to levels during wakefulness.

**Pathophysiology**

Nocturnal hypoventilation can be attributed to decreased ventilatory drive (won’t breathe), which may be due to respiratory dysfunction (polio sequelae, central hypoventilation, amyotrophic lateral sclerosis or Arnold–Chiari malformation), or the following: depression (hypnotics); alteration of respiratory nerve conduction (Guillain–Barré syndrome), transmission to the respiratory muscles (myasthenia) or worsening mechanics (can’t breathe) with respiratory muscle alteration (muscular dystrophy); chest wall deformities; or severe obesity. In the latter situations, lungs are normal and associated hypoxaemia is due to the displacement of oxygen in the alveoli from increasing \( CO_2 \) levels, as predicted by the alveolar air equation. If the lungs are abnormal (chronic obstructive pulmonary disease (COPD), tuberculous sequelae, cystic fibrosis or diffuse bronchiectasis), hypercapnia is mainly due to worsening mechanics and ventilation-perfusion inequalities.

During the night, ventilatory response to hypoxaemia and hypercapnia is largely reduced during rapid eye movement (REM) sleep with dysrhythmic breathing and less reduced during non-REM sleep. The result is a reduction of alveolar hypoventilation by altering minute ventilation and/or dead space volume/tidal volume.

Respiratory mechanics change during sleep and thereby worsen gas exchange, particularly in neuromuscular diseases and obstructive airways diseases. REM sleep induces skeletal muscle hypotonia sparing the diaphragm and not the accessory respiratory muscles, with

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**Key points**

- Sleep-induced hypoventilation is characterised by increased \( P_{a,CO_2} \) levels of \( >45 \) mmHg
- Nocturnal hypoventilation is associated with decreased ventilatory drive, respiratory iatrogenic depression, alteration of respiratory nerve conductance, chest wall deformities or severe obesity
- OHS is the association of obesity and sleep-disordered breathing with daytime hypersomnolence and hypercapnia in the absence of other respiratory diseases
- Polysomnographic evaluation is needed in order to diagnose OHS
- NIV is used as the first-line treatment with supplementary oxygen
deleterious effects in conditions where these muscles are necessary to maintain normal ventilation. REM sleep also alters upper airways patency and reduces chronic respiratory failure.

**Clinical features**

Hypoventilation *per se* generates a clinical syndrome associated with, in typical cases, dyspnoea during activities of daily living in the absence of paralysis, poor sleep quality, excessive daytime fatigue and sleepiness, nocturnal or early morning headache, cyanosis and evidence of right heart failure.

**Diagnosis**

The presence of such symptoms highlights the need to perform a physical examination, pulmonary function tests, a chest radiograph as well as measure arterial blood gases and recordings of sleep, *i.e.* arterial oxygen saturation and transcutaneous carbon dioxide tension. The results of this initial investigation will be concluded by full night ventilatory polygraphy (respiratory signals only) or polysomnography (respiratory and neurological signals; EEG, EOG, EMG). Chronic daytime hypercapnia is associated with and preceded by sleep-related hypoventilation.

**Aetiology**

**Presence of an extrapulmonary restrictive disorder** If obesity is present the most frequent diagnosis is obesity hypoventilation syndrome. Previously called the "Pickwickian syndrome", obesity hypoventilation syndrome (OHS) is defined as the association of obesity (body mass index (BMI) >30 kg·m⁻²) and sleep-disordered breathing with daytime hypersomnolence and hypercapnia ($P_{a,CO_2} >45$ mmHg) in the absence of any other respiratory disease. The prevalence of OHS is 36% in patients with a BMI of 35–40 kg·m⁻² and 48% if BMI is >50 kg·m⁻².

The pathogenesis of OHS involves abnormal pulmonary mechanics with an excessive work of breathing and altered hypoxic and hypercapnic ventilatory responses, linked, in part, to chronic hypoxaemia and poor sleep quality, upper airway obstruction and, possibly, the influence of leptin.

Without adequate treatment, patients with OHS develop cor pulmonale, recurrent episodes of hypercapnic respiratory failure and loss of survival. OHS is one of the many aetiologies of chronic respiratory failure and has become a growing indication to initiate acute and/or long-term noninvasive mechanical ventilation (NIV). Mechanisms of action include resting of the respiratory muscles, an increase in thoracic compliance and resetting of the respiratory centres. In OHS, nocturnal NIV has been shown to be clinically effective because of a rapid and sustained improvement of daytime arterial blood gas levels and a net reduction of daytime sleepiness.

In order to establish a diagnosis of OHS polysomnographic evaluation is needed and the ventilatory treatment needs to be

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**Table 1. Sleep related hypoventilation/hypoxaemic syndromes**

<table>
<thead>
<tr>
<th>Sleep-related hypoventilation/hypoxaemic syndromes</th>
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<tbody>
<tr>
<td>Sleep-related non-obstructive alveolar hypoventilation, idiopathic congenital central alveolar hypoventilation syndrome</td>
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<tr>
<td>Sleep-related hypoventilation/hypoxaemia due to a medical condition</td>
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<tr>
<td>Sleep-related hypoventilation/hypoxaemia due to pulmonary parenchymal or vascular pathology</td>
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<tr>
<td>Sleep-related hypoventilation/hypoxaemia due to lower airways obstruction</td>
</tr>
<tr>
<td>Sleep-related hypoventilation/hypoxaemia due to neuromuscular or chest wall disorders</td>
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*: according to the International Classification of Sleep Disorders-2 classification.

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**Hypoventilation syndromes**
adapted. The sleep respiratory pattern can present as obstructive apnoeas and hypopnoeas (90% of cases), obstructive hypoventilation due to increased upper airway resistance and/or central hypoventilation (10%) (fig. 1).

Recent data from a large cohort of OHS patients who had been treated with NIV and pressure-cycled ventilators showed a very significant decrease in the number of hospital stays for cardiac and/or respiratory illness for the 3 yrs following the initiation of NIV, compared with the year prior to the start of treatment. A dramatic improvement in arterial blood gases was observed and a good compliance suggests that this treatment is cost-effective and improves morbidity and mortality in such patients. NIV is used as first-line treatment with supplemental oxygen; expiratory airway pressure is titrated to control hypopnoeas and apnoeas and inspiratory airway pressure is added to control $P_aCO_2$. If pressure pre-set NIV fails, nasal volume pre-set ventilation may be used. In patients with OHS and predominant OSA, once hypercapnia has improved using NIV (which may take several weeks), NIV may be changed to nasal continuous positive airway pressure (fig. 2). NIV has also largely

Figure 1. A ventilator polygraphy from a patient with severe obesity hypoventilation syndrome. Apnoea/ hypopnoea index: 26 events/h; arterial oxygen tension: 9.6 kPa; arterial carbon dioxide tension: 8.5 kPa. $Sp,O_2$: arterial oxygen saturation measured by pulse oximetry; HR: heart rate.

Figure 2. A ventilator management algorithm in a patient with severe obesity hypoventilation (OHS) presenting with chronic respiratory failure (CRF). OSAS: obstructive sleep apnoea syndrome; NIV: noninvasive ventilation; $P_aCO_2$: arterial carbon dioxide tension; CPAP: continuous positive airway pressure; F: failure; S: success. #: an alternative is assisted control ventilation.
improved the immediate vital prognosis of OHS and acute respiratory failure.

The medical management is mainly orientated towards weight loss. A reduction of 5–10% of body weight can result in a significant decrease in $P_aCO_2$. Unfortunately, weight loss by diet alone is difficult to achieve and sustain; thus, bariatric surgery has been advocated. After significant weight reduction surgery patients with OHS experience long-term improvement of arterial blood gases and dyspnoea.

If obesity is absent or not predominant, the most frequent conditions are: neuromuscular diseases with Duchenne muscular dystrophy; Steiner myotony; polio sequelae; amyotrophic lateral sclerosis; and high spinal injuries with tetraplegia and respiratory paralysis. Less frequent are acid maltase deficiency and spinal muscular atrophy.

Chest wall diseases with kyphoscoliosis and tuberculosis sequelae are a category of diseases that represent the best indication for the application of acute and chronic mechanical ventilation mainly with NIV, and in some severe situations or after failure of NIV with invasive mechanical ventilation with tracheostomy.

**Presence of an obstructive disorder**

COPD, diffuse bronchiectasis and cystic fibrosis are the most frequent conditions. During sleep there is a worsening of awake hypoxaemia and hypercapnia, especially during REM sleep. NIV is generally proposed after failure of long-term oxygen therapy in hypercapnic COPD when frequent episodes of acute respiratory decompensation occur and/or when baseline $P_aCO_2$ progressively worsens. COPD patients with obesity must be investigated for possible overlap syndrome, which is associated with obstructive sleep apnoea and COPD.

**Congenital central hypoventilation syndrome**

Congenital central hypoventilation syndrome is a rare disorder of ventilatory control that typically presents in newborns and mainly results from a polyalanin repeat expansion mutation in the PHOX2B gene. It results in the failure of automatic central control of breathing in infants who do not breathe spontaneously or who breathe shallowly and erratically. Sufferers are generally treated by mechanical ventilation with tracheostomy and, in less severe situations, by NIV. Electrostimulation of the phrenic nerves and or the diaphragm is currently being tested as a new therapeutic option.

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CHAPTER 16: IMMUNODEFICIENCY DISORDERS AND ORPHAN LUNG DISEASE

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PULMONARY DISEASES IN PRIMARY IMMUNODEFICIENCY SYNDROMES

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The definition of primary immunodeficiencies (PID) includes multiple genetic defects that belong to the group of rare diseases. The World Health Organization recognises more than 70 diseases classified as PID. The risk and type of infections change according to the main defects of the immune system, and are classified as antibody deficiencies, combined immunodeficiencies and phagocytic disorders (table 1). In some cases there are unique features of lung abnormalities in specific defects.

Severe and recurrent infections with capsulated bacteria, asthma and bronchiectasis represent the most important morbidity and mortality factors of the patients affected by primary antibody deficiencies. The common pathogens isolated from the sputum are Haemophilus influenzae, Streptococcus pneumoniae and Streptococcus pyogenes, with Pseudomonas aeruginosa and Moraxella catarrhalis occurring less frequently. Chronic lung disease (CLD) represents the principal morbidity factor. In primary antibody deficiencies where the defect is an inability to produce an effective antibody response to pathogens, only immunoglobin (Ig)G antibodies might be replaced. The substitutive therapy with Ig reduces the risk of acute respiratory infections, particularly pneumonia, but has low efficacy in reduction of chronic lung complications, infective exacerbations and asthma, which are promoted by vicious circle infection–inflammation. Despite i.v. Ig treatment, the number of patients with CLD and bronchiectasis increases with time for almost all age groups (prevalence of CLD >50% in adults, 30–40% in children). The overall probability of developing CLD reached ~80% after 17 yrs of follow-up. As already

Key points

- Primary immunodeficiencies (PID) include multiple genetic defects that belong to the group of rare diseases.
- More than 70 diseases are classified as PID.
- The risk and type of infections change according to the main defects of the immune system, and are classified as antibody deficiencies, combined immunodeficiencies and phagocytic disorders.
- A PID diagnosis should be considered in patients presenting with severe and recurrent respiratory infections, with granulomatous diseases or with life-threatening invasive pulmonary infections.
demonstrated in patients with cystic fibrosis, dyspnoea and sputum production are conditioning factors of increased morbidity. Accumulated mucus in the airways is the prominent feature of bronchiectasis, leading to airway obstruction, bacterial colonisation and recurrent infections. The events that define the pathogenesis of an infection depend on a large range of variables, including the specific infecting organism and its virulence and the overall immunological state of the host. IgG antibodies are only one player in the complex network of cells and mediators required to protect the respiratory tract against various insults, including infections. In support of this evidence, data indicate the role of a very low IgA level as a major independent risk factor for all the main PID-associated clinical conditions (pneumonia, chronic lung disease, acute and chronic sinusitis), underlining the well known role of IgA antibodies on immune defence against a variety of potentially pathogenic organisms when they are encountered in the respiratory or the intestinal tracts. The generation of secretory IgA has a basic impact on the epithelial barrier, a function lacking in the majority of PID patients. Moreover, low IgA levels reflect a severely impaired isotype-switching process. Thus, the loss of function of memory B-cells seems to represent the major cause of PID-associated clinical conditions as already demonstrated in common variable immunodeficiency patients with bronchiectasis. Aside from Ig replacement, a strategy to reduce lung damage should then be approached. Prophylactic antibiotics, macrolides as anti-inflammatory agents, inhaled corticosteroids, bronchodilators, mucolytics, or mechanical or rehabilitative respiratory methods need to be considered.

In patients with cellular and combined immunodeficiencies and in patients with PID who require bone marrow transplantation, respiratory viral infections are major causes of morbidity and mortality. All viruses might be detected, all worsening the clinical outcome (table 1). Herpes viruses, paramyxoviruses and adenoviruses are common, significant pathogens in these patients. Aggressive treatments may reduce viral replication and damage. Fungal infections are less frequent compared with bacterial or viral infections among patients with PID. However, fungal infections can result in significant morbidity and potentially fatal outcome if misdiagnosed or not treated correctly. In this context, the knowledge of fungal pathogens likely to cause disease as well as of the expected clinical presentation of the infection is important. Noninfectious associated respiratory diseases might also occur in PID patients and should be taken into consideration in the differential diagnosis. Medical imaging, especially computed tomography, plays a crucial role in

<table>
<thead>
<tr>
<th>Antibody deficiencies</th>
<th>Combined immunodeficiencies</th>
<th>Phagocytic defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viruses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enteroviruses</td>
<td>CMV, respiratory syncytial virus, EBV, parainfluenza type 3</td>
<td>No</td>
</tr>
<tr>
<td>Bacteria</td>
<td>As for antibody deficiencies, also: Salmonella typhi, Listeria monocytogenes, Candida, Pneumocystis carinii</td>
<td>S. aureus, P. aeruginosa, Nocardia asteroides, S. typhi, Aspergillus</td>
</tr>
<tr>
<td>Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Pseudomonas aeruginosa, Staphylococcus aureus, Neisseria meningitidis, Mycoplasma pneumoniae, Campylobacter</td>
<td>Nontuberculous, including BCG</td>
<td>Nontuberculous, BCG</td>
</tr>
<tr>
<td>Mycobacteria</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

CMV: cytomegalovirus; EBV: Epstein-Barr virus; BCG: bacille Calmette-Guerin. Adapted from NOTARANGELO (2010).
the initial detection and characterisation of changes and in monitoring the response to therapy. The spectrum of abnormalities seen at thoracic imaging includes noninfectious airway disorders, infections, CLD, chronic inflammatory conditions, and benign and malignant neoplasms.

In conclusion, a PID diagnosis should be considered in patients presenting with severe and recurrent respiratory infections, with granulomatous diseases or with life-threatening invasive pulmonary infections.

