The European Respiratory Society (ERS) Handbook of Respiratory Medicine, now in its second edition, is a concise, compact and easy-to-read guide to each of the key areas in respiratory medicine. Its 18 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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ERS handbook

Respiratory Medicine

2nd Edition

Editors
Paolo Palange
and Anita K. Simonds
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Eight years ago, the ERS 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 postgraduate training. Based on these findings, the ERS 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. The *Handbook*, together with a vast array of educational material, such as lectures, articles published in *Breathe* and the *European Respiratory Monograph*, and other lectures and courses, all available on the ERS School website, together comprise an unrivalled educational resource for anyone preparing for the European Examination in Adult Respiratory Medicine.

The first edition of the ERS *Handbook of Respiratory Medicine* was published in 2010 with the aim of providing state-of-the-art summaries in all areas of respiratory medicine. This second edition of the *Handbook* has been extensively peer review and revisited, and includes new sections on

- cytology of the lung
- HRCT of the chest
- long-term ventilation
- opportunistic infections in the immunocompromised host
- the pharmacology of asthma and COPD
- HRCT in the diagnosis of interstitial lung disease
- pathology and molecular biology of lung cancer
- palliative care

The *Handbook* is a comprehensive, easily accessible source of the essentials of respiratory medicine for senior medical staff requiring revalidation, and nursing and allied healthcare professionals at all levels who wish to keep their knowledge up to date. All readers can be assured that as they set sail to manage patients across the spectrum of respiratory disorders, they are armed with the best information, access to multiple-choice questions to check their knowledge, and a source guide for more in-depth study.

We are particularly indebted to the ERS School Committee, the ERS Publications Office who curated the entire contents of the *Handbook*, and all the contributors.

**Paolo Palange, Anita K. Simonds**

**Chief Editors**
Get more from this Handbook

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

To log in, simply visit [www.ersnet.org/handbook](http://www.ersnet.org/handbook) and enter the unique code printed on inside of the front cover of the book. Once logged in, you’ll be able to download the entire book in PDF or EPUB format, to read on your computer or mobile device.

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

Also available from the ERS

**ERS Handbook: Self-Assessment in Respiratory Medicine**
*Edited by Konrad E. Bloch, Paolo Palange and Anita K. Simonds*

*Self-Assessment in Respiratory Medicine* is an invaluable tool for any practitioner of adult respiratory medicine. The 111 multiple-choice questions cover the full breadth of the specialty, using clinical vignettes that test not only readers’ knowledge but their ability to apply it in daily practice.

To buy a copy of this *Handbook* for €50 (€40 for ERS members) plus postage, please contact [sales@ersj.org.uk](mailto:sales@ersj.org.uk)
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<td>(C)HF</td>
<td>(Congestive) heart failure</td>
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<td>AHI</td>
<td>Apnoea–hypopnoea index</td>
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<tr>
<td>AIDS</td>
<td>Acquired immunodeficiency syndrome</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CF</td>
<td>Cystic fibrosis</td>
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<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
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<td>CPAP</td>
<td>Continuous positive airway pressure</td>
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<td>CT</td>
<td>Computed tomography</td>
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<td>ECG</td>
<td>Electrocardiogram</td>
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<td>ENT</td>
<td>Ear, nose and throat</td>
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<tr>
<td>FEV₁</td>
<td>Forced expiratory volume in 1 s</td>
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<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
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<tr>
<td>Hb</td>
<td>Haemoglobin</td>
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<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<td>HRCT</td>
<td>High-resolution computed tomography</td>
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<td>KCO</td>
<td>Transfer coefficient of the lung for carbon monoxide</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NIV</td>
<td>Noninvasive ventilation</td>
</tr>
<tr>
<td>OSA(S)</td>
<td>Obstructive sleep apnoea (syndrome)</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>Arterial carbon dioxide tension</td>
</tr>
<tr>
<td>PaO₂</td>
<td>Arterial oxygen tension</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>Pa₄CO₂</td>
<td>Transcutaneous carbon dioxide tension</td>
</tr>
<tr>
<td>SaO₂</td>
<td>Arterial oxygen saturation</td>
</tr>
<tr>
<td>SpO₂</td>
<td>Arterial oxygen saturation measured by pulse oximetry</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TLC</td>
<td>Total lung capacity</td>
</tr>
<tr>
<td>TlCO</td>
<td>Transfer factor for the lung for carbon monoxide</td>
</tr>
<tr>
<td>V'E</td>
<td>Minute ventilation</td>
</tr>
</tbody>
</table>
Genetics addresses the composition, function and transmission of inherited entities (genes) summing up to the genome of an individual. 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. There are also genes not coding for proteins but for catalytic RNAs (tRNA, rRNA) or regulatory RNAs (microRNA (miRNA)). The genotype is the specific composition of genes of an individual that influences its phenotype. However, in contrast to the genotype, which is simply inherited, a phenotype is shaped by epigenetic phenomena, environment, climate, nutrition and other external factors.

Genes are transcribed to RNA and subsequently translated into proteins. Genes do not code 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 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 perform its task.

Diseases caused by the alteration of a single gene with relevance for pulmonologists are CF and α1-proteinase inhibitor (PI) deficiency (formerly α1-antitrypsin (AT) deficiency). 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. This is the case in asthma, sarcoidosis, pulmonary fibrosis and primary pulmonary hypertension. Table 1 shows examples of mutated genes involved in respiratory disorders.

There are also numbers of gene variations that are regarded as neutral variations 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 does not cause 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 these cases the individuals grow up normally and reach adolescence; however, after the BCG (Bacillus Calmette–Gue´rin) vaccination or when they encounter environmental mycobacteria (e.g. *Mycobacterium fortuitum*, *Mycobacterium chelonae*), these individuals develop severe and sometimes fatal disease.

Epigenetics and regulatory genes

The genome is not a static blueprint of the phenotype as it was regarded in the past. Several 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, two of each histone together with the bound DNA build 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 additional histone proteins in turn leading to a compacted nucleosome and subsequently inhibiting gene transcription.

The miRNAs are short, highly conserved, noncoding RNAs that bind to 3′-untranslated regions (3′-UTR) of mRNAs.

### Table 1. Examples of mutated genes involved in respiratory disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Gene product</th>
<th>Mutation(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF</td>
<td>CFTR</td>
<td>Cystic fibrosis transmembrane conductance regulator</td>
<td>&gt;1500</td>
</tr>
<tr>
<td>Emphysema</td>
<td>SERPINA1</td>
<td>Serpin peptidase inhibitor, clade A (α-1 antiproteinase, antitrypsin)</td>
<td>SNP G-342A &gt;90% of cases</td>
</tr>
<tr>
<td>Chronic beryllium disease</td>
<td>HLA-DPB1</td>
<td>Histocompatibility antigen, DP(W2) β-chain</td>
<td>Glutamine at position 69</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>BTNL2</td>
<td>Butyrophilin-like 2</td>
<td>rs2076530 SNP G-11084A causing premature stop codon</td>
</tr>
<tr>
<td></td>
<td>ANXA11</td>
<td>Annexin A11</td>
<td>rs1049550 SNP C→T, arginine to cysteine</td>
</tr>
<tr>
<td></td>
<td>TNF</td>
<td>TNF</td>
<td>SNP G-308A</td>
</tr>
<tr>
<td></td>
<td>TLR</td>
<td>TLR</td>
<td>SNPs in various TLR genes influence disease course</td>
</tr>
<tr>
<td>Cancer</td>
<td>c-Myc</td>
<td>Promoter translocation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ras</td>
<td>Family of GTPases</td>
<td>Various SNPs induce permanent activation</td>
</tr>
<tr>
<td></td>
<td>EGFR</td>
<td>Epidermal growth factor receptor</td>
<td>Deletions, SNPs leading to over expression and permanent activation</td>
</tr>
</tbody>
</table>

SNP: single-nucleotide polymorphism.
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 (NF)-κB leads to the transcription of a variety of immune mediator genes. Simultaneous activation of miRNAs suppresses certain mediators, giving rise to a specific pattern of mediator activation. miRNAs are of strong importance in cancer and pulmonary fibrosis; however, one might expect that transcriptional regulation by miRNAs is also important in other diseases. The pattern of miRNAs expressed in several diseases and tumours is highly specific and might be used as a biomarker.

Genetics in CF

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 inheritance follows an autosomal recessive heredity, i.e. the disease becomes manifest only when CFTR genes on both chromosomes are mutated, albeit 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. It is most common in Caucasians (1:2000 being highest in Scotland and the Faroe Islands (1:500)) but lower in descendants from Africa (1:15,000); and lowest in Asians (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 of proteinase inhibitors

The PI α1-antitrypsin 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 and is, therefore, renamed α1-PI. The lack of α1-PI leads to an incomplete or absent containment of proteinases resulting in severe organ damage (e.g. emphysema), mostly in the lung.

There are several known mutations in the α1-PI gene, such as base substitutions, in-frame deletions, frame-shift mutations and exon deletions. More than 90% of 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 that inhibits post-translational modifications and secretion. Patients bearing the Z allele demonstrate <15% of the normal α1-PI level in serum, which additionally seems to be non-functional.

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. Familial clusters are seen in sarcoidosis and IPF. 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 Swedish population encounters the highest prevalence in Europe (55–64 per 100,000). In contrast, in the Finnish population living at the same latitude, the prevalence is just half of the Swedish (28 per 100,000). This difference points to a strong genetic background in the pathogenesis of sarcoidosis.

An inherited pre-disposition for sarcoidosis is also 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 high interest are the HLA class II antigens. Although some of these linkages are largely dependent on the population investigated, several associations 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 different methods, a variety of candidate genes were identified and found to be associated with the susceptibility or the natural course of the disease. This included genes for co-stimulatory molecules (e.g. butyrophilin-like 2 (BTNL2)), genes involved in cell cycle (e.g. annexin A11 (ANXA11)), and genes involved in immune regulation (e.g. CD40), mediators (e.g. tumour necrosis factor (TNF)-α (TNFA2) or Toll-like receptors (TLR)). These genes may alter the reactivity of the respective cells to external stimuli which subsequently initiate an inadequate immune response.