References


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HIV-RELATED DISEASE

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Most HIV-infected patients experience at least one significant episode of respiratory disease during their lifetime. A very wide variety of illnesses and pathogens can be encountered, and systematic investigation is vital. This chapter will focus upon common causes of HIV-related disease (table 1). It uses blood absolute CD4 counts to categorise the stages of HIV infection. This is a reasonably accurate measure of systemic and local immunity (in HIV-uninfected individuals, the CD4 count is typically $>500 \text{ cells}\cdot\mu\text{L}^{-1}$). In HIV-infected subjects with reasonably preserved immunity, typical community-acquired infections occur but at greater frequency than in the general population. With advancing HIV-induced immunosuppression (CD4 counts $<200 \text{ cells}\cdot\mu\text{L}^{-1}$), the risk of opportunistic infections and malignancy increases. Use of effective combination antiretroviral therapy (CART) leads to 50–90\% reductions in the incidence of many HIV-associated opportunistic infections.

**Key points**

- More than 50\% of HIV-infected patients suffer a respiratory episode during the course of their HIV disease.
- In populations with access to antiretroviral therapy, use of combination antiretroviral therapy (CART) has led to a marked reduction in the incidence of many HIV-associated opportunistic infections.
- *Pneumocystis jirovecii* is the new name for *Pneumocystis carinii*, the cause of *Pneumocystis* pneumonia in humans.
  The acronym PCP still applies.
- Bacterial infections are more common in HIV-infected patients than in the HIV-negative general population.
- In response to starting CART, there may be an overexuberant and uncontrolled immune response to exogenous antigen. This phenomenon is called immune reconstitution inflammatory syndrome.
- Tuberculosis may occur at any stage of HIV infection, is common, and is a public, as well as personal, health issue.

**Infections**

**Bacterial infection** Upper respiratory tract infections, acute bronchitis and acute and symptomatic chronic sinusitis occur more frequently in HIV-infected patients than in the general population.
Bronchiectasis is increasingly recognised in patients with advanced HIV disease. It probably arises as a consequence of recurrent Pneumocystis jirovecii pneumonia or bacterial infection.

Compared with HIV-negative populations, bacterial pneumonia is six to ten times more frequent in HIV-infected subjects not using highly active antiretroviral therapy. Injecting drug users are particularly vulnerable (approximately double that of other HIV risk groups). The presentation of community-acquired bacterial pneumonia in HIV-infected individuals is similar to HIV-negative subjects. However, the chest radiograph may be atypical, and mimic P. jirovecii pneumonia in up to half of cases. The usual pathogens isolated are Streptococcus pneumoniae and Haemophilus influenzae. Infection with Staphylococcus aureus and Gram-negative organisms may occur in advanced HIV disease. Mycoplasma, Legionella and Chlamydia species do not appear to be more frequent.

Bacteraemia is up to 100 times more common in HIV-infected patients with bacterial pneumonia, irrespective of CD4 count. Complications include intrapulmonary cavitation, abscess formation and empyema. There is a high relapse rate, despite appropriate antibiotic therapy.

Immunisation with pneumococcal vaccine is recommended in all adults and adolescents (at diagnosis of HIV infection and after 5 yrs); although humoral responses and clinical efficacy are probably impaired in those with CD4 counts <200 cells·µL⁻¹.

**Fungal infection** P. jirovecii, formerly called P. carinii, is the cause of Pneumocystis pneumonia (the acronym PCP still applies: PneumoCystis Pneumonia). It remains a common problem in individuals unaware of their HIV serostatus and also among HIV-infected patients intolerant of, or nonadherent to, PCP prophylaxis and/or CART.

Patients present with nonproductive cough and progressive exertional breathlessness of several days’ to weeks’ duration, with or without fever. On auscultation the chest is usually clear; occasionally, end-inspiratory crackles are audible. In early PCP the chest radiograph may be normal (~10% cases). The most common abnormality is bilateral, perihilar interstitial infiltrates, which may progress to diffuse alveolar shadowing over a period of a few days. Atypical radiographic appearances include upper zone infiltrates resembling tuberculosis (TB), hilar/mediastinal lymphadenopathy, intrapulmonary nodules and lobar consolidation (present in up to 20%).

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**Table 1. Common causes of HIV-associated respiratory disease**

<table>
<thead>
<tr>
<th>Infectious disease</th>
<th>Non-infectious disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>Kaposi sarcoma</td>
</tr>
<tr>
<td>Acute sinusitis</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Chronic sinusitis</td>
<td>Bronchial carcinoma</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>Nonmalignant conditions</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>HIV-associated pneumonia e.g. NSIP &amp; LIP</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>Pulmonary arterial hypertension</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Fungal infections</td>
<td>HIV therapy causing respiratory symptoms e.g. IRIS</td>
</tr>
<tr>
<td><em>Pneumocystis pneumonia</em></td>
<td></td>
</tr>
<tr>
<td><em>Histoplasma capsulatum</em></td>
<td></td>
</tr>
<tr>
<td><em>Cryptococcus neoformans</em></td>
<td></td>
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</tbody>
</table>

NSIP: nonspecific interstitial pneumonitis; LIP: lymphocytic interstitial pneumonitis; IRIS: immune reconstitution inflammatory syndrome.
Treatment is usually started empirically in patients with typical clinical and radiological features and a CD4 count of <200 cells·μL⁻¹, pending diagnosis by cytological analysis of bronchoalveolar lavage (BAL) fluid or induced sputum samples.

Several factors present at or soon after hospitalisation predict poor outcome from PCP. These include increasing patient age, a second or third episode of PCP, hypoxaemia, low haemoglobin, co-existent pulmonary Kaposi sarcoma and medical comorbidity. Once hospitalised, development of pneumothorax, admission to the intensive care unit and need for mechanical ventilation are associated with worse outcome.

PCP can be stratified clinically as mild (arterial oxygen tension (Pₐ,O₂) >11.0 kPa, arterial oxygen saturation (Sₐ,O₂) >96% (breathing air at rest)), moderate (Pₐ,O₂ 8.0–11.0 kPa, Sₐ,O₂ 91–96%) or severe (Pₐ,O₂ <8.0 kPa, Sₐ,O₂ <91%). This categorisation is helpful, as oral therapy may be given to those with mild disease. First-choice treatment for PCP of all severity is high-dose co-trimoxazole (sulphamethoxazole 100 mg·kg⁻¹·day⁻¹ with trimethoprim 20 mg·kg⁻¹·day⁻¹) in two to four divided doses orally or intravenously for 21 days. Approximately two-thirds of patients will successfully complete this regimen. Treatment-limiting drug toxicity is common and <10% will not respond to treatment (defined by deterioration after ≥5 days of therapy).

In patients who develop toxicity or do not respond to co-trimoxazole, alternative therapy in mild/moderate disease includes clindamycin (450–600 mg q.i.d. orally or i.v.) plus oral primaquine (15 mg daily), oral dapsone (100 mg daily) with trimethoprim (20 mg·kg⁻¹·day⁻¹), or oral atovaquone suspension (750 mg b.i.d.). In severe disease, alternative therapy is clindamycin with primaquine or intravenous pentamidine (4 mg·kg⁻¹ daily).

Patients with an admission Pₐ,O₂ ≤ 9.3 kPa should also receive adjunct glucocorticoids within 72 h of starting specific anti-PCP treatment. A frequently used regimen is prednisolone, 40 mg b.i.d. for 5 days then 40 mg daily on days 6–10 and 20 mg daily on days 11–21. This has been shown to reduce mortality.

Co-trimoxazole, dapsone and primaquine should be avoided in patients with glucose-6-phosphate dehydrogenase deficiency.

Patients are at increased risk of PCP as their CD4 count decreases. Recommended regimens for PCP prophylaxis are listed in table 2.

Indications for primary prophylaxis are:
- blood absolute CD4 count <200 cells·μL⁻¹
- blood CD4 count <14% of total lymphocyte count
- unexplained fever (>3 weeks' duration)
- persistent or recurrent oral/pharyngeal Candida
- history of another AIDS-defining diagnosis e.g. Kaposi sarcoma

Indications for secondary prophylaxis are:
- all patients after an episode of Pneumocystis pneumonia

Indications for discontinuing secondary prophylaxis are:
- patients on combination antiretroviral therapy with sustained increase in blood CD4 count (>200 cells·μL⁻¹) and undetectable plasma HIV RNA for ≥3 months (note that if CD4 count subsequently falls <200 cells·μL⁻¹ and/or the HIV RNA load increases, prophylaxis should be re-instated)

**Tuberculosis** All patients with TB and unknown HIV status should be offered an HIV test. Active TB is estimated to occur between 20 and 40 times more frequently in HIV-infected subjects. Approximately 15% of all new TB cases globally occur in HIV-infected subjects, and it accounts for ~25% of all HIV-related disease.
related deaths. TB is also covered in other chapters, so here the focus is on issues of particular relevance to HIV-infected subjects.

More than two-thirds of patients with TB and HIV co-infection present with pulmonary disease. When blood CD4 counts are normal or only slightly reduced, clinical features are similar to adult post-primary disease. Chest radiography often shows upper lobe infiltrates and cavitary changes. Sputum and BAL fluid are often smear positive.

In advanced HIV disease, and with a low blood CD4 count (<200 cells·µL⁻¹), the presentation is often with nonspecific malaise, fatigue, weight loss and fever. Chest radiographic abnormalities may not be obvious although they can include diffuse or miliary shadowing, mediastinal/hilar lymphadenopathy and pleural effusions; cavitation is uncommon. Sputum or BAL fluid is often smear negative but culture positive. Extrapulmonary TB is common in patients with CD4 counts <100 cells·µL⁻¹. Local or disseminated infection may involve lymph nodes and bone marrow; blood cultures may be positive; and it is worth obtaining specimens from several body sites or fluids if possible, as there is a reasonable yield e.g. from early morning urine cultures.

If smears or unspeciated mycobacterial cultures are positive, treatment should initially include a four-drug anti-TB regimen with rifamycin plus isoniazid, pyrazinamide and ethambutol, until mycobacterial identification and drug sensitivities are known. TB diagnosis using nucleic acid amplification tests is limited by poor sensitivity, although it can distinguish *Mycobacterium tuberculosis* from opportunistic mycobacteria and identify common mutations in the *rpoB* gene associated with rifampicin resistance, as well as isoniazid (*katG* and *inhA* genes).

Response to treatment with a 6-month four-drug regimen is generally good, although patients with disseminated disease are often treated for 9–12 months. Given the reported increased risk of developing drug-resistant disease, it is recommended that HIV patients with high mycobacterial loads (e.g. disseminated disease, as seen in patients with low blood CD4 counts) receive daily and not

<table>
<thead>
<tr>
<th>Table 2. Recommended Pneumocystis pneumonia prophylaxis regimens</th>
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<tbody>
<tr>
<td><strong>First choice</strong></td>
</tr>
<tr>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>Co-trimoxazole (sulphamethoxazole + trimethoprim 5:1)</td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>Second choice</strong></td>
</tr>
<tr>
<td>Aerosolised pentamidine</td>
</tr>
<tr>
<td>Dapsone</td>
</tr>
<tr>
<td><strong>Third choice</strong></td>
</tr>
<tr>
<td>Atovaquone suspension</td>
</tr>
<tr>
<td>Azithromycin</td>
</tr>
</tbody>
</table>

⁸. the use of lower doses of co-trimoxazole may be associated with fewer adverse effects.
higher-dose (twice- or thrice-weekly) intermittent therapy. Compared with non-HIV-infected individuals, there is a possible greater incidence of adverse reactions to anti-TB drugs, and an increased risk of death.

CART reduces short- and long-term mortality in co-infected patients and should be started as soon as possible in subjects receiving treatment for active TB. However, there are issues with its early use in patients on anti-TB therapy. Generally, the lower the blood CD4 count, the more pressing is the clinical need to start CART (i.e. 2–4 weeks).

Issues with early use of combination antiretroviral therapy (CART) in tuberculosis patients:
- high pill burden
- overlapping toxicities, e.g. neuropathy
- drug–drug interactions, e.g. CART and rifamycins
- poor adherence to complex regimen
- immune reconstitution inflammatory disease more likely

Multidrug- and extensively drug-resistant TB has been associated epidemiologically with HIV infection. This is probably due to the rapid development of active (and hence infectious) TB in the HIV co-infected population exposed to drug-resistant cases, and hence reflects general susceptibility to developing mycobacterial disease, rather than to infection with specific drug-resistant strains.

Given the high risk of latent TB infection (LTBI) progressing to active disease, the World Health Organization recommends that HIV-infected patients with LTBI should receive prophylactic treatment. As, by definition, LTBI diagnosis requires a positive immune response (e.g. tuberculin skin test or blood interferon-γ release assay) in an asymptomatic individual, these assessments are hampered by the immune dysregulation present in HIV co-infected subjects.

Malignant conditions

**Kaposi sarcoma** Kaposi sarcoma is the commonest HIV-associated malignancy. Before the advent of CART, 15–20% of AIDS diagnoses were due to Kaposi sarcoma. It is associated with human herpes virus-8 (also called Kaposi sarcoma-associated virus) co-infection. Pulmonary Kaposi sarcoma is almost always accompanied by cutaneous or lymphadenopathic Kaposi sarcoma (palatal disease strongly predicts the presence of pulmonary lesions). Presentation is with nonspecific cough and progressive dyspnoea; haemoptysis is less common.

As Kaposi sarcoma may involve both the airways and lung parenchyma, radiological findings include interstitial or nodular infiltrates and alveolar consolidation. Hilar/mediastinal lymphadenopathy occurs in ~25% of patients and up to 40% have a pleural effusion.

Diagnosis is confirmed at bronchoscopy in >50% cases by the appearance of multiple, raised or flat, red or purple endotracheal and endobronchial lesions. Biopsy is rarely performed since cutaneous Kaposi sarcoma is usually present and diagnostic yield from biopsy is <20%. CART may induce remission of lesions, and is used in addition to chemotherapy.

**Lymphoma** High-grade B-cell non-Hodgkin lymphoma is the commonest HIV-associated thoracic lymphoma, and is usually found in association with disease elsewhere. Presenting symptoms are nonspecific. Chest radiographic abnormalities include mediastinal lymphadenopathy, pleural masses or effusions. The prognosis is better if patients treated with chemotherapy also receive CART.

**Bronchial carcinoma** Lung cancer appears to be two to four times more common in HIV-infected smokers. It is now more frequently diagnosed than in the pre-CART era. Whether this reflects the impact of CART protecting patients from other conditions, or some other mechanism, is uncertain. Presentation is
usually with disseminated disease, and the prognosis is therefore poor.

**Nonmalignant, noninfectious conditions**

**Chronic obstructive pulmonary disease**
HIV-infected smokers appear to be at increased risk (~60%) of developing chronic obstructive pulmonary disease. The synergistic effects of smoking, recurrent bacterial and opportunistic infections, injecting drug use and possibly direct effect of HIV in the lung, argue strongly for scaling up smoking cessation services. This will also impact on other smoking-related illnesses such as cardiovascular disease, which are increasingly prevalent in HIV-infected communities.