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 as a marker. 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 frequently linked with two mutations in the surfactant protein C (SP-C) gene resulting either in a splice deletion of exon 4 in a SP-C variant that cannot be processed and accumulates as pro-SP-C in the cell causing cell stress and apoptosis. The pathological pattern of fibrosis is in both forms consistent with non-specific interstitial pneumonitis in younger patients and usual interstitial pneumonia in the elderly. A recent report points to a mutation in the telomerase reverse transcriptase (TERT) causing short ends in the telomeres and bone marrow hypocellularity. But also mutations in genes regulating cell cycle like TP53 and CDKN1A are found to influence survival times in IPF.

**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 (highest at the South Atlantic island Tristan da Cunha affecting >20% of the population). 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. Again, new genes involved in asthma susceptibility might be expected.

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 germ line: so-called somatic mutations. As these mutations accumulate over years, a growing organism resembles merely 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 over-expression of c-Myc. The regulatory protein c-Myc binds to enhancer boxes in regulatory gene sequences inducing enhanced gene expression. In addition, it recruits histone acetylases leading to histone hyperacetylation. Approximately 15% of the human genes are affected by c-Myc regulation. Over-expression 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, histone modifications or altered miRNA patterns, 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.

Further reading


Understanding lung disease at the cellular and molecular level is crucial to developing new approaches for the diagnosis, treatment and prevention of lung disease. Although our knowledge at the molecular level is steadily increasing, we still have a limited understanding of the molecular events underlying lung diseases, which is reflected by very few therapies targeting 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, modification, and processing of proteins and nucleic acids
- cellular and developmental biology
- genetics, structure and growth cycles of viruses, bacteria and bacteriophages

The following paragraphs focus on selected (signalling) molecules and structures, all of which are altered in various lung disease and are important topics in the field of molecular biological research in respiratory medicine.

### 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 and interstitial cells, and the vascular system has a major impact on lung architecture and function, particularly gas exchange. All lung cell types interact and signal through the ECM via adhesion molecules, surface receptors or growth factors (Suki et al., 2008).

The lung fibroblast is the main producer of pulmonary ECM, which consists of:

- collagens
- elastins
- proteoglycans

The interstitium of the lung parenchyma contains mostly collagen types 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 a 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-dependent enzymes; and 3) inhibition of MMP activity by specific endogenous antiproteases, the tissue inhibitors of metalloproteinases (TIMPs) (Mocchegiani et al., 2011).

### 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 and impaired expression of TIMPs are related to the pathogenesis of many chronic lung diseases, such as MMP-12 in emphysema or MMP-7 in lung fibrosis (Churg et al., 2011).

The impact of the altered matrix or cell–matrix interaction within the diseased lung represents an active area of investigation. While most research in the past focused on the effect of signalling molecules and pathways on matrix deposition and turnover, recent studies aimed to understand how the lung matrix influences cell differentiation and behaviour, and, subsequently, signal transduction (Fernandez et al., 2012).

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. These cells produce and secrete components of the ECM and growth factors thereof, which facilitates restoration of the interstitium and, subsequently, functional alveolar structure. ATII cells serve as progenitor cells for ATI cells, which largely cover the alveolus and are the primary cell responsible for gas exchange. ATII cells are cuboidal secretory cells mainly responsible for surfactant secretion (Herzog et al., 2008). Pulmonary surfactant is a complex mixture of phospholipids and proteins, with surfactant protein (SP)-A, SP-B and SP-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 stretch 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 low surface tension and prevents lung collapse. SP-B and SP-C are the main protein components. Following secretion, both surfactant proteins and lipids are recycled by the respiratory epithelium (Marraro et al., 2008).

Surfactant abnormalities have been described in many infant and adult lung diseases, such as respiratory distress syndrome, bronchiolitis, COPD and interstitial lung disease.

Defense and clearance mechanisms

SP-A and SP-D are involved in innate host defence of the lung. In addition, antimicrobial peptides, such as defensins, cathelicidins and or lactoferrin, are present in the airway and prevent infection. Moreover, cellular defense mechanisms include macrophage- and neutrophil-mediated cytokine release, such as interleukin (IL)-1, IL-8, tumour necrosis factor (TNF)-α and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Suzuki et al., 2008).

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 mucus, which is produced by secretory cells, by forcing the mucus toward the larynx for elimination. Impaired mucociliary clearance is the main feature of CF.

The transforming growth factor-β pathway

The transforming growth factor (TGF)-β superfamily is critically involved in embryonic development, organogenesis and tissue homeostasis (Bartram et al., 2004). TGF-β superfamily members act as multifunctional regulators of cell growth and differentiation. The TGF-β superfamily includes >40 members, including the various isoforms of TGF-β itself. Three different 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-β₁ is secreted in covalent association with the latent TGF-β₁ binding protein, thus providing a reservoir in the ECM.
For active signalling, TGF-β needs to be cleaved from the complex by a mechanism that involves various proteases, such as plasmin or MMPs, as well as interaction with integrins. Active TGF-β ligands bind to the type II TGF-β receptor, which subsequently forms heterotetrameric complexes with the type I TGF-β receptor. Subsequent transphosphorylation of the type I receptor results in recruitment of specific intracellular signal 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. These receptor-regulated Smads (Smad2 and 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 (fig. 1).

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.
Figure 2. The Wnt/β-catenin pathway. The pathway is shown in the a) ‘off’ and b) ‘on’ states, and in lung c) cancer and d) fibrosis. DSH: Dishevelled; GSK: glycogen synthase kinase; APC: adenomatous polyposis coli protein; P: phosphoryl group; CK: casein kinase; TCF: T-cell-specific transcription factor; LEF: lymphoid enhancer-binding factor family protein; EMT: epithelial–mesenchymal transition. Reproduced and modified from Königshoff M et al. (2010) with permission from the publisher.
Furthermore, there is emerging interest in the role of TGF-β in the pathogenesis of COPD, particularly since genetic studies have demonstrated an association of gene polymorphisms of the TGF-β superfamily with COPD. In addition, increased expression of TGF-β in COPD was reported, suggesting an impact of TGF-β signalling in the development and progression of COPD (Königshoff et al., 2009).

The Wnt/β-catenin pathway

The Wnt/β-catenin signalling pathway was originally identified as a developmental signalling pathway. It constitutes a large family of secreted glycoproteins that signal via a variety of membrane-bound receptors. Wnt ligands bind to the membrane receptors Frizzled (FZD) and low-density lipoprotein receptor-related protein (LRP)5/6, resulting in the phosphorylation of LRP6, which subsequently leads to the recruitment of cytosolic proteins that are part of the so-called β-catenin destruction complex. Subsequently, the central mediator β-catenin is dephosphorylated and its degradation attenuated. Accumulated β-catenin then undergoes nuclear translocation and regulates target gene expression via interaction with members of the T-cell-specific transcription factor/lymphoid enhancer-binding factor family (fig. 2) (Moon et al., 2004).

Impaired Wnt/β-catenin signalling has been implicated in a variety of chronic lung diseases, such as lung cancer, fibrosis and COPD/emphysema. In particular, active Wnt/β-catenin signalling has been linked to lung epithelial cell repair and survival mechanisms.

Importantly, Wnt/β-catenin signalling is tightly regulated during lung homeostasis. Several Wnt inhibitors, such as Dickkopf and secreted FZD-related proteins, are differentially expressed during chronic lung disease, thereby impacting proper Wnt/β-catenin signalling (Königshoff et al., 2009).

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 for translocation to the nucleus, bind specific DNA sequences present in the promoters of target genes and initiate transcription. IκBα kinase (IKK) is responsible for the initial phosphorylation. Several different kinases have been shown to activate IKK, such as Akt, MEKK1 and protein kinase C. In the nucleus, NF-κB induces the expression of a variety of genes, particularly mediators of inflammation, cell proliferation, metastasis and angiogenesis (Sun et al., 2008).

Many potentially noxious substances related to lung disease, such as cigarette smoke, radiation, chemotherapeutic agents, cytokines and growth factors, activate NF-κB, and increased NF-κB signalling has been associated with COPD and asthma (Edwards et al., 2009).

Further reading

Anatomy of the respiratory system

Pallav L. Shah

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: costovertebral, 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 costodiaphragmatic recesses are a thin area between the costal and diaphragmatic pleura. The costomediastinal 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 costovertebral 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 peribronchial 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.

Key points

- The anatomy of the thorax can be divided broadly into the pleura, lungs, mediastinum, diaphragm and heart.
- The lungs can be further subdivided into lobes, segments, trachea and bronchi.
- The mediastinal space contains structures including the thymus gland, thoracic lymph nodes, thoracic duct, vagus nerve and autonomic nerve plexus.
- The thoracic structures include the vital organs for respiration and circulation. This section will focus on the pleura, lungs, mediastinum and diaphragm. The anatomy of the heart is not discussed.

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 \( \sim 2.5 \) 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 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 (fig. 1a). The left lung is composed of an upper and lower lobe (fig. 1b). In the right lung there are two fissures. The oblique fissure separates the lower lobe from the upper and middle lobes. 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.

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Figure 1. Medial aspect of a) right and b) left lung. © P.L. Shah.
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 three to six pulmonary acini forming a hexagonal pattern with a central artery, lymphatic and peripheral veins.

**Trachea and bronchi**

The trachea (figure 2) is 100 mm long and made up of anterolateral cartilage rings with a fibromuscular 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 anteromedial, 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 pre-tracheal and para-tracheal 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 tracheobronchial 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 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 pre-tracheal, para-tracheal, subcarinal and para-oesophageal 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 midline 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 brachiocephalic 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 laterally to the super 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 anteromedially to the vagus nerve above the aortic arch and then anteriorly to the left hilum. It then runs along the pericardium (covering the left ventricle) before supplying the diaphragm.

**Diaphragm**

The diaphragm is a musculofibrous sheet that separates the thorax and abdomen. It has an important role in the mechanism of breathing and coughing. It has a convex upper surface and is circumferentially attached to the lower aspect of the thorax by 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 the phrenic arteries. The venous drainage is from the phrenic veins, which drain into the inferior vena cava. The diaphragm is supplied by the phrenic nerve, which primarily originates from the C4, C5 and C6 cervical nerve root (the course of which is described previously).