**HIV-associated pneumonitis**
Nonspecific pneumonitis mimics PCP but often occurs at higher blood CD4 counts. Diagnosis requires transbronchial, video-assisted thoracoscopic or open-lung biopsy. Most episodes are self-limiting, but prednisolone may be beneficial.

Lymphocytic interstitial pneumonitis is generally seen in HIV-infected children and clinically resembles idiopathic pulmonary fibrosis. Diagnosis requires biopsy. Treatment with CART is often effective.

**Pulmonary arterial hypertension**
Pulmonary arterial hypertension is reported to be six to 12 times more common in HIV-infected populations. The presentation and management are similar to nonimmunocompromised individuals, although CART is associated with improved haemodynamics and survival.

**Pneumothorax**
Pneumothorax occurs more frequently in HIV-infected patients than in the age-matched general medical population. Cigarette smoking and receipt of nebulised pentamidine are risk factors. PCP should be excluded in any patient presenting with a pneumothorax.

**HIV therapy causing respiratory symptoms**
In response to starting CART there may be an overexuberant immune response to exogenous antigen (from a current or previous opportunistic infection). This is well described for many conditions, although in particular for mycobacterial disease, and has been given several names including immune reconstitution inflammatory syndrome and immune reconstitution disease (IRD). Using TB as an example, subjects with known TB responding to treatment start CART and within a median of 2 weeks develop new clinical manifestations, e.g. peripheral lymphadenopathy, pleural or pericardial effusions or cerebral disease. There is no specific diagnostic test and drug resistance, patient nonadherence and other disease processes must be actively excluded. It is more likely in subjects with low baseline CD4 counts (<100 cells·μL⁻¹), more rapid suppression of HIV viral load and shorter time between starting anti-TB therapy and CART. It is reported in up to 30% subjects and, while often severe, is rarely fatal. Treatment is largely symptomatic, and may involve oral glucocorticoid therapy.

A second form of IRD is the “unmasking” of TB. Here, a patient with latent, asymptomatic infection will rapidly develop highly inflammatory active TB at a median of 40 days after starting CART. Treatment is generally directed at the underlying mycobacterial infection.

Lactic acidosis, typically due to the (nucleoside analogue) reverse transcriptase inhibitors didanosine and stavudine, may present with progressive breathlessness. Also, the nucleoside analogue abacavir can cause a hypersensitivity reaction (in up to 3% of subjects) with fever, rash and pulmonary symptoms. In these cases, recovery occurs if the drug is withdrawn.

**References**


Graft versus Host Disease

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Pathogenesis

Graft versus host disease (GVHD) is the principal complication of allogeneic bone marrow transplantation (BMT). The number of patients at high risk for GVHD is increasing, as more BMTs are performed from unrelated donors and older patients. Vascular endothelial damage and increased secretion of pro-inflammatory cytokines are involved in systemic disorders post-BMT, including GVHD and cytomegalovirus (CMV) infection. The pathology of acute GVHD can be considered in a framework of sequential phases. Initially, the recipient-conditioning regimen damages host tissues and causes release of pro-inflammatory cytokines; host antigen-presenting cells mature, acquire adhesion and co-stimulatory molecules that activate mature donor T-cells; these cells proliferate and produce additional cytokines inducing inflammatory and cellular effectors that amplify the inflammatory responses that cause tissue damage. Obstacles to the improvement of BMT include the linkage between GVHD toxicity and the beneficial graft-versus-leukaemia effect, as well as the impairment of immune reconstitution leading to life-threatening infections.

Key points

- GVHD is the principal complication of allogeneic BMT.
- Vascular endothelial damage and increased secretion of pro-inflammatory cytokines are involved in the pathogenesis of lung disorders.
- Acute and subacute patterns of lung injury include: idiopathic interstitial pneumonitis, bronchiolitis obliterans syndrome, organising pneumonia, alveolar haemorrhage, capillaritis, posttransplant lymphoproliferative disorders.
- CMV infection is the most frequent viral complication in patients undergoing BMT and acute GVHD significantly affects active CMV infection recurrence.

Treatment

Novel approaches to prevent or treat GVHD are linked to the generation of new monoclonal antibodies, immunomodulatory therapy, innovative strategies that target both soluble and cellular effectors. Among such agents are sirolimus, anti-tumour necrosis factor and antilymphocyte function-associated (LFA)-3 antibodies, extracorporeal photopheresis, mesenchymal stem cells and regulatory T-cells.

Noninfectious pulmonary-associated complications

Common pulmonary complications occur in 25–50% of BMT recipients and are responsible for 50% of transplant related deaths (table 1). Acute and subacute patterns of lung injury have been recognised. The idiopathic pneumonia syndrome occurs within the first 120 days after BMT with a rapidly
progressing fulminant course resulting in death in 60–80% of patients. By contrast, subacute noninfectious lung injury (alloimmune lung syndromes), including idiopathic pneumonia syndrome, bronchiolitis obliterans syndrome and bronchiolitis obliterans with organising pneumonia, can occur in the early post-transplant period or in the months post-BMT. Although long-term disease-free survival after BMT could exceed 60%, pulmonary infiltrates, due to either inflammatory or infectious pneumonitis, occur in 40–60% of BMT recipients causing 80% of transplant-related deaths. In children undergoing BMT, the incidence of pulmonary complications varies from 10–25%. Open lung biopsy has been recommended to make a definitive diagnosis and the appropriate treatment. Idiopathic interstitial pneumonitis and CMV pneumonitis are the most common causes and should be suspected in patients with diffuse interstitial infiltrates.

Epidemiological data suggest that, although GVHD reactions may play an aetiological role, the major contributing factor is conditioning-related toxicity. Moreover, engraftment syndrome, diffuse alveolar haemorrhage and pulmonary veno-occlusive disease are also possible complications.

**Infectious pulmonary-associated complications**

Respiratory virus infections in BMT patients are seen in 1–56%. CMV infection is the most frequent viral complication in patients undergoing BMT. Despite advanced diagnostic methods and pre-emptive antiviral therapy, CMV disease continues to be a life-threatening complication. Clinical manifestations could vary from an asymptomatic infection, defined as active CMV replication in the blood in the absence of clinical manifestations, or organ failure abnormalities characterised by CMV infection with clinical symptoms or organ function abnormalities. Active CMV infection interacts significantly in several ways with GVHD. Acute GVHD increases the chances of a poor outcome. CMV prophylaxis or pre-emptive therapy adopted during the last few years in allogeneic BMT recipients has changed the natural history of the disease. In prophylaxis, antiviral drugs are administered before any evidence of the virus, and in pre-emptive therapy, antiviral drugs are administered when there is laboratory evidence of an active but asymptomatic infection. Acute GVHD significantly affects active CMV infection recurrence. CMV infection recurrence is more frequent with short courses of antiviral therapy. The poor bioavailability of oral ganciclovir may account for this; drug resistance may also be a supplementary factor. Knowledge of these complications is now a part of the contemporary practice of pulmonary medicine, no longer isolated to the transplant pulmonologist.

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**Table 1. Frequency and mortality due to pulmonary complications after bone marrow transplantation**

<table>
<thead>
<tr>
<th></th>
<th>Frequency %</th>
<th>Mortality %</th>
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</thead>
<tbody>
<tr>
<td><strong>Infectious aetiology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV pneumonitis</td>
<td>34.3</td>
<td>50</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>71.4</td>
<td></td>
</tr>
<tr>
<td>PCP</td>
<td>33.4</td>
<td></td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Noninfectious aetiology</strong></td>
<td>65.7</td>
<td>30.4</td>
</tr>
<tr>
<td>Idiopathic interstitial pneumonitis</td>
<td>14.3</td>
<td></td>
</tr>
<tr>
<td>Organising pneumonia</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Alveolar haemorrhage</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Capillaritis</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Posttransplant lymphoproliferative disorders</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

CMV: cytomegalovirus; PCP: Pneumocystis carinii pneumonia. Adapted from Wang et al. (2004)
References

Amyloidosis is a group of diseases caused by accumulation of protein as insoluble fibrillar deposits in the extracellular space. These progressively disrupt the structure and function of affected tissues. Diagnosis is made by biopsy and Congo red staining, and classification is by the fibril precursor protein. Untreated amyloidosis progresses relentlessly, but deposits can regress if the supply of fibril precursors is reduced.

Amyloidosis can present to respiratory physicians in a number of ways: chronic lung conditions can give rise to systemic amyloidosis; systemic amyloidosis may present with respiratory symptoms; and localised pulmonary and respiratory tract amyloid deposits may present symptomatically or incidentally.

### Systemic amyloidosis complicating respiratory diseases

**Amyloid A (AA) amyloidosis** This causes proteinuric renal failure and is a potential complication of any sustained inflammation. The amyloid fibrils are derived from the acute phase reactant, serum amyloid A protein (SAA). The major respiratory disease underlying AA amyloidosis in the industrialised world is bronchiectasis. Previously tuberculosis was common and other associations include cystic fibrosis, sarcoidosis, lung neoplasia and Kartagener's syndrome. The prognosis of AA amyloidosis depends on the degree of renal damage and whether the underlying inflammatory disease can be completely controlled. Treatment depends on the underlying disease and may involve surgery, antimicrobials or immunosuppression.

**Systemic, amyloid light chain (AL) amyloidosis** This may occur in association with any B-cell dyscrasia as it is derived from monoclonal immunoglobulin light chains. A number of chest-localised conditions can underlie systemic AL amyloidosis including Sjögren's syndrome, plasmacytomas and Castleman's tumours.

### Respiratory system symptoms arising from systemic AL amyloidosis

Although lung deposits are universal at post mortem, symptoms are rare and dyspnoea generally reflects amyloid cardiomyopathy. Chest radiographs are usually normal. Lung function tests may be restrictive and extensive alveolar deposits can reduce gas transfer. Persistent pleural effusions are usually due to...
cardiac infiltration by amyloid but can rarely be caused by amyloidotic disruption of the pleura and may require recurrent drainage or pleurodesis. Treatment of systemic AL amyloidosis is chemotherapy directed against the underlying B-cell clone.

**Amyloidosis localised to the respiratory tract**

This results either from local production of fibril precursors, or from a microenvironment that favours fibril formation from a widely distributed protein. The majority of deposits are AL type associated with monoclonal B-cells confined to the affected site. Apparently localised amyloid deposits can be manifestations of systemic disease and should always be fully investigated to exclude systemic amyloidosis.

**Laryngeal amyloidosis**

Amyloid represents 0.5–1% of benign laryngeal disease and the incidence increases with age. It usually presents as hoarseness and is relatively benign but can be progressive or recur after treatment. Fatal haemorrhage has been reported. Endoscopic or laser excision is the treatment of choice, aiming to preserve voice quality and airway patency. Very rarely apparently localised laryngeal amyloid deposits can be a feature of hereditary apolipoprotein AL amyloidosis.

**Tracheobronchial amyloidosis**

This typically presents in the fifth or sixth decades with dyspnoea, cough and haemoptysis. Airway narrowing may cause pneumonia or lobar collapse and solitary nodules can mimic endobronchial neoplasia. There is no proven therapy although chemotherapy has been tried in patients with progressive disease. Management is dictated by symptoms and includes resection, stenting or laser ablation. Survival is <45% at 6 yrs.

**Parenchymal pulmonary amyloidosis**

This is typically an incidental finding on chest radiography of solitary/multiple nodules or a diffuse alveolar-septal pattern. Although the lesions must be differentiated from neoplasia the prognosis is usually excellent and no treatment is required.

**Mediastinal and hilar amyloid lymphadenopathy**

The lymphadenopathy may be massive and typically complicates a low-grade lymphoma. Disease progression is slow and calcification frequent. Tracheal compression or superior vena cava obstruction occasionally result.

**Conclusion**

Amyloidosis can both complicate longstanding pulmonary disease and be deposited within the respiratory system. The presentation and prognosis of amyloid deposits depend on their aetiology and distribution and can be benign or life threatening. In most cases of localised disease, management is essentially supportive or involves resection of symptomatic deposits. In contrast, systemic treatment can be extremely effective in patients with generalised AA and AL amyloidosis.

**References**

PULMONARY ALVEOLAR PROTEINOSIS

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Pulmonary alveolar proteinosis (PAP) is a rare syndrome occurring worldwide with an estimated prevalence of 0.1 per 100,000 individuals. PAP is characterised by accumulation of surfactant within alveolar macrophages in the alveoli and terminal airspaces, with impairment of gas transfer, and by a variable clinical course, ranging from spontaneous resolution to progressive respiratory failure.

A surfactant clearance impairment is the likely common pathophysiology of PAP, which can be classified as follows.

Primary PAP is due to disruption of granulocyte macrophage-colony stimulating factor (GM-CSF) signalling, either by the presence in plasma and lungs of high levels of neutralising anti-GM-CSF autoantibodies (GMAb; autoimmune PAP, formerly known as idiopathic PAP), or to mutations in the GM-CSF receptor α or β chains.

Secondary PAP occurs as a consequence of the presence of several underlying diseases associated with PAP, such as haematologic disorders (mostly myelodysplastic syndrome), immunodeficiency status, dust inhalation, or lysinuric protein intolerance.

A third group (PAP-like diseases) is characterised by surfactant production impairment and includes genetic disorders due to mutations in the SP-B and SP-C genes, as well as in the ABCA3 gene.

According to a recently published meta-analysis and large cohort report, >90% of immune PAP patients are middle-aged adults, complaining about progressive exertional dyspnoea and cough; interestingly, about one-third of a large Japanese PAP series was asymptomatic. Physical examination of PAP patients is often unremarkable. Pulmonary function tests may be normal, but usually the first abnormality is represented by a decrease in lung diffusing capacity, and exertional increased alveolar–arterial oxygen tension gradient. The classic chest radiographic presentation is a diffuse bilateral infiltrate, with a distribution sometimes similar to pulmonary oedema (fig. 1a). More typical is the high-resolution computed tomography

Key points

- Pulmonary alveolar proteinosis (PAP) is a rare syndrome caused by surfactant clearance impairment.
- More than 90% of PAP cases are associated with the presence of neutralising autoantibodies anti-GM-CSF (GMAb; primary autoimmune PAP).
- Diagnosis of primary autoimmune PAP is based of the following triad: 1) crazy paving pattern at HR CT scan; 2) milky appearance and cytology of BALF; 3) elevated serum level of GMAb.
- Whole lung lavage is the current standard of care of PAP, but alternative therapy (especially GM-CSF administration) are under active investigation.
(HRCT) presentation defined as “crazy paving” (thickening of interlobular and intralobular septa, and ground-glass opacities, with patchy distribution) (fig. 1b). Although surgical biopsy is traditionally considered mandatory to establish the diagnosis of PAP, more recently the triad represented by: 1) typical radiological findings on HRCT; 2) macroscopic appearance of milky fluid and cytology of bronchoalveolar lavage (BAL) fluid; and 3) elevated serum level of GMAb (whose sensitivity and specificity for diagnosing PAP is approximately 100%) is now considered sufficient to establish the diagnosis of autoimmune PAP. Lung biopsy should be considered when one or more of the previous findings are unclear. Histopathology usually shows well preserved alveolar wall architecture, and alveolar spaces filled with lipoproteinaceous, eosinophilic, Periodic Acid–Schiff-positive material and foamy macrophages.

The natural history of the PAP has been greatly influenced by the treatment. In the pre-whole-lung lavage (WLL) era, progressive deterioration occurred in ~30% of PAP patients. Death occurred mostly because of irreversible respiratory failure and, to a lesser extent, respiratory infection. The latter is a typical complication of the clinical course of PAP: pulmonary and systemic infections due to opportunistic organisms such as Nocardia, mycobacteria and Cryptococcus are often reported. Increased susceptibility to lung infections is traditionally attributed to the impairment of alveolar macrophages engulfed by surfactant, but systemic infections have been ascribed more recently to GM-CSF signalling impairment.

The adoption of WLL, first described in the mid-1960s has changed the natural history of PAP, by dramatically reducing the death rate. It is considered the standard care of PAP, and 95% of PAP patients respond positively to the procedure, although a considerable fraction of patients may show relapses or incomplete resolution. GM-CSF administration, based on the pathophysiology of the disorder, is considered an attractive alternative to WLL. Unfortunately, limited experience and, more importantly, difficult access to the drug have so far precluded diffusion of this therapeutic option. Possible alternatives are plasmapheresis or immunosuppressive agents such as rituximab, but data are so far insufficient. Lung transplantation is considered in end-stage disease, but PAP may recur.

References


Figure 1. a) Radiographic and b) high-resolution computed tomography ‘crazy paving’ presentation of pulmonary alveolar proteinosis.
ADULT PULMONARY LANGERHANS’ CELL HISTIOCYTOSIS

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Langerhans’ cell (LC) histiocytosis (LCH) in adults may involve especially the lungs, bone, the skin, and the pituitary gland. The disease presentation in childhood is different, with acute disseminated disease with a poor prognosis, and in older children and adolescents with multifocal involvement including bone. Single-system involvement by LCH is possible.

Epidemiology
Pulmonary LCH in adults is a rare disease with an estimated prevalence <1 in 200,000. It occurs almost exclusively in smokers, with no gender predominance, between the ages of 20–40 yrs, and is more common in the white population.

Pathologic features
Pulmonary LCH is characterised by the granulomatous bronchiolocentric organisation of LCs associated with inflammatory cells including eosinophils. The LCs do not differ from their counterparts in other tissues, exhibiting convoluted irregular nuclei with characteristic Birbeck granules on electron microscopy. These cells stain positive with anti-CD1a and anti-CD207 antibodies. Some features of alveolar macrophage pneumonitis (desquamative interstitial pneumonia) or respiratory bronchiolitis with interstitial lung disease are often associated. The progression of the bronchiole-centered granulomatous lesions results in fibrosis with end-stage stellar fibrotic scars and adjacent cystic cavities.

Clinical features
The respiratory manifestations are not specific, with cough (often overlooked since patients are smokers), and dyspnoea on exercise. Spontaneous pneumothorax is the first manifestation leading to diagnosis in ~10-20 % of patients. A number of patients have almost no reported symptoms and diagnosis is made by routine chest radiography.

Pulmonary LCH is solitary in a large majority of patients; however, involvement of other systems may be the first manifestation of the disease. These include bone lesions (which are often characteristic, well demarcated and osteolytic on imaging; rib involvement with chest pain is possible), hypothalamic–pituitary involvement resulting in diabetes insipidus (polyuria, polydipsia) and skin lesions.

Key points
• Pulmonary LCH is characterised by cough, dyspnoea on exercise, and diffuse pulmonary nodules and cysts on chest imaging in smokers that may evolve to respiratory failure.
• Smoking cessation should be obtained.
• No medical therapy has demonstrated efficacy.
Imaging

Chest radiography is usually abnormal with micronodular and reticular opacities sparing the lower lobes. In advanced disease, the nodules are absent and chest radiography may suggest emphysema.

High-resolution computed tomography (HRCT) of the chest usually shows characteristic features in early disease with disseminated infracentimetric nodules, which may show cavitation and may further spontaneously disappear. The cavitated nodules may evolve to thick then thin-walled cysts (figure 1). The cysts may then enlarge and become confluent with HRCT features resembling emphysema.

The differential diagnoses with other multiple cystic lung diseases on imaging comprise especially lymphangioleiomyomatosis, Birt-Hogg-Dubé and spontaneous familial pneumothorax related to FLCN mutations, Sjögren syndrome and nonamyloid immunoglobulin deposition disease. Pleural effusion and mediastinal lymphadenopathy is exceptional. Pulmonary artery enlargement is present in patients with pulmonary hypertension.

Lung function tests

Lung function tests may be normal or only mildly impaired in patients with nodular involvement. However transfer factor of the lung for carbon monoxide is usually decreased, even in patients with relatively few lesions on imaging. About one-third of patients develop airflow obstruction with inflation, which may progress to severe obstructive respiratory failure.

Diagnosis

The gold standard for diagnosis is lung biopsy showing the characteristic features described above. Surgical biopsy is often obtained during pleurodesis for refractory or relapsing pneumothorax. Because of the plurifocal distribution of the lesions in the lung, the yield of transbronchial lung biopsy is usually limited. Bronchoalveolar lavage (BAL) is currently considered of little if any value for diagnosis. It shows an increase in total cell counts with a large predominance of macrophages with possible slight increase in eosinophils. The CD4/CD8 lymphocyte ratio is decreased. The identification of Langerhans’ cells in BAL with antibodies against CD1a has only poor sensitivity and specificity and their proportion is usually similar to that in smokers without LCH. Common laboratory tests are not contributive.

A presumptive diagnosis of pulmonary LCH may be accepted in patients with characteristic HRCT features and limited symptoms and impaired lung function. Lung biopsy is indicated in those patients with significant symptoms and deteriorating lung function who are considered for treatment. In patients with diffuse cystic lesions on HRCT with fixed lung function impairment, lung biopsy is of limited benefit especially as it may not show characteristic granulomatous lesions.

Evolution

About half of patients improve spontaneously or with corticosteroid treatment (which has not been evaluated). Poor outcome with respiratory failure may occur especially in older patients with systemic involvement and deteriorating lung function tests. Pulmonary hypertension, occasionally severe, is common in advanced disease. Lung cancer may develop resulting from smoking habits.

Figure 1. High-resolution computed tomography of the chest demonstrating numerous thin-walled cysts in a patient with LCH.
Treatment
Given the possibility of spontaneous recovery in a number of patients and the absence of controlled therapeutic trials, there is no evidence for efficacy of any treatment.

However, the strong association between pulmonary LCH and smoking suggests that smoking cessation should be obtained (at least to prevent further development of chronic obstructive pulmonary disease and/or lung cancer).

Corticosteroid treatment is often used in patients with symptomatic disease and worsening lung function, starting with prednisone 0.5–1 mg.kg\(^{-1}\) then tapered over 6–12 months. Whether improvement, when it occurs, results from treatment efficiency or is spontaneous cannot be established.

Cytotoxic agents (especially vinblastin) have occasionally been used with no conclusive efficiency. 2-chloro-deoxyadenosine (cladribin) has consistently been shown to be efficient in isolated cases, however it may be proposed and evaluated only in referral centres.

Pulmonary hypertension, when present, may be improved by pulmonary arterial hypertension treatment in some patients.

Lung transplantation (single- or double-lung, or heart–lung) may be considered in patients with end-stage disease. The majority of these present with moderate-to-severe pulmonary hypertension. Posttransplant survival is rather good with 10-yr survival >50%; however, pulmonary LCH may recur in about one-fifth of patients.

References
Epidemiology and genetics

Lymphangioleiomyomatosis (LAM) is a rare (so-called orphan) lung disease affecting about 1 in 400,000 adult women (usually of childbearing age). It may be sporadic, or associated with tuberous sclerosis complex (TSC) where it affects 30–40% of adult women and, exceptionally, men.

TSC is associated with inherited mutations of the TSC1 and TSC2 genes, while acquired somatic mutations of TSC2 are associated with sporadic LAM, resulting in constitutive activation of the kinase mammalian target of rapamycin (mTOR) signalling pathway.

Pathology

In LAM, the lung parenchyma is progressively replaced by cysts associated with a proliferation of immature smooth muscle cells and perivascular epithelioid cells (LAM cells). LAM cell proliferation usually develops around lymphatic vessels in the lung and possibly the axial lymphatics and the thoracic duct. LAM cells are stained with antibodies against smooth muscle actin, desmin, and HMB-45 (detecting characteristic pre-melanocyte proteins).

Clinical manifestations and lung function tests

Dyspnoea on exertion is the most common symptom, and pneumothorax the most common mode of presentation (often relapsing, and may be bilateral). Chyloous effusion (chylothorax, chylous ascites) may be present.

Lung function tests are characterised by airflow obstruction and impaired gas transfer with decrease in transfer factor of the lung for carbon monoxide ($T_{L,CO}$). Exercise performance and maximal oxygen uptake are impaired. Hypoxaemia is present in advanced disease.

Imaging

Chest radiography shows reticular opacities and cysts, with further possible pleural effusion or pneumothorax.

High-resolution computed tomography (HRCT) of the chest has a major role in diagnosis. It shows characteristic multiple round cysts involving the whole parenchyma; these may progressively become confluent (fig. 1).

The differential diagnoses with the other multiple cystic lung diseases on imaging comprise especially Birt–Hogg–Dubé syndrome and spontaneous familial pneumothorax related to folliculin gene mutations, Langerhans' cell granulomatosis,
Sjögren syndrome and nonamyloid immunoglobulin deposition disease.

Cysts may be associated with some small nodules in TSC (corresponding to multifocal micronodular pneumocyte hyperplasia), pleural effusion or pneumothorax. The axial lymphatics in the thorax and the retroperitoneum may be dilated with lymphadenopathy, and abdominal cystic lymphatic collections called lymphangiomas (in up to 20% of patients) that may result in abdominal discomfort or compression.

**Angiomyolipoma**

Angiomyolipomas (AML) of the kidney (which are benign tumors composed of blood vessels, smooth muscle, and adipose tissue easily identified on HRCT) are associated with LAM in 50% of sporadic LAM and 80% of patients with TSC (where these are more often bilateral and larger). AML may enlarge with time and become prone to bleeding, especially when >4 cm in size (embolisation or nephron-sparing surgery is therefore indicated). Screening for AML in patients with LAM is recommended.

**Diagnostic criteria**

Diagnostic criteria for LAM have recently been proposed by a European Respiratory Society Task Force (table 1). The gold standard for diagnosis of LAM is lung biopsy fitting the pathological criteria for LAM. However, the association of characteristic HRCT features with AML or other characteristic features of LAM may obviate the need for biopsy. The differential diagnosis comprises other multiple cystic lung diseases including especially the Birt-Hogg-Dubé syndrome associated with mutations of the folliculin gene, familial.

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**Table 1. European Respiratory Society diagnostic criteria for lymphangioleiomyomatosis (LAM)**

<table>
<thead>
<tr>
<th>Definite LAM</th>
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<tbody>
<tr>
<td>1. Characteristic(^a) or compatible(^b) lung HRCT and lung biopsy fitting the pathological criteria for LAM OR</td>
</tr>
<tr>
<td>2. Characteristic(^a) lung HRCT and any of the following:</td>
</tr>
<tr>
<td>angiomyolipoma (kidney)(^a)</td>
</tr>
<tr>
<td>thoracic or abdominal chylous effusion(^b)</td>
</tr>
<tr>
<td>lymphangioleiomyoma(^a) or lymph-node involved by LAM(^a)</td>
</tr>
<tr>
<td>definite or probable TSC</td>
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<tr>
<th>Probable LAM</th>
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<tbody>
<tr>
<td>1. Characteristic(^a) HRCT and compatible clinical history(^c) OR</td>
</tr>
<tr>
<td>2. Compatible(^a) HRCT and any of the following:</td>
</tr>
<tr>
<td>angiomyolipoma (kidney)(^a)</td>
</tr>
<tr>
<td>thoracic or abdominal chylous effusion(^b)</td>
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<table>
<thead>
<tr>
<th>Possible LAM</th>
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<tbody>
<tr>
<td>Characteristic(^a) or compatible(^b) HRCT</td>
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</table>

\(^a\): characteristic: multiple thin-walled round well-defined air-filled cysts; compatible: only few multiple (>2 and ≤10) < 30-mm such cysts; \(^b\): diagnosed by characteristic computed tomographic features and/or on pathological examination; 
\(^c\): based on visual and/or biochemical characteristics of the effusion; \(^d\): based on pathological examination; \(^e\): compatible clinical features include pneumothorax (especially multiple and/or bilateral) and/or altered lung function tests as in LAM.

Reproduced from JOHNSON et al. (2010).
isolated primary spontaneous pneumothorax (also associated with mutations of the same gene), cysts associated with lymphoid interstitial pneumonia, nonamyloid immunoglobulin deposition disease, etc. A diagnostic workup for the preceding alternative causes of multiple cystic lung disease is mandatory in patients with probable and especially possible LAM.

**Evolution and prognosis**

Disease progression is variable with some patients remaining relatively stable for long periods whereas others deteriorate rapidly with ensuing respiratory insufficiency. Repeated measurement of forced expiratory volume in 1 s and TLCO is used to assess disease progression with arterial oxygen measurement in advanced disease. Pulmonary hypertension, usually mild, may develop. 10-yr survival was about 70–90% in recent large series.

**Management**

As LAM occurs in women of childbearing age, oestrogens have been suspected to enhance and progestatives to prevent its development. However, hormonal interventions have not demonstrated significant advantages. Nevertheless, oestrogens (contraceptive pill, hormone replacement) should be avoided.

No effective treatment for LAM is available. The mTOR inhibitors, which transiently reduce the volume of AML, may mildly improve or stabilise pulmonary LAM; however, only limited evidence is currently available and tolerance may be poor.

There is a greater risk of pneumothorax and chylous effusion during pregnancy. To become pregnant is the patient’s decision; however, pregnancy may be discouraged in patients with severe disease.

Influenzal and pneumococcal vaccination should be offered to patients with LAM. Inhaled bronchodilators should be prescribed to patients with airflow obstruction and continued if an response is observed.

In patients with end-stage disease LAM, transplantation (single or bilateral) is an efficient procedure with results comparing favourably with transplantation for other pulmonary diseases. As many LAM patients are rather young, lung transplantation may be proposed in most severe cases with poor prognosis. Recurrence of LAM on transplant is possible but does not affect survival.

**References**

Respiratory physiotherapy spans a broad range of services, advice and nonpharmacological interventions used to help patients with a variety of respiratory conditions. Its use has been documented for over a century: postural drainage (PD) was reported for secretion removal in bronchiectasis in 1901 and, in 1915, breathing exercises and physical exercise for chest injuries.