**Development**

The development of the respiratory system occurs at ~26 days of gestation with proliferation of a diverticulum that originates from the foregut. The laryngotracheal 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 are then formed. Alveolar development occurs from 28 weeks gestation and continues during early childhood.

**Further reading**

The appropriateness of the ventilatory ($V^e$) response to challenges, such as hypoxia or altered metabolic rate, depends on $V^e$ and on whether the pulmonary gas-exchange and acid–base requirements are achieved: i.e. regulation of $P_{aCO_2}$, arterial pH (pHa) and $P_{aO_2}$ within the relatively narrow range for optimal functioning. This involves a cascade of mechanisms: airflow and volume generation; pulmonary oxygen uptake ($V'^O_2$) and carbon dioxide output ($V'^CO_2$); and $V^e$ 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 $V^e$ demands of the task and, in turn, the costs of meeting these demands in terms of respiratory-muscle work, perfusion and oxygen consumption.

**Key points**

- The mechanical work of breathing comprises elastic (volume-related) and resistive (flow-related) components.
- With expiratory efforts causing $P_{ip}$ to become positive, an EPP is created that results in expiratory flow limitation.
- Arterial hypoxaemia can result from alveolar hypoventilation, diffusion limitation, $V^e$-Q’ mismatch and/or right-to-left shunt. Only the latter three mechanisms also lead to a widened $PA_{aO_2}$, (i.e. inefficient pulmonary oxygen exchange).

**Ventilatory requirements**

Alveolar, and hence arterial, carbon dioxide and oxygen tensions ($P_{aco_2}$, $P_{aO_2}$, $P_{co_2}$ and $P_{ao_2}$, respectively) can only be regulated if alveolar ventilation ($V'A$) increases in an appropriate proportion to $V'^CO_2$ and $V'^O_2$, respectively. For carbon dioxide exchange (Fick’s principle):

$$V'A = 863 \cdot V'^CO_2 / P_{aco_2} \quad (1)$$

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 gas tension.

Similarly, for oxygen:

$$V'A = 863 \cdot V'^O_2 / (P_{iO_2} - P_{ao_2}) \quad (2)$$

where $P_{iO_2}$ is inspiratory oxygen tension ($P_{O_2}$) and $*$ is a relatively small correction factor ($F_{an}/F_{in}$, where $F_{an}$ and $F_{in}$, are alveolar and inspiratory nitrogen fractions, respectively) that takes account of inspired ventilation normally being slightly greater than the expired. This reflects the body’s metabolic processes releasing less carbon dioxide relative to the oxygen used for a normal western diet, with a respiratory quotient ($RQ = $ metabolic carbon dioxide production/metabolic oxygen consumption) of ~0.8.

As $V'A$ is common to equations 1 and 2, then:

$$\frac{(863 \cdot V'^CO_2) / P_{aco_2}}{(863 \cdot V'^O_2) / (P_{iO_2} - P_{ao_2})} \quad (3)$$

If $V'^CO_2$ and $V'^O_2$ are equal (i.e. respiratory exchange ratio ($R$) =1), both $P_{aco_2}$ and $P_{ao_2}$...
can be regulated. However, both cannot be regulated if \( V'\text{CO}_2 \) and \( V'\text{O}_2 \) differ, e.g. when:

1) RQ changes as a result of dietary- or activity-related alterations in metabolic substrate utilisation; or

2) there are transient variations in body gas stores (particularly the carbon dioxide stores) as metabolic rate changes.

Under such conditions, \( V'A \) changes in closer proportion to \( V'\text{CO}_2 \) than to \( V'\text{O}_2 \), with \( \text{PACO}_2 \) consequently being more closely regulated than \( \text{PAO}_2 \); as these associated \( \text{PO}_2 \) changes normally occur over the relatively flat region of the oxygen dissociation curve, arterial oxygen content (\( \text{CaO}_2 \)) is not greatly affected. However, the regulatory outcome is more complex if, for example:

1) significant arterial hypoxaemia develops, causing \( V'A \) to increase out of proportion to \( V'\text{CO}_2 \) (hyperventilation) so as to constrain the fall in \( \text{PAO}_2 \); or

2) with metabolic acid–base disturbances that evoke compensatory respiratory responses to ameliorate the \( \text{pHa} \) change.

Importantly, it is the total \( V'E \), rather than \( V'A \), that is controlled to effect these regulatory functions. Substituting \( V'E'\cdot(1-\text{Vd}/\text{VT}) \) for \( V'A \) in equation 1 (where \( \text{Vd} \) is the physiological dead space volume, \( \text{VT} \) is the tidal volume and \( \text{Vd}/\text{VT} \) is the physiological dead space fraction of the breath), and assuming \( \text{PACO}_2 \) to equal to \( \text{PAO}_2 \), yields:

\[
V'E = (863 \cdot V'\text{CO}_2)/(\text{PACO}_2 \cdot (1-\text{Vd}/\text{VT}))
\]

Thus, the \( V'E \) requirement is determined by \( \text{PACO}_2 \), \( V'\text{CO}_2 \) and \( \text{Vd}/\text{VT} \). Furthermore, the influence of metabolic acid–base disturbances can be accommodated by substituting \( \text{PACO}_2 \) from equation 4 into the Henderson–Hasselbalch equation, i.e.

\[
\text{pH}_a = \text{pK}^+ + \log([\text{HCO}_3^-]/\alpha \cdot \text{PACO}_2)
\]

Thus, \( \log[\text{HCO}_3^-]/25.6 \) represents the set point, \( V'\text{E}/V'\text{CO}_2 \), the ‘control’ term and 1-\( \text{Vd}/\text{VT} \) represents gas exchange efficiency.

**Respiratory mechanics**

A particular \( V'E \) requirement can, in theory, be accomplished with an infinite combination of \( \text{VT} \) and respiratory frequency (\( f \)). The \( \text{VT} \)-\( f \) combination, in turn, influences the inspiratory-muscle pressure (\( P_{\text{mus}} \)) needed to effect inspiration:

\[
P_{\text{mus}} = E \cdot V + R \cdot V' + I \cdot V''
\]

where \( V \), \( V' \) and \( V'' \) are volume, air (and pulmonary tissue) flow and acceleration, and \( E \), \( R \) and \( I \) are the pulmonary elastance, resistance and inertance, respectively. Normally, the inertance-related term makes an insignificant 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 having an abnormally increased thoracic mass).

Thus, \( P_{\text{mus}} \) has static (volume-related, with no associated air flow) and resistive (flow-related) components.

The static component of \( P_{\text{mus}} \) equals the increment in transpulmonary pressure (\( \text{Pp} \)) required to effect the required degree of lung distension under static conditions:

\[
\text{Pp} = \text{Pav}-\text{PIP} = V/\text{Cl}
\]

where \( \text{Pav} \) and \( \text{Pp} \) are alveolar and intrapleural pressures, respectively, and \( \text{Cl} \) is lung compliance. \( \text{Cl} \) is determined by the elastic properties of the lung parenchyma and the surface-active forces operating at the alveolar air–liquid interface, which are constrained by the influence of surfactant.

The normal static \( V-\text{Pp} \) relationship (line 2 in fig. 1) shows \( \text{Cl} \) to be largely independent of \( V \) over the tidal range but to decline as TLC is approached. When \( \text{Cl} \) is decreased (e.g. restrictive lung disease), a greater than normal increase in \( \text{Pp} \) is required to effect a given lung inflation (line 1 in fig. 1); an increased \( \text{Cl} \) (e.g. emphysema) requires a smaller \( \text{Pp} \) increment (line 3 in fig. 1). Also, as functional residual capacity (FRC) and the associated \( \text{PIP} \) are determined by the
Turbulent flow develops when the Reynolds number (Re) exceeds a value of ~2000. As $Re = \frac{\nu \cdot D}{\mu}$, where $\nu$ is the linear velocity and $\mu$ is gas density, turbulent flow will predominate when $\nu$ is high, at branch points or across constricted regions. Hence, reducing $\mu$, for example 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 $C_L$ 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), where $\Delta$ represents a change, 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 (right-hand panels of fig. 2a) 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 that, when related to their oxygen consumption ($Q'O_2$), allows considerations of overall respiratory muscle efficiency. It is only at very high levels of $V'E$ (e.g. at peak exercise in very fit endurance athletes) or when respiratory impedance is abnormally high (as in pulmonary disease) that $W$, $W'$ and $Q'O_2$ can become significant, predisposing 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 \( P_{alv} \) (left-hand panels of fig. 2a):

\[
P_{tp}=P_{REC}=P_{alv}-P_{IP}=R \cdot \nu'
\]  

(10)

Flow at any point in expiration is thus determined by the interplay between static lung recoil, \( P_{IP} \) and \( R \):

\[
\nu'=P_{REC}+P_{IP}/R
\]  

(11)

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

\[
V/CL=R \cdot \nu'
\]  

(12)

which can be rearranged as:

\[
\nu'/V=1/R \cdot CL
\]  

(13)

The term \( R \cdot CL \) is the mechanical time constant (\( \tau \)) of the respiratory system, and has the unit of time, i.e. \((\text{cmH}_2\text{O} \cdot \text{L}^{-1} \cdot \text{s}) \cdot (\text{L} \cdot \text{cmH}_2\text{O}^{-1}) = \text{s}\). Thus, if \( R \) or \( CL \) (or both) are large, then \( \nu' \) 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 \( 4 \cdot \tau \) for an exponential process). With a normal \( \tau \) of \( \approx 0.4 \text{s} \) (\( R \) and \( CL \) being \( \approx 2 \text{cmH}_2\text{O} \cdot \text{L}^{-1} \cdot \text{s} \) and \( 0.2 \text{L} \cdot \text{cmH}_2\text{O}^{-1} \), respectively), this minimum period is \( \approx 1.6 \text{s} \) and translates to a total breath time (\( t_{tot} \)) of \( \approx 3 \text{s} \), assuming an inspiratory duty cycle (\( t_t/t_{tot} \), where \( t_t \) is inspiratory time) of \( \approx 0.4 \). Thus, if \( f_t \) exceeds \( \approx 20 \text{breaths} \cdot \text{min}^{-1} \), complete emptying requires expiratory flow to be augmented by expiratory muscle action; without this, end-expiratory lung volume will be greater than FRC. Such

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**Figure 2.** a) \( V_T, P_{IP} \) and \( \nu' \) changes for normal resting and exercising breaths. The dashed line on the \( P_{IP} \) curve represents pressure needed to produce lung inflation statically. The blue area is the extra \( P_{IP} \) required to generate flow. b) Dynamic inspiratory \( V–P_{IP} \) curve. The red area represents static inspiratory work of breathing; the blue area is the dynamic component. I: inspiration; E: expiration.
Dynamic hyperinflation is a hallmark of the exercising COPD patient (fig. 3b), where disease-related increases in $R$ and/or $C_L$ can lower this limiting $f_R$ quite considerably.

That the maximal volitionally generated expiratory $v'_9$ is greater at high than at low lung volumes (fig. 3) is, of course, implicit in equation 11. That is, $R$ and $P_{REC}$ are each volume-dependent: at high volumes, $R$ is relatively low, reflecting a modest degree of airway distension (whose effect is amplified through the $r^4$ term) while $P_{REC}$ is relatively high. Indeed, for a given $t$, $v'_9$ decreases as a linear function of $V$ (equation 13), accounting for the descending limb of the maximal expiratory flow–volume curve normally being so linear (fig. 3a).

In COPD, however, the lower maximal $v'_9$ at TLC, despite the higher absolute lung volume (line 3 in fig. 1), is indicative of an increased $R$ and, for emphysema, decreased $P_{REC}$ (fig. 3b), and thus $v'_9$ at a particular lung volume is lower than normal. In contrast, for restrictive lung disease, while maximal $v'_9$ at TLC is low owing to poor distensibility (line 1 in fig. 1), $v'_9$ at a particular lung volume can even be slightly higher than normal owing to an increased $P_{REC}$. Furthermore, when there is regional nonuniformity of $t$, for example, as in COPD, this can contribute to the typically ‘scooped’ maximal expiratory $v'$ profile (fig. 3b).

However, the effects of $P_{IP}$ on expiratory $v'$ are not quite as straightforward as those of $R$ and $P_{REC}$ (equation 13). $P_{IP}$ is an index of the effort transmitted from the respiratory muscles to the lungs via the chest wall. During expiration, $P_{IP}$ 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 $P_{alv} = P_{IP} + P_{REC}$ (equation 10), $P_{alv}$ will be more positive than $P_{IP}$ by an amount equal to $P_{REC}$. Airway pressure ($P_{aw}$) declines from the alveolar value down to zero at the mouth as a result of frictional losses along the airways. At the point where $P_{aw} = P_{IP}$ (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 main stem 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 ($v'_{max}$):

$$v'_{max} = \frac{P_{REC}}{R_{us}}$$

where $R_{us}$ 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,

![Figure 3](image-url)

*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 COPD. Reproduced from Klas et al. (1989), with permission from the publisher.*

![Figure 4](image-url)

*Figure 4. Airflow limitation in expiration. An EPP results when $P_{aw}$ declines to a value equal to $P_{REC}$. Values are expressed in cmH$_2$O.*
although leading to a progressively more positive $P_{IP}$, do not lead to a progressively greater $\nu'$; greater expiratory effort simply compresses the airways more, raising downstream $R$ in proportion to the increased effort. Therefore, $\nu'$ becomes maximised at a constant value (at that lung volume), independent of effort.

With the loss of lung recoil and/or increases in small airway resistance, however, the EPP migrates upstream. If it encroaches into the small unsupported airways, airways collapse occurs – with profound effects on $\nu'_{\text{max}}$ (equation 14).

**Pulmonary gas exchange**

The effectiveness of pulmonary oxygen exchange is conventionally judged by the magnitude of the alveolar–arterial oxygen tension difference ($P_{A}-P_{A}$), using $P_{AI}O_{2}$, which is the $P_{AI}O_{2}$ of the ‘ideal lung’ (one that hypothetically exchanges gases ideally). $P_{AI}O_{2}$ thus circumvents the difficulty of providing a single representative value for $P_{AI}O_{2}$ when there are regional variations in gas-exchange efficiency. It can be derived by re-arranging and amalgamating equations 1 and 2:

$$V^{'CO}/V^{'O_2} = (V^{'A} - (\frac{P_{AI}O_{2} \cdot F_{IO_{2}}}{F_{IN_{2}}}) - P_{AI}O_{2})/(V^{'A} - P_{AI}O_{2})$$  \hspace{1cm} (15)

$$P_{AI}O_{2} = P_{IO_{2}} - P_{CO_{2}} + P_{CO_{2}} \cdot F_{IO_{2}} \cdot (1 - R)/R$$  \hspace{1cm} (16)

where $P_{IO_{2}}$ is the inspiratory oxygen fraction. It is common practice to neglect the term $P_{CO_{2}} \cdot F_{IO_{2}} \cdot (1 - R)/R$, as it is zero when $R=1$, and only contributes a few mmHg or so when $R \neq 1$. Therefore:

$$P_{AI}O_{2} = P_{IO_{2}} - P_{CO_{2}}/R$$  \hspace{1cm} (17)

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 $P_{AI}O_{2}$ (ambient hypoxia as with ascent to altitude, reduced RQ and alveolar hypoventilation) and three affect $P_{A}-P_{AI}$ (diffusion limitation, increased right-to-left shunt and $V^{'A}/\text{perfusion (Q')}$ maldistribution).

**Reduced RQ** Recalling that $V^{'E}$ operates to regulate $P_{AI}CO_{2}$ by responding in a proportional fashion to $V^{'CO}_{2}$, when the RQ of the dietary substrate is reduced (i.e. by ingestion of a high-fat diet), the associated reduction in metabolic carbon dioxide production requires less ventilation to maintain a stable $P_{AI}CO_{2}$ (equation 3). This leads to hypoventilation relative to oxygen, i.e. $V^{'E}$ is normal relative to $V^{'CO}_{2}$, but low relative to $V^{'O_{2}}$. Thus, $P_{AI}O_{2}$ and $P_{AI}CO_{2}$ will fall.

**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 increased small airway resistance and a high resistive work of breathing. Arterial hypoxaemia and hypercapnia result (equations 2 and 1, respectively), with the fall of $P_{AI}O_{2}$ being related to the rise of $P_{AI}CO_{2}$ through $R$ (equation 17). When $R=1$, the increase in $P_{AI}CO_{2}$ and fall in $P_{AI}O_{2}$ that result from a reduction in $V^{'A}$ are equal, as notionally are the corresponding changes in $P_{AI}CO_{2}$ and $P_{AI}O_{2}$. However, as $R$ is normally $\sim 0.8$ at rest, for each 10-mmHg decrease in $P_{AI}O_{2}$ that results from a fall of $V^{'A}$, $P_{AI}CO_{2}$ will increase by only 8 mmHg. It should be noted that the hypoxaemia can be offset by administration of supplementary oxygen.

**Diffusion impairment** Fick’s law indicates that impairments in the pulmonary diffusive flux of oxygen (or carbon dioxide) can result from

1) a reduction in the driving pressure (for oxygen, $\Delta P_{O_{2}}$),

2) a reduction in the available surface area for diffusion ($A$) and/or

3) an increased path length for diffusion ($l$):

$$V^{'O_{2}} = A l d \cdot \Delta P_{O_{2}}$$  \hspace{1cm} (18)

where $d$, the diffusion coefficient for oxygen, 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 ($d=s/MW$). Hence, as oxygen is lighter than carbon
dioxide, it diffuses 18% more rapidly in the gas phase for the same gas tension gradient. In the blood phase, however, carbon dioxide is 20 times more diffusible than oxygen, owing to its greater solubility.

During inspiration, oxygen 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 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 \( \sim 100 \mu m \), 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 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 oxygen and carbon dioxide exchange.

More commonly, however, diffusion limitation reflects exchange impairments between alveolar gas and pulmonary capillary blood. The rate of diffusive uptake of oxygen into blood is given by:

\[
V^\prime O_2 = A/l' \cdot (P_{A02} - P_{CO2})
\]  

(19)

where \( A \) is the alveolar surface area in contact with perfused pulmonary capillaries; \( l \) is the diffusion path length between the alveolar surface fluid lining and the erythrocyte interior that includes alveolar epithelium, interstitial space, capillary endothelial cells, plasma, erythrocyte cell membrane and, for a reactive gas species such as oxygen, its chemical combination with haemoglobin; and \( P_{CO2} \) is mean pulmonary capillary \( P_{O2} \). It is conventional to combine \( A, l \) and \( d \) into a single term, the transfer factor of the lung for oxygen (TLO2):

\[
V^\prime O_2 = TLO2 \cdot (P_{A02} - P_{CO2})
\]  

(20)

TLO2 can be usefully subdivided into its functional components: the 'membrane' component (TMO2) and that due to chemical combination:

\[
1/TLO2 = 1/TMO2 + 1/\theta \cdot V_c
\]  

(21)

where \( \theta \) is the reaction rate coefficient for chemical combination of oxygen with haemoglobin and \( V_c \) is pulmonary capillary blood volume. Because of technical limitations associated with estimating \( P_{CO2} \), it is conventional to determine transfer factors of the lung and membrane for carbon monoxide (TLCO and TMCO, respectively), as the high affinity of haemoglobin for carbon monoxide ensures that the pulmonary capillary carbon monoxide tension (PcO2) is effectively zero.