**General principles of physiotherapy**

Physiotherapy is aimed at treating or alleviating problems rather than diseases. Strategies are used to restore, improve or maintain movement and/or function, and maximise participation in everyday life.

Physiotherapists are thus vital to the delivery of effective pulmonary rehabilitation (PR).

Physiotherapy is provided across all healthcare settings, from the patient’s own home to the critical care unit. Physiotherapists are well qualified to provide assessment and monitoring of, for example, ventilatory function and cough effectiveness or exercise tolerance, including for ambulatory oxygen \((O_2)\) assessment. Interestingly, there is wide variance in tasks undertaken by physiotherapists across countries.

**Airway clearance**

To help the patient better manage their secretions, a range of airway clearance techniques are available, including:

- independent techniques, *e.g.* the active cycle of breathing techniques, autogenic drainage
- mechanical or other devices, *e.g.* positive expiratory pressure (PEP)/oscillating PEP and high frequency chest wall oscillation
- PD or modified PD
- nebulised substances, *e.g.* hypertonic saline
- techniques for cough enhancement or support, *e.g.* maximum insufflation techniques and manually assisted coughing

Physiotherapists’ physiological knowledge and practical skills means they are well placed to assist in the delivery of pharmacotherapy (inhalers) and their timing with respect to the

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**Key points**

Physiotherapy is indicated in most respiratory conditions, both for groups and individuals, for:

- self-management advice and education on lifestyle modifications related to physiotherapy strategies
- breathlessness management
- improvement or maintenance of mobility and function
- airway clearance in well-defined cases
- prescription of exercise and exercise training
- prescription of walking aids
Physiotherapy intervention. Physiotherapists can also help in the delivery and correct application of O2 therapy, including ambulatory O2, as well as offering improvement of poor ventilatory function, including in the sedated and paralysed patients.

**Strategies to enhance ventilation and gas exchange**

Strategies to enhance ventilation and gas exchange include:

- positioning
- breathing techniques
- manual hyperinflation
- intermittent positive pressure breathing (IPPB)
- continuous positive airway pressure (CPAP)
- noninvasive ventilation (NIV)

Physiotherapists are considered by many to be invaluable in the delivery of an effective NIV service.

Physiotherapy is commonly helpful for postural problems and/or musculoskeletal dysfunction and pain as well as for improving continence. With an increased prevalence compared with that of nonrespiratory populations, this is especially warranted during coughing and forced expiratory manoeuvres.

**Disease-specific physiotherapy**

**Chronic obstructive pulmonary disease (COPD)** Taking account of the altered mechanics of breathing in those with COPD is essential for effective breathlessness management and advice.

Breathlessness management includes:

- positioning to fix the shoulder girdle passively
- forward-leaning postures to improve the length tension ratio of the diaphragm

“Thank you for giving me my life back.”

- breathing techniques to help the patient better control dyspnoea and panic, both at rest and during exertion

Physical activity and exercise should be encouraged throughout the course of the disease, including during hospital admission where possible and appropriate. When supervised and carried out at appropriate intensity these exercises are more effective. Exercise training programmes are indicated for patients who have symptoms and impaired physical activities in daily life.

Selected patients may benefit from inspiratory muscle training.

In both the acute and domiciliary settings:

- Wheeled walking aids (rollator frame) reduce the ventilatory requirements of ambulation.
- Wheeled walking aids are especially useful for those who are more disabled by breathlessness and those using ambulatory O2.
- Patients severely disabled by breathlessness may find using a high gutter rollator frame allows some mobility.
- Along with occupational therapists, physiotherapists may promote energy conservation strategies to minimise the work of activities of daily living.
Airway clearance techniques should be used where indicated and IPPB may be considered in acute exacerbations of COPD for patients with retained secretions who are too weak or tired to generate an effective cough. NIV is now the first-line therapy for hypercapnic respiratory failure and both NIV and O₂ therapy should be delivered according to current guidance.

**Asthma** Some form of breathing retraining using reduced volume and/or frequency with relaxation is indicated to reduce symptoms and improve quality of life, along with prescribed medication. Several schools advocate specific techniques, but it is important to stress that these techniques are adjunctive to medication and not a replacement therapy.

Routine or regular airway clearance is rarely indicated in the asthmatic patient.

**Disordered breathing (hyperventilation syndrome)** Breathing exercises combined with relaxation (technique as for asthma) is an effective strategy to reduce symptoms once the diagnosis is confirmed.

**Cystic fibrosis (CF) and non-CF-related bronchiectasis** Physiotherapy is integral to the management of patients with bronchiectasis from any cause, including CF, with airway clearance and exercise central to this therapy. The acceptability of techniques and regimes, to enhance concordance with treatment, is vital to the success of therapy.

A variety of airway clearance techniques, including those with and without mechanical assistance if necessary, should be offered, in order to find one that is both acceptable and effective. The simplest technique that impinges the least on the patient’s life is a good starting point.

Effective treatment might need to be supported by inhaled therapies, *e.g.* bronchodilators or hypertonic saline, O₂ and NIV or IPPB. These supportive therapies and PD to enhance airway clearance or exercise tolerance should be assessed for benefit on an individual basis. Regular review is advised to ensure continuing effectiveness and concordance with therapy; appropriate adjustment of treatment can be made if necessary.

- Physiotherapy for patients with CF should include assessment and treatment for musculoskeletal and postural disorders.
- Physiotherapists need to be scrupulous about hygiene for infection control in this population.
- For those with either CF or bronchiectasis continence problems should be identified and treated.
- For patients with bronchiectasis, PR is indicated when dyspnoea is impacting on exercise tolerance or functional activities.
- Exercise for the patient with CF must be undertaken individually to reduce risk of cross-infection.

**Interstitial lung diseases** There is little published evidence on physiotherapy for these conditions. Studies on the effectiveness of engaging in exercise training are emerging and patients with interstitial lung diseases can gain benefit from PR providing they are referred early in the disease process. Patients at a later stage of disease may benefit from wheeled walking aids, ambulatory O₂, breathlessness management and energy conservation strategies.

**Community-acquired pneumonia (CAP)** Traditional airway clearance techniques are rarely indicated.

For patients admitted to hospital with uncomplicated CAP:

- Regular use of PEP may reduce length of stay.
- Medical condition permitting, early mobilisation is indicated.
- Patients should be encouraged to sit out of bed for at least 20 min on the first day,
increasing the time and general mobility on each subsequent day.

CPAP may be helpful for patients in type I respiratory failure who remain hypoxaemic despite optimum medical therapy and O₂, and NIV may be an option for selected patients in type II respiratory failure, especially those with underlying COPD.

Chest wall disorders PR is indicated in a patient with chest wall deformity from any cause with reduced exercise capacity and/or breathlessness on exertion. The need for ambulatory O₂ or NIV should be assessed before undertaking exercise. Respiratory muscle training may have a role. It has yet to be established whether breathing or thoracic mobility exercises are helpful in this client group.

Neuromuscular disease and spinal cord injury (SCI) Respiratory problems are the commonest cause of morbidity and mortality for those with respiratory muscle weakness; physiotherapy therefore provides vital assistance with airway clearance. Difficulty clearing secretions may be due to inspiratory, expiratory and/or bulbar muscle weakness, depending on the underlying condition and stage of disease.

- Regular monitoring of O₂ saturation, vital capacity and peak cough flow can indicate impending problems with either ventilation or cough effectiveness.
- The use of respiratory aids when these measures fail may prevent or reduce complications.

O₂ therapy should be administered with great care in patients with neuromuscular disease because of the risk of increasing ventilation/perfusion mismatch and increasing hypercapnia. NIV should be considered in those at risk of developing hypercapnia. These actions are done together with the treating physician.

Traditional physiotherapy techniques are not useful in this client group.

Strategies to enhance maximal insufflation capacity are indicated and include:
- resuscitation bags
- NIV
- mechanical insufflation, and
- breath stacking via the above or
- glossopharyngeal (frog) breathing

The presence of severe bulbar dysfunction or paralysis renders breath stacking ineffective. Maximal insufflation capacity used regularly is also a means of maintaining range of movement to the lungs and chest wall. These techniques should be used along with strategies to enhance cough effectiveness: manually assisted coughing or mechanical insufflation-exsufflation.

Ventilatory function can be improved with careful positioning to optimise the effect of gravity on weak muscles, as can the use of abdominal binders for those with SCI.

In patients with SCI, exercise should be encouraged; respiratory muscle training and functional electrical stimulation may enhance muscle strength or vital capacity. Some patients with early neuromuscular disease may benefit from respiratory muscle training but caution is advised in Duchenne muscular dystrophy.

Patients with critical illness The principles of care remain the same; physiotherapists provide rehabilitation for the prevention and treatment of the common complications associated with prolonged bed rest, immobility and recumbency, including deconditioning, weakness and dyspnoea. Physiotherapy is also used to target specific respiratory problems, such as retained airway secretions, atelectasis and weaning failure.

References
Clinical Information/Physiotherapy/PhysiotherapyGuideline.


Pulmonary rehabilitation is a recognised therapy for patients with respiratory diseases. The European Respiratory Society and the American Thoracic Society define pulmonary rehabilitation 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 individualized treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimize functional status, increase participation, and reduce health care costs through stabilizing or reversing systemic manifestations of the disease". Although this is a long definition, it captures the core elements important in the selection and design of pulmonary rehabilitation. Importantly, pulmonary rehabilitation may be an integrated part of other care plans for chronic obstructive pulmonary disease (COPD) patients, such as self-management programmes, lung transplantation programmes, noninvasive ventilation or smoking cessation programmes.

**The evidence base for pulmonary rehabilitation**

Several reviews have summarised the evidence for pulmonary rehabilitation and practice guidelines are available. Briefly, pulmonary rehabilitation improves health-related quality of life and symptoms unequivocally and clinically significantly in patients with COPD, to a degree similar to or even larger than that obtained by pharmacotherapy. When exercise training is provided at adequate intensity, exercise tolerance is enhanced and functional exercise capacity improves. These improvements are also clinically relevant if an appropriate exercise stimulus is provided. Other improvements are also important but are to date less studied.

A significant proportion of patients referred for pulmonary rehabilitation suffer from psychiatric morbidity, most commonly anxiety and depression. A recent meta-analysis showed the potential small benefit of multidisciplinary pulmonary rehabilitation on mood status. The relatively small effect size may be a result of the dilution of depressed patients in the larger patient pool: effects on these variables can only be expected in patients with symptoms of depression and/or anxiety.

A less studied effect of rehabilitation is enhanced self-efficacy. Self-efficacy is the

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**Key points**

- Pulmonary rehabilitation is an evidence-based treatment that improves health-related quality of life and symptoms in chronic obstructive pulmonary disease.
- Programmes should be tailored to the patient in terms of content, location, duration, frequency and exercise training.
- In order for the effects to be durable, patients’ everyday activity should be higher after rehabilitation than before.
confidence patients have in their ability to carry out a specific task or manage a specific condition (e.g. breathlessness). Patients’ confidence that they can manage dyspnoea improves after pulmonary rehabilitation, and one seminal study also showed an improvement in self-efficacy with walking. It is unclear to what extent this contributes to an effective change in behaviour after pulmonary rehabilitation.

The amount of activity patients carry out in daily life is an important outcome for rehabilitation. The systemic consequences of COPD, such as cardiovascular morbidity, muscle weakness and osteoporosis, originate largely – directly or indirectly – from an inactive lifestyle. When pulmonary rehabilitation aims at achieving a sustained effect, an inactive lifestyle after rehabilitation should be avoided. The effect of pulmonary rehabilitation programmes on physical activity levels is as yet unclear. Changing physical activity behaviour is a challenging task. Our research group showed that walking time in daily life changed only modestly after 3 months of pulmonary rehabilitation. After 6 months there was a more significant improvement in physical activity levels. Changing physical activity may not simply follow increased exercise capacity. Indeed, physical activity levels are a complex integration of exercise capacity and willingness to use that capacity. In recent years, appealing new strategies have been developed that may help to increase the effects of classical rehabilitation on physical activity. Providing real-time feedback with pedometers may, along with setting achievable goals, enhance daily activity levels in- or outside the context of pulmonary rehabilitation. Walking at home has been stimulated effectively using modern interfaces such as mobile phone technology, which included paced walking to the rhythm of music adapted to the capabilities of the patient. Future research should focus on further strategies that may help to lead to sustainable behavioural change.

An important spin-off of pulmonary rehabilitation may be a decrease in the use of healthcare resources, most importantly hospital admissions. There is a body of data suggesting that pulmonary rehabilitation reduces the number of hospital days. In more fragile patients, such as those recently admitted to hospital and at risk for readmission, a meta-analysis showed that the risk for readmission was reduced substantially following pulmonary rehabilitation.

**Programme content and maintaining effects**

As indicated above, programmes need to be individualised and aim at improving the systemic consequences (physiological and psychological) of the underlying disease, guiding patients and their families towards a long-term change in physical activity and self-management. Several options are possible in terms of programme content (the disciplines contributing), location, duration and frequency. These are summarised in table 1. Studies comparing different modalities of rehabilitation are scarce and no unequivocal preference has been reported. Studies comparing hospital-based outpatient rehabilitation to rehabilitation at home found no differences on short-term outcomes. More research is needed to evaluate the criteria for assigning patients to a specific form of rehabilitation. In addition, it remains unclear to what extent home rehabilitation results in more durable effects.

For the essential exercise training component, the programme needs to be individualised in terms of exercise modalities, specificity of training, training intensity and specific inspiratory muscle training. In order to obtain significant physiological improvements in skeletal muscle function it is important to train patients at an intensity that is high relative to their maximum capacity. In order to combine an effective training programme with patient comfort, clinicians have the choice of several exercise training modalities, including endurance, interval and resistance training. The duration of an exercise training programme is ≥8 weeks and at least three sessions per week are needed. One of these sessions can be conducted outside the
formally supervised setting, provided that the session is comparable in terms of duration and intensity to the supervised sessions.

There has been much debate as to whether the effects of a rehabilitation programme can be maintained. From earlier studies it is indeed difficult to claim durable effects for short-term (6–8 weeks) pulmonary rehabilitation programmes. Long-term studies (using up to 6 months of rehabilitation) did find more long-term effects.

Current understanding of the development of systemic consequences of COPD may help in the design of successful longer-term strategies to maintain the effects of pulmonary rehabilitation. First, efforts should be made to change the physical activity behaviour of patients. Physical inactivity is likely to be the most important contributor to the development of systemic consequences in COPD. If patients are not more active after the rehabilitation programme, it is likely that the effects of rehabilitation on enhanced exercise capacity and skeletal muscle force will be short lived. Longer programmes are more successful in achieving this goal than short-term programmes, but changes in the programme content, for example providing patients with direct feedback on their physical activity levels or using structured behavioural interventions, may yield results more rapidly. Secondly, exercise at home should be facilitated. This can be done using feedback on home exercises, or incentives. Such exercises need to be individually tailored to achieve effective intensity in order to provide a continued training stimulus. Ideally, exercises should be regularly supervised. Lastly, specific attention should probably go to patients who suffer from exacerbations, as these events acutely reduce muscle force and functional exercise capacity. Prevention of such events can be done in patients at risk by implementing self-management strategies and providing a case manager. There is currently little evidence for a short "booster" programme after a hospital admission to maintain the benefits of rehabilitation.