The initial driving pressure across the alveolar–capillary membrane (i.e. at the entrance to the capillary bed) is given by the difference between \( P_{A02} \) (normally \( \sim 100 \text{ mmHg} \)) and mixed venous \( P_{O2} \) (\( P_{A02} \)) (normally \( \sim 40 \text{ mmHg} \) at rest, although decreasing in exercise). The rate at which oxygen is taken up into the blood as it traverses the capillary declines, reflecting the increasing \( P_{CO2} \) (and consequent decrease in \( P_{A02} \)), which in turn reduces the instantaneous \( \Delta P_{O2} \). Diffusion equilibrium is normally reached within 0.25–0.3 s (i.e. well before blood reaches the end of the capillary); thus, pulmonary end-capillary \( P_{O2} \) (\( P_{cO2} \) = \( P_{A02} \)). This large safety margin becomes compromised, however, when \( T_{TR} \) is shortened to such a degree that there is insufficient time for the attainment of diffusion equilibrium, i.e. \( P_{cO2} < P_{A02} \). As \( T_{TR} = Vc/Q' \), an increase in \( Q' \) (e.g. high-intensity exercise) can compromise diffusion equilibrium, resulting in arterial hypoxaemia. However, the decrease in \( T_{TR} \) with increases in \( Q' \) is less than expected, because the capillary blood volume (Qc) 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 \( P_{A02} \), as occurs with ascent to high altitude, when a subject breathes an
hypoxic inspirate or with hypoventilation, slows the $P_{aO_2}$ rise time. This is because the initial driving pressure ($P_{aO_2}-P_{vO_2}$) is smaller, as the operating slope of the oxygen dissociation curve ($\beta$) is steeper, with the arteriovenous oxygen content difference expressing a smaller arteriovenous $P_{aO_2}$ difference.

A useful expression relating to the interplay of factors that dictate whether or not diffusion equilibrium will actually be attained (i.e. whether $P_{aO_2}=P_{vO_2}$) is:

$$ (P_{aO_2}-P_{vO_2}) = (P_{aO_2}-P_{vO_2}) e^{\frac{L_{O_2}}{Q' \cdot \beta}} $$

(22)

The term $L_{O_2}/Q' \cdot \beta$ has been termed the ‘equilibrium coefficient’ by Piiper et al. (1980) and the ‘diffusive-perfusional conductance’ ratio by West et al. (1998). Thus, diffusion equilibrium is less likely to be attained if $L_{O_2}$ is low and/or $Q'$ and $\beta$ are high. For example, an increased path length (e.g. alveolar proteinosis or pulmonary oedema) and/or a reduced surface area for exchange (e.g. pulmonary embolism or restrictive lung disease) slow the diffusive flux of oxygen because of their effects on $L_{O_2}$. With very high levels of $Q'$ (e.g. very fit endurance athletes exercising at or close to maximum) or very high linear capillary-blood velocities (e.g. pulmonary embolism, where there are fewer participating capillaries), the reduction in $TR$ can lead to a widened $PA-aO_2$ and arterial hypoxaemia. Supplemenetal oxygen can, through its effects on $P_{aO_2}$, and, therefore, driving pressure, speed the increase of $P_{aO_2}$, and thus ameliorate the degree of gas-exchange impairment.

However, although severe degrees of arterial hypoxaemia can result from diffusion impairment, carbon dioxide retention is rarely a problem. This is because any increase in $P_{aCO_2}$ that might occur tends to be corrected by ventilatory control mechanisms, which are considered to be exquisitely sensitive to carbon dioxide (i.e. central and carotid body chemoreflexes); in contrast, hypoxic ventilatory stimulation only becomes appreciable when $P_{aO_2}$ falls below ~60 mmHg. Hence, moderate diffusion impairment is accompanied by a decreased $P_{aO_2}$, a widened $PA-aO_2$, and a relatively normal $P_{aCO_2}$; with more severe impairment, which leads to hypoxic ventilatory stimulation, there will be a more marked arterial hypoxaemia, greater widening of the $PA-aO_2$, and a low $P_{aCO_2}$.

Right-to-left shunt A right-to-left shunt ($Q'$) occurs when venous blood bypasses the pulmonary capillary circulation, thus providing a degree of venous admixture with blood from exchanging alveolar units. It normally reflects venous drainage from the larger airways (which enters the pulmonary veins) and from coronary vessels (which enters the left ventricles via the Thebesian veins). This represents only a small percentage of $Q'$ and, therefore, amounts to a reduction in $P_{aO_2}$ of only a few mmHg below $P_{aO_2}$. However, $Q'/Q'$ can be markedly increased in congenital heart disease (e.g. atrial or ventricular septal defects, and 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 oxygen 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 $Q'=Q'+Q'$,

$$ Q' = Q' + Q' $$

(23)

were $Cc_{O_2}$ is the end-capillary oxygen content and $Cv_{O_2}$ is the mixed-venous oxygen content, which rearranges to yield:

$$ Q'/Q' = (Cc_{O_2}-Cc_{O_2})/(Cc_{O_2}-Cc_{O_2}) $$

(24)

$Cc_{O_2}$ and $Cc_{O_2}$ can be measured directly from blood samples, while $Cc_{O_2}$ is derived through the standard oxygen dissociation curve, assuming $P_{vO_2}=P_{aO_2}$ (equation 17). 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 $Q'/Q'$ thus provides an overestimate of the true shunt, as it incorporates a fraction of the perfusion draining from alveolar 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 $C_aO_2$, owing to the influence of the nonlinear oxygen dissociation curve. The severity of the hypoxaemia will depend both on $Q'/Q'$ and $C_aO_2$, 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 elevation of $P_AO_2$ in response to administration of 100% oxygen is appreciably less than expected. This is because the shunt flow cannot ‘see’ the elevated $P_AO_2$ in the exchanging alveoli, and also that further increases in $P_AO_2$ will have little effect on $C_cO_2$, because the blood is already essentially fully saturated; it is only the dissolved component of the oxygen content that can be increased, and this will be relatively small because of the low solubility of oxygen in plasma.

A right-to-left shunt also has the potential to cause carbon dioxide retention but this is rarely observed owing to the normally small mixed venous-to-arterial carbon dioxide tension ($PCO_2$) difference (~6 mmHg at rest versus ~60 mmHg for oxygen) and also (see earlier) the mechanisms of ventilatory control that normally restore an increased $P_ACO_2$ to normal. Again, however, should $P_AO_2$ fall sufficiently to cause hypoxic stimulation of the carotid chemoreceptors, then $P_ACO_2$ will fall; but, without this, $P_ACO_2$ will rise. Thus, a moderate right-to-left shunt leads to a reduced $P_AO_2$ and a widened $P_A-\Delta O_2$, but a relatively normal $P_ACO_2$. Severe right-to-left shunts cause a markedly reduced $P_AO_2$ and a markedly widened $P_A-\Delta O_2$, with the possibility of a lowered $P_ACO_2$.

$V'A/Q'$ 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 $P_AO_2$ and high $P_ACO_2$) and, in the extreme, alveolar shunt ($V'A/Q'\rightarrow0$) (see previously); gas and blood from normal $V'A/Q'$ regions will have a normal $P_AO_2$ and $P_ACO_2$; and gas and blood from high $V'A/Q'$ regions will reflect hyperventilation (i.e. high $P_AO_2$ and $P_ACO_2$) with, in the extreme, alveolar dead space ($V'A/Q'=\infty$).

An analogous formulation to that for estimation of $Q'/Q'$ can be applied to the estimation of $Vd/Vt$ (recalling that $Vd$ reflects the sum of the anatomical and alveolar dead spaces). That is, the assumption is made that the volume of carbon dioxide cleared in exhalation originates solely from a homogeneous exchanging alveolar compartment (Bohr technique):

$$Vt \cdot FECO_2 = VA \cdot FACO_2$$  \hspace{1cm} (25)

where $FECO_2$ is mixed expired carbon dioxide fraction and $VA$ is the volume of exchanging alveoli. Substituting $Vt \cdot Vd$ for $VA$, converting fractional concentrations to gas tensions, making the reasonable assumption that $PACO_2 = P_ACO_2$ (attributable to Enghoff) and rearranging yields:

$$Vd/Vt = (P_ACO_2 - FECO_2)/P_ACO_2$$  \hspace{1cm} (26)

Even in the normal lung, there is evidence of mild $V'A/Q'$ mismatch. 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 are smaller, as the hydrostatic pressure in the surrounding interstitium is greater. They are therefore constrained to operate over the steeper, lower portion of the $C_aCO_2$ curve, in contrast to the larger apical units. Thus, the smaller basal units undergo a greater expansion for a given increase of $P_{TP}$ during inspiration and are therefore better ventilated than are the apical units. The apical units thus have a relatively high $V'A/Q'$ while the basal units have a low $V'A/Q'$. Naturally, the degree of $V'A/Q'$ mismatch is considerably greater in many pulmonary disease states (e.g. COPD, diffuse interstitial fibrosis and pulmonary
vascular occlusive disease) and its
topographical location is not predictable.

The overall (or mean) $P_{\text{AO}_2}$ and $P_{\text{ACO}_2}$ result
from an averaging of the respective gas
concentrations from each individual gas
‘stream’, in proportion to the local $V' \alpha$.
Likewise, the overall (or mean) $P_{\alpha O_2}$ and
$P_{\alpha CO_2}$ will result from a flow-weighted
averaging of the respective gas contents
from each individual blood ‘stream’.
However, it is important to recognise that
account has also to be taken of the shape of
the oxygen and carbon dioxide dissociation
curves in order to derive these $P_{\alpha O_2}$ and
$P_{\alpha CO_2}$ values (fig. 5).

Owing to the sigmoid shape of the oxygen
dissociation curve, low $V' \alpha/\alpha$ regions lead
both to low $P_O_2$ and low oxygen content in
pulmonary end-capillary blood; in contrast,
while high $V' \alpha/\alpha$ regions lead to a high
$P_{cO_2}$, $C_{cO_2}$ is only slightly increased above
the normal value because the oxygen
dissociation curve is relatively flat in this
range (fig. 5). Mixing blood from low $V' \alpha/\alpha$ regions with blood from high $V' \alpha/\alpha$ regions
will therefore result in a mean $P_{\alpha O_2}$ that is
weighted towards low $V' \alpha/\alpha$ blood values
(fig. 5). $P_{\alpha O_2}$ will also depend on the volumes of blood from each region contributing to
the mixed arterial blood. Thus, the high
$V' \alpha/\alpha$ regions (even if haemoglobin is
completely saturated) are unable to
compensate for the low $V' \alpha/\alpha$ regions, as
their perfusion is usually less. Consequently,
even though the overall $V' \alpha/\alpha'$ may be
normal, $V' \alpha/\alpha'$ mismatch results in arterial
hypoxaemia, with mean $P_{\alpha O_2}$ being lower
than the actual mean $P_{\alpha O_2}$, or its ‘ideal’
representation; i.e. $P_{\alpha-aO_2}$ is widened.