Examination of the strategies used to maintain the benefits of rehabilitation reveals that it is important to achieve a durable change in physical activity behaviour and that patients should continue to carry out planned exercises at high intensity to maintain the physiological benefits of rehabilitation. Interventions that are not regular or are less structured are not successful in maintaining the benefits of rehabilitation. More research is needed to identify optimal maintenance strategies after pulmonary rehabilitation.

<table>
<thead>
<tr>
<th>Aspects to be individualised</th>
<th>Possible choices or options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Programme content</td>
<td>Disciplines typically involved: chest physician, physiotherapists, nurse, exercise specialist, occupational therapist, psychologist, social worker, dietician, general practitioner</td>
</tr>
<tr>
<td>Location</td>
<td>Rehabilitation centre: in-patient, outpatient, home based but supervised from a specialised centre Community based: outpatient in centre or primary care office Home based: supervised by primary care team</td>
</tr>
<tr>
<td>Duration</td>
<td>≥ 8 weeks, but longer is typically more desired</td>
</tr>
<tr>
<td>Frequency</td>
<td>≥ 3 sessions per week of which 2 are supervised</td>
</tr>
<tr>
<td>Exercise training component</td>
<td>Exercise modalities (walking, cycling, upper limbs, etc.) Exercise intensity Exercise type: interval, endurance, resistance Additional interventions: inspiratory muscle training, oxygen therapy, noninvasive mechanical ventilation, neuromuscular electrical stimulation</td>
</tr>
</tbody>
</table>
Patient selection: patients with ‘systemic consequences’

Extrapolating from the definition of pulmonary rehabilitation, the ideal candidate for rehabilitation is symptomatic, has impaired functional status and participation, is a heavy user of healthcare resources and should suffer from the “systemic consequences of COPD”’

Extrapulmonary consequences of COPD

In the context of pulmonary rehabilitation, the most important “systemic consequence” of COPD is skeletal muscle dysfunction. In clinical practice, this can be assessed by skeletal muscle force or local skeletal muscle endurance, which is often even more affected. Approximately 70% of patients referred to an outpatient COPD clinic suffer from skeletal muscle weakness, and skeletal muscle force is acutely further reduced during acute exacerbations. Reversal of skeletal muscle dysfunction is an important goal of the exercise training component of a lung transplantation or lung volume reduction, a programme of noninvasive ventilatory support or oxygen therapy. Such programmes do not exclude pulmonary rehabilitation. On the contrary, pulmonary rehabilitation is often strongly recommended for these patients. Figure 1 gives an overview of the selection process and the design of the programme for patients with COPD.

Figure 1. Flow chart for referral to pulmonary rehabilitation programmes. It should be emphasised that patients who are not candidates for pulmonary rehabilitation may still benefit from exercise training as an intervention to prevent morbidity.
rehabilitation programme and hence patients suffering from skeletal muscle weakness are particularly good candidates for exercise training. Improving skeletal muscle strength can be done particularly effectively by including resistance training exercises in the exercise training sessions. When successful, muscle force increases and muscle oxidative capacity is enhanced.

More research is needed on pharmacological interventions that may assist pulmonary rehabilitation to restore muscle function more effectively. The short-term benefit of testosterone supplements in selected hypogonadal patients, in combination with resistance training, is an example of how pharmacotherapy and rehabilitation may have synergistic effects.

Impaired exercise tolerance and functional exercise capacity result from the pulmonary and systemic consequences of COPD. In the context of pulmonary rehabilitation, exercise tolerance is best formally assessed before the programme, using an incremental exercise test. This will help to guide the programme's intensity, training modalities and safety. Functional exercise capacity is best assessed using field tests such as the 6-min walking test, for which reference values exist and benchmark improvements for programme quality and clinical and statistical importance have been reported. When a patient's exercise tolerance is not abnormal, the indication for exercise training is questionable.

Another important extrapulmonary consequence of COPD is the derangement of body composition. It is important to pick up and treat both obesity and cachexia in pulmonary rehabilitation programmes. Obese patients may experience less dyspnoea than non-obese patients for a given oxygen consumption due to a favourable mechanical effect of obesity on operating lung volumes. Nevertheless, obesity (body mass index $>30$ kg·m$^{-2}$) limits the functional abilities of patients with limited ventilatory capacity as it increases the ventilatory needs for exercises against gravity. Cachexia, an involuntary loss of fatfree mass, leads inevitably to skeletal muscle weakness. It is a complex problem and its origin is not yet fully understood. The treatment of cachexia is an important aspect of rehabilitation in patients with COPD and requires individualised interventions by nutritional specialists. In order to appropriately assess this aspect, body composition should be assessed using DEXA-scan or bio-electrical impedance measures.

**Symptoms** The most disabling symptom in COPD is clearly shortness of breath. Patients report dyspnoea, particularly during exercise or activity, as a significant burden. Another important symptom is fatigue. Symptoms can be assessed during exercise using Borg symptom scores or during daily activities using specific questionnaires.

**Physical activity** Participation in daily activities is not easily assessed. Several questionnaires have been used, but increasingly activity monitors are preferred. In the future it is likely that benchmark values for physical activity will become available for patients with COPD. As indicated above, patients not meeting guidelines on healthy physical activity (30 min of moderate intense exercise on 5 days of the week) can be considered candidates for pulmonary rehabilitation.

**Severe exacerbations** Patients with COPD who have been hospitalised with an acute exacerbation are particularly good candidates for pulmonary rehabilitation programmes. These patients have lost muscle force and functional exercise tolerance and health-related quality of life acutely as the result of an exacerbation. Physical activity levels are also dramatically low during hospital admission and at least 1 month afterwards. Patients admitted to hospital for COPD are very likely to face new hospital admissions in the subsequent year. The risk of readmission is particularly high in patients who remain inactive after a hospitalisation. In these patients, the rehabilitation programme may need significant modification, with an emphasis on acquiring appropriate
self-management skills to prevent subsequent admissions. Exercise training may need to be adapted to more severe ventilatory and/or skeletal muscle limitation, using resistance training or interval training at high intensities. A recent meta-analysis of a handful of studies showed that patients who suffered from exacerbations are very good candidates for pulmonary rehabilitation. Clearly these patients may impose a higher burden on the rehabilitation team and drop-out is a particularly important problem.

Summary
Pulmonary rehabilitation is an evidence-based intervention for patients with COPD. It is individually tailored to the needs of patients, both in terms of programme structure and its components. The aim of the rehabilitation programme is to reverse the systemic consequences of COPD, minimise healthcare use and lead to a durable change in physical activity and self-management behaviour. Although the short-term effects of rehabilitation are well known, the long-term effects are not always guaranteed. Further research should focus on the strategies to ensure the long-term benefits for patients with COPD. Further knowledge on the processes underlying a durable shift in lifestyle, as well as better understanding of the pathophysiological mechanisms leading to the systemic consequences of COPD and its treatments, may lead to major advances in the future.

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References
When reduced to the simplest terms, all medical research may be defined as the study of relationships (differences or associations) among variables. A variable is any quality, constituent or characteristic of a person, animal, thing or environment that can be measured. A variable is, by definition, something that changes and the values associated with its measurements are usually grouped in a set or “scale”. There are four basic types of scales of which definitions and examples are reported in table 1.

Any measurement performed by using an interval or a ratio scale (continuous scales) can be translated to a category of an ordinal or nominal scale (categorical scales). For example, body temperature above or under a defined point of the Celsius or Fahrenheit scale can be used to identify subjects affected or not by fever, in this way translating from an interval to a nominal scale. Another example is the use of some values of forced expiratory volume in 1 s to identify subjects affected by different levels of severity of chronic obstructive pulmonary disease (COPD) according to a conventional ordinal scale. In general, clinical research is mainly involved with patient-centred outcomes that are variables measured using nominal or ordinal scales, e.g. dichotomous variables grouping diseased or not diseased, or exposed or not exposed subjects, whereas interval or ratio scales are more frequently used in basic research. However, clinicians should be aware of the basic methods used to study the relationships of variables measured using continuous scales, such as lung function, as well as understanding relationships of nominal or ordinal variables. The aim of this chapter is to provide basic knowledge about measures and methods commonly used to define the occurrence of clinical conditions, and to study the relationships among those variables and other variables that characterise the individual and the environment. These methods have been mainly developed for epidemiological research, but they should be the landmark of any clinical reasoning. We hope to improve the skill of the readers of this book by discussing the relevance of information about the burden of diseases as assessed by their distribution, the panel of related risk or protective factors, and the evaluation of the effectiveness of preventive measures and therapies in respiratory medicine.

**Measuring occurrence**

Epidemiology is the study of the distribution and determinants of disease frequency in human populations. The application of this study to determine valid and precise
Information about the causes, preventions and treatments for disease in order to control health problems is of outstanding clinical relevance. One of the main goals of any epidemiological study is to measure the occurrence or frequency of health outcomes, a disease (asthma, COPD or lung cancer, etc.) or the intake of a medication, for instance. Epidemiological studies allow also estimation of the occurrence of exposure (smoking, air pollution or occupational hazards, etc.). Risk, incidence proportion, and incidence and prevalence rates are popular measures of frequency. They all are proportions and rates and their values are meaningless if the denominator is not clearly and sensibly stated. For example, imagine you read in a newspaper, reported from an important scientific journal, that men who are 40 yrs old have a more than 5% risk of developing COPD. Of course, the dimension of this risk changes according to the time interval used in the denominator: the risk is high or low according to short or long time interval. In many similar cases, the undefined denominator is the entire life span of individuals, but the reader should understand that the life span, which varies between individuals and populations, is not the best denominator to produce a broadly valid measure of risk. Unfortunately, reliable figures of risk are not available for many health problems, including many respiratory diseases.

Incidence and risk  Incidence is a measure of the risk of developing some new health condition or outcome within a specified period of time, expressed as a proportion or a rate.

The risk, or incidence proportion (also known as cumulative incidence), is the number of new cases within a specified time period divided by the size of the population initially at risk, and can be expressed by the following formula:

\[
\text{Risk} = \frac{a}{N} \tag{1}
\]

in which “a” is the number of subjects developing a health outcome out of N people followed for a time period. Of course, any particular non-communicable disease has a very low risk over a very short time period and the cumulative risk increases with time. However, the risk may change during the lifetime of individuals. As an example, many chronic respiratory diseases are associated with ageing and their risk is clearly increasing from the first to the last decade of life. However, defining risk is not as simple as it may appear from the above formula. Actually, the value of N may decrease over the time period for two main reasons: the competing risk and the loss to follow-up. First, let us consider a study aiming to define the risk of death from lung cancer in a cohort of smokers (i.e. a group of individuals sharing a particular

<table>
<thead>
<tr>
<th>Nominal scale</th>
<th>Uses names or symbols to assign each measurement to a limited number of categories that cannot be ordered one above the other</th>
<th>Race, gender, geographic area, diseased (yes versus no)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ordinal scale</td>
<td>Assigns each measurement to a limited number of categories not equally spaced and ranked in a graded order</td>
<td>Patient status, cancer stage, COPD stage</td>
</tr>
<tr>
<td>Interval scale</td>
<td>Assigns each measurement to an unlimited number of categories that are equally spaced without an absolute zero point</td>
<td>Body temperature</td>
</tr>
<tr>
<td>Ratio scale</td>
<td>As the interval scale but measurements can be referred to a true zero point</td>
<td>Length, time, mass and all the derived physical units</td>
</tr>
</tbody>
</table>

COPD: chronic obstructive pulmonary disease.
demographic characteristic). It is plausible that, during the follow-up period, many subjects in the cohort will die from many different diseases and not from lung cancer. However, some of these subjects may have developed lung cancer but, before clinical manifestation, die of another disease. If we include those subjects in the denominator, the ratio will give an underestimation of the true risk of death from lung cancer. Secondly, suppose that some subjects included in the cohort were lost during the follow-up period (this is usual in cohort studies in which the individuals are followed up for long periods). Those subjects may not develop the outcome we are interested in, and their inclusion in the denominator will give an underestimation of risk. In conclusion, it is sensible to pay the same attention to measuring both the numerator and the denominator of a ratio.

Competing risk or loss to follow-up can be managed using a different measure of health outcome occurrence: the incidence rate expressed as the number of new cases during some time period, according to the following formula:

\[\text{Incidence rate} = \frac{a}{\text{time}}\]  

(2)

in which “a” is the number of incident cases in the cohort, as in equation 1, and “time” is the total time interval experienced by the subjects followed. “Time” is calculated by summing up the time each subject has been at risk to develop the outcome. For events that may recur during the follow-up period, “time” is calculated by adding the contribution of each subject according to one of the following options: the time experienced up to the first occurrence (in this case the numerator includes only one occurrence per subject) or all the time intervals the subject was at risk of getting any of these occurrences (in this case the numerator includes all the occurrences experienced by each subject). The exacerbation of COPD is a typical example of a recurrent event. Readers should be aware that different results may be produced by the different methods of calculating “time” for this outcome and that, whichever the choice, its rationale should be clearly pre-specified in clinical trials. The interpretation of incidence rate is not as simple as for the incidence proportion. The latter is a probability and is expressed by a number in the range 0–1; however, the incidence rate may assume any value from 0 up to infinity. We may represent the incidence rate as the instantaneous velocity of a vehicle and the incidence proportion as the proportion of a journey covered by the same vehicle in a defined time period. Using this representation, we may suggest that incidence rate and risk for a health outcome may be related by the following formula:

\[\text{Risk} = \text{incidence rate} \times \text{time}\]  

(3)

We must remember that this formula may hold for short time intervals but not for longer intervals, during which the loss to follow-up and the competing risk will complicate the relationship between the two measures of occurrence. It is possible to find a solution to that complication by dividing a long time into shorter time intervals, for which equation 3 may hold, and measuring the risk (or probability) of developing the outcome in each time interval. The overall probability will be equal to the product of probabilities of developing the outcome through all time intervals. This method is what is generally known as a survival analysis, and it can be applied to any outcome with a well-defined time of appearance during the follow-up of a cohort. In respiratory medicine, the results of many trials on chronic disease have been analysed using the survival analysis approach.