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

The pattern of arterial blood and alveolar gas
tensions in $V' \alpha/\alpha'$ mismatch is such that
with mild or moderate mismatch, $P_{\alpha O_2}$ is
low, $P_{\alpha-aO_2}$ is widened, with $P_{\alpha CO_2}$ being
normal or low depending on the degree of
ventilatory stimulation consequent to the
hypoxaemia. In severe $V' \alpha/\alpha'$ impairment
associated with severe airway obstruction,
hypoventilation can ensue owing to the
increased work of breathing and, therefore,

![Figure 5](image-url)

**Figure 5.** Influence of altered $V' \alpha/\alpha'$ on mean $P_{\alpha O_2}$ and $P_{\alpha CO_2}$ tensions. a) The sigmoid oxygen
dissociation curve leads to arterial hypoxaemia (arrow) compared with ‘normal’ (×). b) This effect is not
evident for carbon dioxide, because the carbon dioxide dissociation curve is linear. Reproduced from Whipp
(2002) with permission from the publisher.
cause an increased $P_{aCO_2}$. This, of course, reduces $P_{aO_2}$ even more.

Further reading

Cytology of the lung

Venerino Poletti, Giovanni Poletti, Marco Chilosi and Bruno Murer

The role of cytological techniques for investigation of respiratory disorders has been recognised since the earliest days of clinical cytology. Improvement in sampling techniques, and in particular, the advent of fibreoptic bronchoscopy, transparietal fine-needle aspiration, cytological sampling assisted by echoendoscopy, the use of immunocytochemical and, more recently, molecular biology methods, recent advances in liquid-based cytology, and the use of cell block processing methods have increased the clinical impact of cytological diagnoses. Finally, the rapid, on-site analysis of cytological samples or of preparations obtained from biotic samples (smears or touch imprints) has also improved the diagnostic yield of the investigative methods. A knowledge of ‘basic cytology’ should be part of the education for becoming a pulmonologist and this knowledge should be maintained in daily clinical practice.

Technical notes

The routine staining procedures that pulmonologists should be familiar with are Diff-Quik, May–Grünwald–Giemsa (MGG), Papanicolaou, haematoxylin–eosin and Gram staining, and a staining for acid-fast bacilli (Ziehl–Neelsen and/or Kinyoun). Papanicolaou stain is a polychrome stain: the nucleus stains deep blue, nuclear details are sharp, the nucleolus stains red, and the cytoplasm stains eosinophilic, cyanophilic or orange. Keratin stains deep orange. The slides must be wet-fixed swiftly and rapidly. Diff-Quik is a three step procedure requiring about 20–30 s to complete. The staining kit includes fixative solution A (trimethane dye and methyl alcohol, but 95% ethyl alcohol is valid), solution I that contains xanthene dye and solution II that contains a buffered solution of thiazine dyes. Slides are air dried and then fixed. Material obtained by fine-needle aspiration techniques should be used for smears and for cell-block preparations, cytofluorimetric analysis and genetic studies when deemed necessary. Summaries of the routine staining procedures, cytological preparations and genetic studies feasible on cytological material are presented in tables 1–3, respectively.

Key points

- BAL is an important source of cytological samples.
- Fine-needle aspiration has increased the impact of cytological diagnoses.
- Cell blocks are easy to prepare and useful for immunocytochemistry.
- Reactive cytological features in respiratory samples can be characteristic but nonspecific.
- Cytology can be used to diagnose respiratory infections.
- Lung carcinoma presents a variety of characteristic patterns.
- Lymphoproliferative disorders are more readily diagnosed in BAL fluid or fine-needle aspirates.
- Immunocytochemistry and molecular biology add to cytological diagnoses.
General cytological findings in respiratory samples

_Squamous cells_ are the most common cells in sputum but are less frequent in other specimens, being inconsistently found or absent. They appear as irregularly polygonal or rectangular cells with well-demarcated borders, small nuclei, abundant clear pale cyanophilic to eosinophilic cytoplasm in Papanicolaou preps. The intermediate-type cells have a small central nucleus with thready chromatin and a lack of nucleoli.

_Bronchial epithelial cells_ are columnar or triangular in shape, and lie singly, in short ribbons or in flat sheets. They have a bluish grey cytoplasm with MGG or Diff-Quik stains, or cyanophilic in Papanicolaou preps, tapering at the point of previous anchorage. Their nuclei vary considerably in size and shape but are usually basal, rounded or oval with open granular or condensed chromatin and a single small nucleolus. Cilia (red in Papanicolaou preparations) are often well preserved, arising from a dark-stained terminal bar at the end of the cell.

_Goblet cells_ are columnar, with a basally placed nucleus and supranuclear cytoplasm distended by globules of mucin. Cilia are absent. These cells increase in number in bronchial irritation.

_ Reserve cells_ are small (slightly larger than lymphocytes), regular cells grouped to form sheets. Their nuclear/cytoplasmic ratio is high, the chromatin is coarse and there is a narrow rim of cytoplasm (green in Papanicolaou preps, or blue in Diff-Quik or MGG preps).

<table>
<thead>
<tr>
<th>Table 1. Routine staining techniques</th>
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<tr>
<td><strong>Stain</strong></td>
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| Papanicolaou | Very useful to:  
  detect and classify neoplastic cells  
  identify vital inclusions | Time consuming |
| Diff-Quik | Very easy to perform for rapid, on-site examination | Not precise in defining nuclear details |
| MGG | The reference to classify ‘haematologic’ cells  
  Very useful to identify viral cytoplasmic inclusions | Tends to overestimate ‘dysplastic’ changes |
| Gram | To identify and classify bacteria | |
| Kinyoun | For weakly acid-fast bacilli | |

<table>
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<th>Table 2. Routine ‘cytological’ preparations</th>
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| **Smear** | Used for:  
  fine-needle aspiration samples  
  rapid, on-site examination of bioptic material (squash or touch preparations) |
| **Cytospin** | The standard for cytological analysis of BAL fluid |
| **Thin preparations** | The standard for bronchial washing or lavage and pleural fluid |
| **Cell block preparations** | Easy to prepare  
  Very useful for immunocytochemical studies |
| **Flow cytometry** | The standard for lymphocyte subset identification, and for demonstration of B-cell monoclonality and characterisation of myeloid cells |
Club cells (Clara cells), Feyrter cells and type II pneumocytes are prone to rapid degenerative changes and are not recognisable in respiratory samples unless hyperplastic/dysplastic.

Macrophages are round or oval cells, usually >10 \( \mu \text{m} \) in diameter, and possess generally abundant pale cytoplasm, with an oval or reniform nucleus showing a sharp nuclear membrane, finely granular, evenly dispersed chromatin, micronucleoli and sometimes also macronucleoli. Binucleation is common and giant cells with numerous nuclei are not uncommon. These cells are phagocytic and their cytoplasm may be vacuolated or may contain small particles coated by iron, coarse granules of haemosiderin or inhaled particles.

Inflammatory cells A variety of inflammatory cells may be recognisable in lung specimens:

- polymorphonuclear leukocytes
- lymphocytes
- eosinophils
- mast cells
- plasma cells

Megakaryocytes can be identified in pulmonary arterial samples and may be misinterpreted as malignant.

Mesothelium Tissue fragments of benign mesothelium are often collected during a transthoracic aspiration procedure. Most mesothelial tissue fragments appear as flat, two-dimensional sheets that present a honeycomb pattern. Mesothelial cells are, however, mainly found in pleural fluid. They are usually 15–30 \( \mu \text{m} \) in diameter but may be significantly larger. They may be present as solitary cells or in small cohesive clusters. The cytoplasm usually shows two zones: in Diff-Quik-stained smears, the endoplasm is lightly stained with peripheral darker ectoplasm. The peripheral cell border is ruffled with blebs. As mesothelial cells imbibe water from the surrounding fluid, their cytoplasm may acquire a foamy macrophage phenotype. Mesothelial cell nuclei have crisp, thin nuclear membranes, evenly distributed, finely granular chromatin, one or two micronucleoli, and occasionally grooves.

Other components of respiratory samples Mucus appears as a pale, thin, translucent shroud or as strings stained with varying intensity and with enmeshed cellular elements. Insipissated mucus appears as darkly stained blobs. Coils of compressed mucus are known as Curschmann's spirals and represent casts of the small bronchioles. Charcot–Leyden crystals, derived from the breakdown products of eosinophil granules, appear as orange-, yellow- or pinkish-stained diamond- or needle-shaped crystals. They are mainly observed in conditions evoking pulmonary eosinophilia. Calcific blue bodies and corpora amylacea are similar in routine preps. The former consists largely of calcium carbonate and shows central birefringence. Corpora amylacea are noncalcified, rounded structures composed of pulmonary surfactant proteins, epithelial membrane antigen and glycoproteins including amyloid. They stain pale pink, are Congo red positive and exhibit birefringence. Psammoma bodies (calcipherites) are laminated, nonrefractile, calcified concretions sometimes found in the presence of malignancy. Ferruginous bodies are formed when filamentous dust particles such as asbestos become coated with protein and iron in the lung parenchyma. They vary from 5 to 200 \( \mu \text{m} \) in length and are golden brown in colour with a characteristic segmented or beaded bamboo shape with knobbed or bulbous ends and stain blue with Perl's stain for iron. Other noncellular entities that may be found in respiratory specimens are calcium oxalate crystals (frequently associated with

### Table 3. Molecular studies on cytological material

<table>
<thead>
<tr>
<th>Molecular marker</th>
<th>Description</th>
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<tr>
<td><strong>EGFR</strong> mutations (exons 18–21)</td>
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<tr>
<td><strong>ALK–EML4</strong> fusion</td>
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</tr>
<tr>
<td><strong>BRAF</strong>V600E mutation</td>
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<tr>
<td>MicroRNA profiles</td>
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<tr>
<td>Heavy chain monoclonal rearrangement</td>
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<tr>
<td>T-cell receptor monoclonal rearrangement</td>
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**Aspergillus infection**, Schaumann bodies, asteroid bodies, elastin fibres and amyloid.

**Nonspecific reactive changes of the respiratory epithelium**

Benign disorders of the respiratory tract may be manifested by characteristic but nonspecific abnormalities of the squamous epithelium, bronchial epithelium and alveolar epithelium. Reactive squamous cells from the upper respiratory tract have slightly enlarged hyperchromatic nuclei. Anucleate, keratinised squamous cells, if present in large numbers, suggest an area of hyperkeratosis. Squamous metaplasia is defined as the replacement of the respiratory mucosa by squamous epithelium, and is a common reaction to injury in the trachea and in the bronchial tree. Particularly severe squamous atypia has been described in the trachea of patients with prolonged tracheal intubation and patients with tracheitis sicca occurring in patients who have permanent tracheostomy or in patients with tracheal inflammatory conditions, bronchial and parenchymal tuberculotic or mycotic lesions. The loss of cilia and the terminal plate (ciliocytophthoria) is a common response of the respiratory epithelium to acute injury; this phenomenon is observed mainly in viral infections. Papillary hyperplasia of the respiratory epithelium is most commonly observed in chronic inflammatory bronchial disorders (bronchiectasis and bronchial asthma) and appears cytologically as characteristic pseudopapillary cell clusters (Creola bodies) showing well-preserved bronchial epithelial cells with cilia or terminal plates or goblet cells at the periphery and a central core containing small cells. Reserve cell hyperplasia is represented by clusters of tightly packed small cells with uniform, dark, round or oval nuclei. Nucleoli may be observed but are tiny. Nuclear moulding is not present or at least not prominent. Type II alveolar cell hyperplasia has been typically reported bronchoalveolar lavage (BAL) fluid obtained from patients with acute respiratory distress syndrome (ARDS) but it is the cytological hallmark of diffuse alveolar damage (DAD) observed in a variety of acute lung disorders. Pneumocytes appear singly, in flat plates or in rosette-like groups, are polygonal or rectangular in shape, have large nuclei with single or multiple prominent nucleoli and a pale or dense chromatin. The cytoplasm appears basophilic in Diff-Quik preps, often with vacuolation. Extracellular osmiophilic or metachromatic material representing fragments of hyaline membranes is sometimes surrounded by these reactive cells.

**Cytological changes in pulmonary infections**

Bacteria may be detected by specific stains, or by immunofluorescence or immunocytochemistry. Acid-fast mycobacteria are easily recognised when present in significant quantity in Ziehl–Neelsen preparations. *Nocardia*, a weakly acid fast, aerobic, branching filamentous bacterium, is seen better using the Kinyoun method. *Actinomyces*, anaerobic or microaerophilic Gram-positive bacteria form colonies of radiating, thin filamentous organisms better seen by silver staining. *Legionella* organisms are tiny Gram-negative bacilli that can be demonstrated by silver stains and by immunofluorescence. Numerous other cocci or bacilli may be recognised in Diff-Quik or MGG preps but are better identified using Gram staining. Granulomatous reaction, mainly associated with TB, is cytologically characterised by the presence, in fine-needle aspiration preparations, of pale histiocytes with elongated nuclei collected in nodular structures with poorly demarcated borders, surrounded by inflammatory cells (lymphocytes and neutrophils), necrosis and cellular debris. Malakoplakia due to *Rhodococcus equi* manifests cytologically with epitheloid macrophages with abundant foamy and granular cytoplasm, and intracellular osmiophilic, concentrically laminated bodies (Michaelis–Gutmann bodies).

Viral infections may determine cytopathic effects providing a background to the diagnosis. Furthermore, necrosis, inflammation, ciliocytophthoria, and bronchial and alveolar cell hyperplasia/
dysplasia may be associated with these cytopathic changes or may be the only cytological manifestation of these infections. The cellular alterations suggesting a herpes simplex infection are: cells with multiple nuclei, which may contain eosinophilic irregular inclusion bodies with a halo separating the inclusion from the nuclear membrane (Cowdry type A inclusions) (fig. 1) or exhibit a peculiar type of nuclear degeneration that appear as slate grey, homogenised contents (Cowdry type B inclusions). Cells infected by cytomegalovirus (CMV) are larger with large amphophilic, smooth, intranuclear inclusions, surrounded by very prominent halos and marked margination of chromatin on the inner surface of the nuclear membrane. Intracytoplasmic small inclusions well seen by Diff-Quik or MGG stains are also identifiable. Infection with adenovirus produces two types of intranuclear inclusions: the first consists of a small red body surrounded by a well-circumscribed clear halo and the second is a homogenous basophilic mass almost completely replacing the nucleus. The most characteristic cytological finding in measles pneumonia is the presence of multinucleated giant cells containing eosinophilic inclusions both within the nucleus and cytoplasm. Respiratory syncytial virus (RSV) also stimulates a proliferation of multinucleated giant cells with cytoplasmic basophilic inclusions surrounded by halos. Other viruses that may give characteristic inclusions in respiratory cells are: parainfluenza viruses, rubella, coronavirus, polyomavirus and human papillomavirus. Immunoreactivity using specific monoclonal antibodies increases the capacity to recognise virus elements in cytological specimens.

Fungal infections may also be documented cytologically; however, the distinction between colonisation and pneumonia requires clinical and radiological data. Candida species may appear as small, oval, 2–4 µm budding yeasts; occasionally, they may elongate into pseudohyphal forms with additional budding at the points of constriction. Filamentous fungal organisms are identified by routine stains but silver staining is more precise in identifying septation and the angle of branching. Fragmented hyphae usually identified in silver methenamine-stained preps along with numerous eosinophils, necrotic debris and neutrophils are the cytological hallmark of allergic bronchopulmonary aspergillosis. As angioinvasive mycoses are associated with parenchymal haemorrhage, iron-laden macrophages are usually found in the background. Cryptococcus may be identified also using a simple technique: adding some drops of India ink to the sample, the fungus appears as transparent oval or round microorganisms in a dark background. Pneumocystis jiroveci is easy to identify in BAL fluid using routine stains: finely vacuolated or foamy proteinaceous casts are typical. Diff-Quik or MGG preps are useful to recognise cysts and, within cysts, up to eight tiny, dot-like trophozoites or sporozoites, measuring 0.5–1 µm in diameter. The wall of the cyst is also stained by Grocott’s methenamine silver stain. Numerous fungi are identifiable by routine staining procedures or using silver staining or immunocytochemistry using monoclonal antibodies.

Typical features may also be due to parasites (Toxoplasma gondii, Entamoeba histolytica, Strongyloides stercoralis, Ancylostoma duodenale, Echinococcus, Paragonimus)
Benign non-neoplastic disorders with characteristic cytological findings

Sarcoid granulomas have typical cytological features that are easy to recognize in fine-needle aspiration material and smears obtained by biopsy: nodular structures with sharp borders, consisting of epithelioid multinucleated cells in the central portion and of mature lymphocytes at the periphery. Alveolar proteinosis is the cause of a characteristic milky or opaque BAL fluid recovery: on microscopy, a dirty background consisting of amorphophilic granules is associated with the presence of globules or chunks of amorphous, amorphophilic, periodic acid–Schiff (PAS)-positive material. Foamy macrophages with PAS-positive cytoplasmic inclusions, cholesterol crystals, scattered hyperplastic type II pneumocytes and mature lymphocytes complete the pattern. Exogenous lipid pneumonia may be diagnosed when large macrophages with large cytoplasmic empty vacuoles (that may displace the nuclei at the periphery), or abundant bubbly or lacy, vacuolated cytoplasm are detected. Oil material is easy to detect using Oil Red O or other specific stains. In BAL, an increase of lymphocytes may be an ancillary finding. In individuals smoking ‘crack’ cocaine, BAL fluid contains alveolar macrophages that accumulate large quantities of carbonaceous material in their cytoplasm; the material is also present extracellularly, imparting black discoloration to the specimen. Organising pneumonia, hypersensitivity pneumonitis, eosinophilic pneumonia, DAD, chronic or acute alveolar haemorrhage, amiodarone lung injury, pulmonary fat embolism, and rarer disorders (Gaucher’s disease and Neimann–Pick disease) present characteristic or specific cytological features in BAL fluid. Organising pneumonia also presents characteristic aspects in touch imprints: globules of metachromatic purple amorphous material (Masson bodies) mingled with lymphocytes and scattered mast cells (fig. 2). Cellular nonspecific pneumonitis, idiopathic or secondary and lymphocytic interstitial pneumonitis (LIP) are usually associated with lymphocytosis in BAL fluid. Alveolar macrophages in smokers or recently former smokers show small brown or dark particles in the cytoplasm; these particles are Perl’s positive because they also contain iron. However, in desquamative interstitial pneumonitis (DIP), a smoking-related interstitial disease in most cases, BAL eosinophilia is a typical finding. Giant cell pneumonitis, a hard-metal pneumoconiosis, is characterised by numerous giant cells with multiple nuclei, with leukocytes in the cytoplasm (cannibalism); the metals may be documented by analytical electron microscopy. Cytotoxic effects of chemotherapy or radiation and chronic thermal injury determine alterations in nuclei and cytoplasm with aspects mimicking those observed in neoplastic cells (squamous metaplasia/dysplasia; multinucleation, nuclear enlargement with prominent nucleoli, and nuclear or cytoplasmic vacuolisation). Immunocytochemistry is needed to identify Langerhans’ cells (monoclonal antibodies against CD1a or langerin).

Lung tumours

Squamous carcinoma

The grading of squamous dysplasia is based on nuclear morphology, the amount of cytoplasm and...
the nuclear/cytoplasmic ratio. Well-differentiated keratinising squamous carcinomas are characterised by a polymorphous population of neoplastic cells: very large squamous cells may appear next to very small cells; spindly cells and tadpole cells are quite characteristic. In Papanicolaou preparations, the keratin accumulation in cytoplasm is easy to detect; the nuclei are hyperchromatic with coarsely textured chromatin, and irregular. Nucleoli are evident in poorly differentiated tumours. In nonkeratinising cancer, cytoplasm appears basophilic or amphophilic. In fine-needle aspiration samples, neoplastic cells are more frequently grouped in sheets or smooth clusters. The background may be necrotic. Immunocytochemistry documents expression of p63/p40 protein in the nucleus. Thyroid transcription factor (TTF)-1 staining is negative.