**Prevalence**

Prevalence is the proportion of subjects affected by a disease (or symptom or dysfunction) or, more generally, presenting the health outcome in a defined population. Risk and incidence rate are measures of disease onset. Prevalence is a measure of disease status. The value of prevalence is related not only to disease incidence but also to disease duration. The relationship of prevalence to
incidence and duration of disease is expressed by the following formula:

$$P/(1-P) = ID$$

(4)

in which $P$ is prevalence, $I$ is incidence and $D$ is the mean duration of the health outcome. The ratio on the left side of equation 4 is known as the prevalence odds. (In general, the odds of an event happening is the ratio of the probability that it happens to the probability that it does not.) For a low prevalence, equation 4 may be written as:

$$P \approx ID$$

(5)

In this case, the prevalence proportion may be approximately considered as the product of incidence and duration. It is clear that prevalence is a good measure of the burden of a disease and can be quite useful for public health research and decision making. However, prevalence cannot be used for causal inference about risk factors for a disease, except in some rare cases. Factors that may determine a health outcome or may increase its duration can be associated with an increased prevalence. A well-known example of this situation in respiratory medicine is offered by the prevalence studies in asthma published in recent decades. Many factors have been found to be associated with an increased prevalence of asthma, but for most of them the crucial question “Is it a cause or a factor that increases the duration of asthma and the reporting of symptoms?” is still an open debate. Of course, a reliable prevalence proportion or ratio depends on both a satisfactory measurement of population and prevalent cases. Sometimes, the definition of a prevalent case for a specific health outcome may be different among studies, and this may lead to quite different prevalence estimates. Prevalence studies on COPD using different clinical definitions (e.g. diagnosis of chronic bronchitis or emphysema) or, more recently, different cut-off values of spirometric data, are good examples of this situation. Prevalence can be used for causal inference in the case of genetic factors, as genetic background precedes the development of the diseases.

**Measuring the effects: types of study**

The second major goal of epidemiology is to measure the effect of exposure on the health outcome and to estimate the associated risk, i.e. the probability that the health outcome will occur following the exposure. This is obtained through different types of study designs, according to the research question. Epidemiological study design is divided into experimental studies, which include clinical or prevention trials (field trials and community trials), and observational studies, which including cross-sectional studies, cohort studies, case–control studies and panel studies, according to the particular research question (table 2). In experimental studies, the investigator assigns subjects to treatments (vaccination, treatment and prevention, etc.) and evaluates their effectiveness, whereas in observational studies, the researcher observes subjects and waits for the outcome to happen.

Each type of study design represents a different way of harvesting data and information. In experimental studies, the study population is enrolled on the basis of eligibility criteria that reflect the purpose of the prevention or clinical trial, as well as scientific, safety, ethical and practical considerations. Scientific, safety, ethical and practical considerations are also applied in observational studies. An example of a cross-sectional study is given by the prevalence studies on asthma published in the past few decades, such as the International Study of Asthma and Allergies in Childhood (ISAAC). Case–control design was used to find risk factors for lung cancer and for all the diseases with a low occurrence frequency. Cohort studies have provided proof of the cause effect between tobacco smoking and lung cancer. Another type of study is represented by the panel study. A panel study is defined as an investigation that collects information on the same individuals at different points in time. Panels of asthmatics have been involved in the study of the short-term effects of air pollution. A panel study is, therefore, a
Table 2. Main types of epidemiological study

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Description</th>
<th>Type of estimation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Experimental studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical studies</td>
<td>Trial in which subjects are randomly given the treatment or placebo.</td>
<td>Effectiveness of the treatment by comparing the two groups (the treatment and control group, respectively)</td>
</tr>
<tr>
<td>Intervention studies</td>
<td>Inference study in which individuals receive an intervention in order to modify a supposed causal factor for disease incidence</td>
<td>Estimation of the effect of the intervention on the health outcome</td>
</tr>
<tr>
<td><strong>Observational studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional studies</td>
<td>Descriptive study in which health outcome and exposure status are measured simultaneously in a given population It can be thought of as providing a “snapshot” of the frequency and characteristics of health and exposure in a population at a particular point in time</td>
<td>Prevalence of acute or chronic health outcomes in a population Relationship between exposure and health outcome; however, since exposure and disease status are measured at the same point in time, it may not be possible to distinguish whether the exposure preceded or followed the health outcome, and thus cause and effect relationships cannot be established</td>
</tr>
<tr>
<td>Cohort studies</td>
<td>Longitudinal investigation in which the occurrence of a particular health outcome is compared in well-defined groups of people who are alike in most ways but differ by a certain characteristic, such as (but not uniquely) an exposure Cohort studies are both retrospective (backward-looking) or prospective (forward-looking) In a prospective investigation, at the beginning the individuals do not present the health outcome The prospective cohort design can establish whether having been exposed is a cause of the disease development</td>
<td>Incidence of health outcome Relationship between exposure and health outcomes Causal relationship (through the relative risk) in the case of prospective cohorts.</td>
</tr>
<tr>
<td>Case-control studies</td>
<td>Investigation that compares two groups of people: those with the disease or condition under study (cases) and a very similar group of people who do not have the disease or condition (controls) Medical and lifestyle histories including exposures of the people in each group are analysed to learn what factors may be associated with the disease or condition Case–control studies are usually retrospective but they can be prospective</td>
<td>Relationship between the exposure and the health outcome (through the odds ratio)</td>
</tr>
</tbody>
</table>
longitudinal study; it differs from other studies that collect information over time, such as time series and cohort studies, in that it studies the same persons longitudinally. All these studies are based on individual data for both health outcomes and exposure. Ecologic studies also exist in which the unit of analysis is a population rather than an individual. For instance, an ecologic study may look at the association between smoking and lung cancer deaths in different countries. The geographical information system is a very useful new tool that improves the ability of ecologic studies to be able to determine a link between health data and a source of environmental exposure. These ecologic studies allow the development of hypotheses that provide limited information.

**Quantitative assessment of the relationship between exposure and health outcome** There are two ways to quantitatively measure the effect of a factor on the health outcome or the condition of interest: the ratio of the measures of disease frequency according to the presence or absence of the exposure to the factor or the difference between these two measures. The ratio is the measure of the strength of the association between a factor and the health outcome, whereas the difference is an estimate of the health impact of the factor under the hypothesis that the association is of cause–effect type and of the consequences of avoiding or diminishing the exposure to the factor. Specific statistical tests are necessary to confirm the existence of an effect. In the case that both the health outcome and the exposure are dichotomous variables, their relationship can be quantified and its statistical significance can be established by organising a $2 \times 2$ (two columns and two rows) contingency table, as represented in table 3.

A visual presentation of the relationship between a factor and a health outcome when both are a dichotomous variable is provided by figure 1 where, for instance, the highest number (“a”) is observed for individuals that were exposed to the factor and that presented the health outcome and the lowest (“b”) for individuals that were exposed to the factor and that did not present the health outcome. In addition, the number of unexposed that did not present the health outcome (“d”) is more elevated than the number of unexposed presenting the health outcomes (“c”). All these elements support the hypothesis that in this case there is a relationship between the exposure and the health outcome. The statistical significance of the relationship can be determined by applying statistical testing.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Health outcome</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Not exposed</td>
<td>c</td>
<td>d</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>a + c</td>
<td>b + d</td>
</tr>
</tbody>
</table>

"a" is the number of individuals in the studied sample exposed to the potential risk factor who have experienced the health outcome; "b" is the number of individuals exposed who have not experienced the health outcome; "c" is the number of individuals unexposed who have experienced the health outcome; and "d" is the number of individuals unexposed who have not experienced the outcome.

The principal measure of relative risk is the risk ratio or cumulative incidence ratio, which is the ratio of the cumulative incidence in the
exposed group \((a/(a + b))\) to that in the unexposed group \((c/(c + d))\) (table 4).

Thereafter, the relative risk is given by the formula:

\[
RR = \frac{a/(a + b)}{c/(c + d)}
\]

(6)

An RR of 1 means there is no difference in risk between the two groups. An RR > 1 means the health event is more likely to occur in the exposed group than in the unexposed group. An RR < 1 means that the health event is less likely to occur in the unexposed group than in the exposed group. To be statistically significant greater than 1, the RR has to belong to a confidence interval greater than 1. The need to introduce the confidence interval is due to the fact that the studied population is limited and variable due to random errors in selecting it. Similarly, to be statistically lower than 1, the RR has to belong to a confidence interval lower than 1. The method used to calculate the 95% confidence interval for a RR is shown in Appendix 1. The case of a RR > 1 with a 95% confidence interval that does not include 1 has to be interpreted as a positive association between the exposure and the health outcome at the 5% significance level and a RR < 1 with a 95% confidence interval that does not include 1 as a negative association between exposure and outcome at the 5% significance level.

In case–control studies in which the subjects are selected on the basis of disease status and the incidence of the health outcome is not available in the exposed and unexposed groups, the effect of the exposure on the health outcome is measured by the ratio of the odds of exposure among the individuals presenting the outcome to that among the individuals not presenting the outcome. (The odds of the event is the quotient \(p/(1-p)\), in which \(p\) is the probability in favour of the event; this value may be regarded as the relative likelihood that the event will happen.) This ratio is called the odds ratio (OR) and is generally estimated through the ratio between the odds in exposed and nonexposed individuals:

\[
OR = \frac{a/(a + b)/b/(a + b)}{c/(c + d)/d/(c + d)} = \frac{a/b}{c/d} = \frac{ad}{bc}
\]

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\[
OR = \frac{a/(a + b)/b/(a + b)}{c/(c + d)/d/(c + d)} = \frac{a/b}{c/d} = \frac{ad}{bc}
\]
An odds ratio of 1 indicates that the health event under study is equally likely to occur in both groups. An odds ratio $>1$ with a 95% confidence interval that does not include 1 indicates that the event is more likely to occur in the exposed group at the 5% significance level. An odds ratio $<1$ with a 95% confidence interval that does not include 1 indicates that the condition or event is less likely to occur in the exposed group at the 5% significance level. It can be shown that there exists the following mathematical relationship between the odds ratio and the relative risk:

$$RR = \frac{1 - \left(\frac{a}{a+b}\right)}{1 - \left(\frac{c}{c+d}\right)} \times OR \quad (8)$$

As a consequence, when a disease is rare, “a” and “c” are small, and the odds ratio provides a valid estimate of the RR.

**Difference** Several types of differences exist between the measures of health outcome frequency according to the presence or the absence of the exposure to the factor. They include the attributable risk, preventive fraction and the population attributable risk (table 5). It must be noted that these differences have to be computed under the assumption that the factor is causally related to the health outcome, a condition encountered in prospective cohort studies, having assessed causation and disposing of the entities like incidences and relative risks necessary to compute the differences of risks. These differences can be estimated in several ways, the most used are presented in table 5.

**Statistical association between exposure and health outcomes** The existence of a significant relationship between exposure and health outcome can be established independently from the estimation of the associated risk (odds ratio, relative risk, etc.). The main statistical methods that allow the determination of the existence of a significant statistical association between a factor and the health condition of interest are indicated in Appendix 2. They depend on the type of measurement scales used for the variables.

**Causation**

The existence of a statistically significant association between the exposure to a factor and the health outcome does not imply that the factor is a cause of the health outcome. Assessing causation implies several criteria introduced by Austin Bradford Hill (table 6). Of note, none of the proposed criteria can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required *sine qua non*.

**Bias and errors**

Occurrence of health outcomes and exposure, measures of associations and causation are challenged by biases and errors. Random error corresponds to imprecision and bias to inaccuracy. Error is defined as the difference between the true value of a measurement and the recorded value of a measurement. There are many sources of error in collecting clinical data. Error can be described as random or systematic. Random error is also known as variability, random variation, or “noise in the system”. The heterogeneity in the human population leads to relatively large random variation in clinical trials. Random error has no preferred direction, so we expect that averaging over a large number of observations will yield a net effect of zero. The estimate may be imprecise, but not inaccurate. The impact of random error, imprecision, can be minimised with large sample sizes. Systematic error, or bias, refers to deviations that are not due to chance alone. There are several types of biases: recall bias, selection bias, information bias and confounding. Recall bias, selection bias and information bias can be reduced by good protocol. Confounding occurs when a variable is associated with both the exposure and the health outcome that we are studying. When the effect of an exposure is mixed with the effect of another variable (the confounding variable), we may incorrectly conclude that the disease is caused by the exposure. We might then attempt to eliminate
the exposure in the hope that the disease could be prevented. If, however, the association between the exposure and the disease is due to confounding and is not causal, elimination of the exposure will not have any effect on the incidence of the disease. The existence of confounding variables in smoking studies made it difficult to establish a clear causal link between active smoking and lung cancer, unless appropriate methods were used to adjust for the effect of the confounders. An example of confounding variable in the relationship between active smoking and lung cancer is air pollution that

<table>
<thead>
<tr>
<th>Measure</th>
<th>Definition</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attributable risk (AR)</td>
<td>The rate (excess risk) of the outcome in exposed individuals that can be attributed to the exposure. It is given by the difference of cumulative incidences or incidence densities of the disease in the exposed ( l_e ) and the unexposed individuals ( l_0 ).</td>
<td>[ AR = \frac{a}{a + b} - \frac{c}{c + d} ] (9)</td>
</tr>
<tr>
<td>Preventive fraction (PF)</td>
<td>The attributable risk in the case that the exposure is preventive, so that ( a/(a+b) ) is greater than ( c/(c+d) ).</td>
<td>[ PF = \frac{(c/(c + d)) - (a/(a + b))}{(c/(c + d))} ] (10)</td>
</tr>
<tr>
<td>Attributable risk percent or aetiologic fraction (AR%)</td>
<td>The attributable risk divided by the rate of disease among the exposed.</td>
<td>[ AR% = \frac{AR}{a/(a + b)} \times 100 ] (11)</td>
</tr>
<tr>
<td>Population attributable risk (PAR)</td>
<td>The incidence of a disease in a population that is attributable to the exposure. Given by the difference between the rate of the disease in the entire population ( (I_{TOT}) ) and in the unexposed group ( (I_0) ).</td>
<td>[ PAR = \frac{a + c}{a + b + c + d} - \frac{c}{c + d} ] (13)</td>
</tr>
<tr>
<td>Combined PAR</td>
<td>The PAR for a combination of risk factors is the proportion of the disease that can be attributed to any of the risk factors studied.</td>
<td>[ \text{Combined PAR} = 1 - (1 - PAR_1)(1 - PAR_2)(1 - PAR_3) \ldots ] (15)</td>
</tr>
</tbody>
</table>

\( * \): when there is no multiplicative interaction (no departure from multiplicative scale), combined PAR can be manually calculated by this formula.
can cause cancer and is also associated with the exposure of interest, smoking. The effect of a confounder can be taken into account by adjusting for it with an appropriate statistical model, or through a matching of the individuals according to it.

Bias has a net direction and magnitude so that averaging over a large number of observations does not eliminate its effect. In fact, bias can be large enough to invalidate any conclusions. Increasing the sample size will not eliminate all the biases. In epidemiological and clinical studies, bias can be subtle and difficult to detect. A study can be invalidated by the presence of bias. Thus, the design of clinical or epidemiological trials has to focus on removing known biases. Another important element to be introduced in epidemiological investigations is the effect modifier, a factor that modifies the effect of a putative causal factor under study. Effect modification (also known as statistical interaction) occurs when the effect measure depends on the level of another factor. For example, bacillus Calmette-Gue´rin (BCG) immunisation is an effect modifier for the consequences of exposure to the various strains of mycobacteria responsible for tuberculosis (TB) and has to be taken into account when investigating risk factors for TB. Effect modification is detected by varying the selected effect measure for the factor under study across levels of the other factor. In the previous example, modification effect of BCG immunisation could be estimated by computing the odds ratio between tobacco smoking and TB according to the presence or the absence of BCG immunisation. The effect of a modifier can be taken into account

Table 6. Criteria for assessing evidence of causation (HILL, 1965)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1) Strength</strong></td>
<td>The larger the association, the more likely that it is causal. However, a small association does not mean that there is not a causal effect.</td>
</tr>
<tr>
<td><strong>2) Consistency</strong></td>
<td>Consistent findings observed by different persons in different places with different samples strengthen the likelihood of an effect.</td>
</tr>
<tr>
<td><strong>3) Specificity</strong></td>
<td>The more specific an association between a factor and an effect is, the bigger the probability of a causal relationship. Causation is likely in case of a very specific population at a specific site and disease with no other likely explanation.</td>
</tr>
<tr>
<td><strong>4) Temporality</strong></td>
<td>The effect has to occur after the cause.</td>
</tr>
<tr>
<td><strong>5) Biological gradient</strong></td>
<td>Greater exposure should generally lead to greater incidence of the outcome.</td>
</tr>
<tr>
<td><strong>6) Plausibility</strong></td>
<td>A plausible mechanism between cause and effect is helpful although, very often, knowledge of the mechanism is limited.</td>
</tr>
<tr>
<td><strong>7) Coherence</strong></td>
<td>Coherence between epidemiological and laboratory findings increases the likelihood of an effect of the exposure on the health outcome. Of note, sometimes we lack such laboratory evidence.</td>
</tr>
<tr>
<td><strong>8) Experiment</strong></td>
<td>“Occasionally it is possible to appeal to experimental evidence“.</td>
</tr>
<tr>
<td><strong>9) Analogy</strong></td>
<td>The effect of similar factors may be considered.</td>
</tr>
</tbody>
</table>
through a matching of the individual according to different level of the modifier (stratification).

**Sensitivity and specificity**

In the ascertainment of the health outcome, sensitivity and specificity can be used. Sensitivity is the probability that the criterion used to define the case will produce a true positive result when used on a population (as compared to a reference or “gold standard”). Specificity is the probability that the used criterion will produce a true negative result when used on a population (as determined by a reference or “gold standard”). Using a contingency table relating reference and new criterion results (table 7), the following formulae are obtained for sensitivity and specificity, where TP is the number of true positive specimens, FP is the number of false positive specimens, FN is the number of false negative specimens and TN is the number of true negative specimens.

\[
\text{Sensitivity} = \frac{TP}{TP + FN}
\]

\[
\text{Specificity} = \frac{TN}{TN + FP}
\]

Sensitivity and specificity can be applied to identify and validate biomarkers, for instance.

**Conclusion**

Epidemiology provides methods for measuring the occurrence and the causation of respiratory diseases. In assessing occurrence and relationships between exposure and health outcomes, criteria of relevance should include: 1) the representativeness of the studied samples particularly in studies with samples of the general population; and 2) clear definitions of both the health outcome (or dependent variables) and the exposure (or independent variables) to be included in the models.

**References**


<table>
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<tr>
<th>Reference criterion results</th>
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<th>Negative</th>
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</thead>
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<tr>
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<td>TP</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>FN</td>
</tr>
</tbody>
</table>

TP: number of true positive specimens; FP: number of false positive specimens; FN: number of false negative specimens; TN: number of true negative specimens.
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Appendix 1: 95% confidence intervals for the relative risk and the odds ratio

Given the $2 \times 2$ contingency table relating the exposure to the health outcome seen before, a common way to calculate the 95% confidence interval (CI) is as follows.

In the case of the relative risk (approximate estimate):

Upper limit $= \exp(\log RR + 1.96 \times \sqrt{v \log RR})$

Lower limit $= \exp(\log RR - 1.96 \times \sqrt{v \log RR})$

with $\sqrt{v \log RR}$ representing the square root of the natural log of the risk ratio, as defined by $\log RR = \log(a/(a+b))/(c/(c+d))$, which is asymptotically normal with variance $v \log RR = 1/a - 1/(a+b) + 1/c - 1/(c+d)$

When there are zeros, a common convention is to add 1/2 to each cell.

In the case of the odds ratio:

Upper limit $\log OR = \log OR + 1.96 \times \text{se}(\log OR)$

Lower limit $\log OR = \log OR - 1.96 \times \text{se}(\log OR)$

which become:

Upper limit $OR = \exp(\text{upper limit } \log OR)$

Lower limit $OR = \exp(\text{lower limit } \log OR)$

with $\text{se}$ being the standard error of the natural log (OR) = (variance $\log OR$), in which variance of $\log OR = (1/A) + (1/B) + (1/C) + (1/D)$

Appendix 2: Main methods used to assess the relationship between exposure and health outcome

We have presented how to assess the relationship between the health outcome and the exposure in the case both variables are dichotomous. Table 8 introduces the methods that can be used in other cases.

Table 8. Main statistical methods for assessing the relationship between health outcomes and exposures

<table>
<thead>
<tr>
<th>Statistical methods</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation</td>
<td>A single number that describes the degree of relationship between two continuous variables</td>
</tr>
<tr>
<td>Linear regression</td>
<td>Approach to modelling the relationship between a continuous variable $y$ and one or more variables denoted $x$ that may be either continuous or categorical</td>
</tr>
<tr>
<td>Analysis of variance</td>
<td>A statistical test of whether or not the means of several groups are all equal (i.e. are not statistically significantly different)</td>
</tr>
<tr>
<td>Logistic regression model</td>
<td>Approach to predict the probability of occurrence of an event by fitting data to a logit function It makes use of several predictor variables that may be either continuous or categorical Usually used to estimate the odds ratio between the exposure and the health outcome after adjustment for potential confounders</td>
</tr>
</tbody>
</table>
SELF-ASSESSMENT

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The questions presented here are purely for self-assessment purposes and are not CME accredited.

Notes on the questions
1. Always read the entire question and related answers carefully.
2. For Type A questions (in red), only one answer is correct.
   For Type K’ questions (in blue), more than one answer may be correct.

Q1. Which of the following surfactant protein(s) play(s) an active role in innate immunity?
A. SP-A
B. SP-B
C. SP-C
D. SP-D

Q2. With regard to the anatomy of the respiratory system, which of the following statements is incorrect?
A. The right main bronchus is deep and measures about 20 mm in adults
B. The left main bronchus curves laterally and measures about 40 mm in adults
C. The right upper lobe always has three segments and has a tri-partite division at its origin
D. Each segment is a functional independent with its own blood supply and envelope by connective tissue that originates from the parietal pleura
E. The right middle lobe is a branch from the anterior portion of the right main bronchus

Q3. Why is alveolar dead space present at rest in young healthy subjects in the upright posture?
A. Alveoli at the base of the lung are small, and therefore poorly ventilated
B. Pulmonary capillaries at the base of the lung may collapse because of low intravascular pressures
C. Alveoli at the top of the lung are large, and therefore better ventilated
D. Pulmonary capillaries at the top of the lung may collapse because of low intravascular pressures

Q4. A 55-yr-old woman presents with a 2-yr history of paroxysms of dry cough when talking or bending. Which of the following investigations is mandatory at this stage?
A. Spirometry with reversibility
B. Chest radiography
C. Full blood count
D. Bronchoscopy
E. Feno
Q5. Which of the following is the most common nonrespiratory condition associated with chronic cough?
A. Sinusitis
B. Heartburn
C. Irritable bowel syndrome
D. Nasal polyposis
E. Congestive cardiac failure

Q6. Which of the following regarding examination of a patient with superior vena cava obstruction is/are true?
A. Giant 'V' waves are visible in the JVP
B. Peri-orbital oedema may be present
C. Dilated vessels are visible over the lower anterior abdominal wall
D. Signs and symptoms are more noticeable at the end of the day

Q7. Which of the following statement(s) is/are correct with regard to airway resistance measurements by whole-body plethysmography?
A. $P_{box}$ provides an estimate of $P_{alv}$
B. $P_{box}$ provides an estimate of $P_{pl}$
C. Inspiration increases $P_{box}$
D. Expiration decreases $P_{box}$

Q8. For which type of patients is medical thoracoscopy/pleuroscopy mainly indicated?
A. Patients with transudative pleural effusion of indeterminate origin
B. Patients with exudative pleural effusion of indeterminate origin
C. Patients with localised chest wall lesions
D. Patients with diffuse lung disease

Q9. The causes of exercise intolerance are best evaluated by the use of:
A. Walking tests
B. Cardiopulmonary exercise testing
C. Resting lung function measurements
D. All the above

Q10. The increase in functional residual capacity in airflow obstruction is the result of:
A. A decrease in lung elastic recoil
B. Dynamic mechanisms such as an increase in breathing frequency and/or expiratory flow limitation within the tidal breathing range
C. An increase in time constant of the respiratory system exceeding the expiratory time
D. A decrease in inspiratory muscle force

Q11. A 68-yr-old male with nonsmall cell lung cancer presents with increasing breathlessness. His chest radiograph shows complete collapse of the left lung and at bronchoscopy he has a polypoid tumour obstructing the left main bronchus. Which of the following is the most appropriate intervention?
A. Bronchoscopy and endobronchial sampling
B. Bronchoscopy with endobronchial tumour ablation with electrocautery or laser
C. Chemotherapy
D. Bronchoscopy with insertion of endobronchial stent
E. Treatment with antibiotics and steroids

Q12. Which of the following statement(s) regarding long-term oxygen therapy (LTOT) is/are true?
A. LTOT should be prescribed in all COPD patients with $P_{a,O_2}$ in range 7.3-8.0 kPa
B. LTOT should be prescribed in a COPD patient with $P_{a,O_2}$ 8.0 kPa and secondary polycythaemia
C. LTOT should be given during the daytime only
D. LTOT should be accompanied by ambulatory $O_2$ in active users
Q13. Which of the following statement(s) regarding home noninvasive ventilation is/are true?
A. It can be combined with cough assist devices in patients with neuromuscular disease and reduced cough efficacy
B. It increases survival in patients with COPD
C. It improves quality of life in COPD patients
D. It may reduce readmission in COPD patients with frequent hypercapnic exacerbations (revolving door admissions)

Q14. In which of the following patient(s) is/are the risk(s) of transition from latent tuberculosis infection to active tuberculosis increased?
A. Patients with end-stage renal disease
B. Patients after lung transplantation
C. Patients after cornea transplantation
D. Patients with Epstein–Barr virus infection

Q15. Which of the following diseases must be excluded before prolonged use of macrolides is considered?
A. Tuberculosis
B. Nontuberculous mycobacteria
C. Pseudomonas aeruginosa
D. Aspergillus fumigatus
E. HIV

Q16. A 60-yr-old farmer with moderate asbestos exposure 30 yrs ago presents with diffuse pulmonary fibrosis, predominantly basal, inspiratory crackles on chest examination, no plaques or pleural thickening on chest computed tomography and slowly deteriorating lung function. What is the likely diagnosis?
A. Asbestosis
B. Sarcoidosis
C. Idiopathic pulmonary fibrosis
D. Hypersensitivity pneumonitis
E. Nonspecific interstitial pneumonia

Q17. Which of the following statement(s) about occupational asthma (OA) is/are true?
A. Inhaled corticosteroids and bronchodilators are the preferred medications in symptomatic patients with OA
B. OA may occur in subjects without atopy
C. The diagnosis of OA cannot be excluded in a patient with pre-existing asthma
D. Twice daily peak flow measurements are the most commonly used diagnostic test in OA

Q18. Which are the most investigated indoor pollution sources?
A. Fossil fuel
B. Biomass fuel, environmental tobacco smoke, mould/dampness
C. Environmental tobacco smoke
D. Furniture

Q19. Which is the most frequent aetiology of pleural effusions?
A. Infectious
B. Malignant
C. Immunological
D. Cardiac
E. Idiopathic

Q20. Which is the most common respiratory complication associated with neuromuscular disorders?
A. Obstructive sleep apnoea
B. Pulmonary embolism
C. Tracheal stenosis
D. Acute respiratory distress syndrome
E. Bronchial asthma
Q21. A 72-yr-old Caucasian male presents with chronic cough. He is a retired teacher, enjoys gardening, quit smoking 10 years ago, takes medications for hypertension and gastroesophageal reflux, and drinks 1–2 glasses of wine daily with dinner. Chest radiography shows a mass in the right upper lobe; a thorax computed tomography scan confirms the presence of a mass and shows that the subcarinal lymph nodes are enlarged. Biopsies obtained bronchoscopically show nonsmall cell lung cancer adenocarcinoma. Staging investigations reveal metastatic lesions in the liver. Which initial therapy would be most appropriate?

A. Neoadjuvant chemotherapy followed by lobectomy
B. Targeted therapy with erlotinib
C. Cisplatin-etoposide with concurrent radiation therapy
D. Cisplatin-pemetrexed chemotherapy

Q22. Metastatic pleural effusions are most frequently observed in:

A. Prostate cancer
B. Pancreatic cancer
C. Breast cancer
D. Kidney cancer
E. Lymphomas

Q23. Which of the following symptoms does not necessarily impede a radical treatment approach?

A. Liver metastasis
B. Bone metastasis
C. Vena cava superior syndrome
D. Brain metastasis
E. Axillary lymphadenopathy

Q24. Which of the following treatment options will most likely improve the left ventricular ejection fraction in a patient with congestive heart failure and Cheyne–Stokes respiration?

A. Nocturnal oxygen
B. Nocturnal CPAP
C. Acetazolamide
D. Nocturnal CO₂ inhalation
E. Theophylline

Q25. What has positively changed the natural history of cytomegalovirus infection post-bone-marrow transplant?

A. Immunosuppressive therapy
B. CMV prophylaxis or pre-emptive therapy
C. Extracorporeal photopheresis
D. Immunoglobulins
E. Antibiotic therapy

Answers

025. B
024. A
023. C
022. C
021. D
020. A
019. D
018. B
017. A/B/C
016. C
015. B
014. A
013. B/D
012. C
011. D
010. A/B/C
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The European Respiratory Society (ERS) Handbook of Respiratory Medicine is a concise, compact and easy-to-read guide to each of the key areas in respiratory medicine. Its 17 chapters, written by clinicians and researchers at the forefront of the field, explain the structure and function of the respiratory system, its disorders and how to treat them.

The Handbook is a must-have for anyone who intends to remain up to date in the field, and to have within arm’s reach a reference that covers everything from the basics to the latest developments in respiratory medicine.

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