**Adenocarcinoma** Cell aggregates are a characteristic feature. These clusters have a three-dimensional papillary or approximately spherical configuration. Sheets or rosettes of neoplastic cells are frequent in fine-needle aspiration preparations. The papillary or acinar clusters of cancer cells may resemble and must be distinguished from the so-called Creola bodies. Cancer cells are large, usually round or polygonal, but occasionally columnar or cuboidal. Nuclei are large, pleomorphic and eccentric, with a vesicular chromatin pattern and prominent nucleoli. Cytoplasm may contain mucin or appear vacuolated, mimicking that observed in foamy macrophages. The expression of TTF-1 is evident in nonmucinous adenocarcinoma cells. Immunocytochemistry (napsin positive and p63/p40 negative), and molecular biology investigations regarding EGFR (epidermal growth factor receptor) mutations, ALK (anaplastic large cell lymphoma kinase) rearrangement with EML4 (echinoderm microtubule-associated protein like 4) gene and BRAFV600E mutation are also feasible in cytological specimens.

**Small cell lung cancer** Here, the neoplastic cells are small and can be misinterpreted as lymphocytes in sputum. However, in samples obtained by fine-needle aspiration or in smears from biotic specimens, the proportion of well-preserved viable cells is larger, and they appear two or three times larger than lymphocytes with nuclei showing a vesicular–granular chromatin pattern, inconspicuous nucleoli and a small rim of cytoplasm. The neoplastic cells are in short chains and the moulding of adjacent nuclei in clusters of tumour cells is very common (fig. 3). Hyperchromatic or pyknotic cells and a necrotic background are other elements useful to confirm the diagnosis. Small cell carcinomas are predominantly TTF-1 positive, CD 56 positive, chromogranin and/or synaptophysin positive, p63 negative, Cytokeratin 5 negative and Cytokeratin 8 positive. Tumour cells closely resembling small cell carcinoma may be observed in pulmonary cytology from children with lung metastases of neuroblastoma, embryonal rhabdomyosarcoma, Ewing’s sarcoma, desmoplastic small round cell tumours, lymphomas, and Wilms' tumours and from adults with metastases of Merkel cell carcinoma, poorly differentiated synovial sarcoma, mixoid/round cell chondrosarcoma.

**Figure 3.** Touch imprint of a transbronchial biopsy showing cells two or three times larger than lymphocytes with nuclei showing a vesicular chromatin pattern, inconspicuous nucleoli and a small rim of cytoplasm. The neoplastic cells are in short chains and the moulding of adjacent nuclei in clusters of tumour cells is evident. The pattern is characteristic of small cell lung cancer.
**Large cell carcinoma** The cytological findings that suggest a diagnosis of large cell carcinoma are: disorganised groups of large pleomorphic cells or giant cells with clear malignant nuclear aspects (prominent nucleoli and coarse granulation of chromatin), intracytoplasmic neutrophils and a necrotic background. A neuroendocrine differentiation documented by immunocytochemistry (chromogranin, synaptophysin and CD56) is observed in a minority of cases.

**Carcinoid** tumours are cytologically usually diagnosed on fine-needle aspiration samples as they rarely, if ever, shed neoplastic cells into the sputum. Cells appear dispersed, isolated, in loosely cohesive groups or in syncytial tissue fragments, as cords, nests or anastomosing ribbons with occasional acinar pattern. They are small and round to cuboidal, with poorly defined cell borders and stippled chromatin. Some pleomorphic large cells with bizarre nuclei may also be detected. Spindle cells are more typical of the peripheral neoplasms. Markers such as chromogranin and synaptophysin are unequivocally positive; TTF-1 is negative. Necrosis and mitoses (or a significant positivity for Ki-67 (MIB-1)) suggest the diagnosis of atypical carcinoid.

**Other malignant epithelial tumours** may be recognised by cytological criteria: adenoid cystic carcinoma (the diagnostic features are the presence of hyaline globules of basement membrane material with intervening small hyperchromatic cells), mucoepidermoid carcinoma and metastases (in these cases, immunocytochemistry may be diriment).

**Lymphoproliferative and myeloid disorders** Primary lymphoid tumours in the lung are rare while lymph node-based lymphomas frequently affect the lung during the course of the disease. Acute myeloid leukaemia (M4–M5) may clinically debut with acute respiratory failure. These malignantities are more readily diagnosed on BAL or fine-needle aspiration preparations. Flow cytometry of suspended cells or immunocytochemistry, mainly on cell block preparations, are the usual ancillary studies required for a more precise definition of the lesions. Primary MALT (mucosa-associated lymphoid tissue) lymphomas in the lung are characterised by noncohesive lymphoid cells with centrocytic, monocytoid or plasmacytoid-like appearances. Flow cytometry is necessary to identify a light chain monoclonal restriction. In addition, other low-grade B-cell lymphomas/leukaemias may be recognised by cytological and flow cytometry analysis. More sophisticated tools are promising regarding specificity and sensitivity; however, they are not yet included in clinical practice. Large B-cell lymphomas and highly malignant natural killer (NK) T-cell lymphomas may be captured by cytological/immunocytochemical analyses, and this may be sufficient to confirm lung recurrence but a cytological diagnosis in primary tumours is not feasible. Typical Reed–Sternberg (bilobed or multilobulated cells with distinct nucleoli and an abundant pale-grey cytoplasm on Diff-Quik or MGG preps) or Hodgkin cells (large mononuclear cells with prominent nucleolus and abundant cytoplasm), which are CD30 and CD15 positive, may be recognised in respiratory specimens associated with reactive, small CD3-positive lymphocytes and scattered eosinophils, and this may confirm the diagnosis of relapse of the tumour in the thorax. Myeloid neoplastic cells have been recognised in acute leukaemia, mainly M4 and M5, and in chronic myelomonocytic leukaemia, but also in other forms, either in BAL fluid or in fine-needle aspiration samples (fig. 4).

**Thymomas**, although rare, are the most common thymic tumours in adults. Cytological findings are: cohesive aggregates of epithelial cells with an associated variable lymphocytic infiltration. Tissue fragments composed of epithelial cell aggregates intimately associated with lymphocytes are called lymphoepithelial complexes, and their presence is generally diagnostic of thymoma. There are two epithelial cell types in thymoma.

1. **Spindle/oval type**, which possesses oval or fusiform, normochromatic nuclei...
with dispersed or unevenly distributed chromatin, indistinct or small nucleoli, and lightly stained or indistinct cytoplasm: type A or mixed (AB) thymoma.

2. Polygonal/round cells, which possess round, normochromatic, often clear nuclei, conspicuous round nuclei, and variable amounts of light green-stained cytoplasm: type B thymoma.

Malignant thymic carcinomas present clear-cut cytological features of malignancy. Immunocytochemistry is useful to highlight epithelial cells or mature and immature lymphocytes.

**Germ cell tumours** The mediastinum is the most common site for the development of extragonadal germ cell tumours. In seminoma, mixed inflammatory cells rich in lymphocytes surround cohesive malignant cells with delicate cytoplasm and a pale nucleus with prominent nucleoli. Embryonal carcinoma has a cytological aspect similar to adenocarcinoma. Yolk sac tumour (endodermal sinus tumour) is characterised by the presence of clusters of epithelial, highly malignant cells containing eosinophilic, PAS-positive, spherical hyaline bodies. Choriocarcinoma can be recognised in aspirates by the presence of large, multinucleated syncytiotrophoblastic cells with eosinophilic cytoplasm. Immunocytochemistry is very useful to mark the β-subunit of human chorionic gonadotropin or α-fetoprotein. Germ cell tumours may be a cause, along with Hodgkin’s disease, of sarcoïd-like granulomas collected by fine-needle aspiration techniques.

**Mesenchymal tumours** Chondroid hamartochondromas may be easily recognised cytologically. In fine-needle aspiration samples, the combination of fibrillar myxoid connective tissue, hyaline cartilage, entrapped bronchiolar epithelium and fat are pathognomonic. The cytological features that are more or less distinctive of other benign or malignant neoplasm of mesenchymal origin (primary in the lung or metastatic) have been described for sclerosing haemangiomata (pneumocytoma), granular cell tumour, solitary fibrous tumour, meningioma, schwannoma, gastrointestinal stromal tumour (fig. 5), neurofibroma, ganglioneuroma, glomus tumour, pulmonary blastoma, ganglioneuroblastoma, melanoma, glioblastoma and a wide variety of sarcomas. Cytology in malignant mesothelioma has been deeply investigated, as collection of pleural fluid is very easy during thoracentesis, and cytological features of malignancy and immunocytological...
markers (calretinin, etc.) indicating the origin of neoplastic cells are now well known.

Further reading

Each day, 10,000–15,000 L of air are inhaled by the respiratory system, air containing microorganisms and pollutants 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 infections (Reynolds, 1997).

The first line of defence against pathogens is represented by the epithelial barrier of the airways. The epithelium is composed of several different cell types, the structural and functional features of which are described in table 1.

Between the epithelium and the lamina propria there is a thin basal membrane, formed by a lamina propria and a lamina reticularis; these two laminae have a different protein compositions, the basal being composed of connective proteins (Bucchieri et al., 2009). Additional protection comes from polypeptide mediators of the innate, non-antibody-mediated host defence, and professional phagocytes. Once innate host defense systems are activated by the cytokine and chemokine pathways, acquired, antibody-mediated immune responses and subsequent tissue repair and remodelling are orchestrated by immunocompetent cells and mediators.

Anatomical barriers

In the upper respiratory tract (URT), the density of microbes is greater than in the lower respiratory tract (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 cleaning the LRT of bacteria is due to mechanical barriers and reflex mechanisms. The nose itself can be considered a first-line barrier. The vibrissae present on the vestibular region of the nasal cavity are able to trap 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 difficult physical barrier system to overcome (Reynolds, 1997). Dichotomous branching and angulation of the airways favour the impact of inhaled particles on the bronchial mucosa surface. At points of impaction, bronchial-associated lymphoid tissue (BALT) is able to interact with inhaled airborne microbes and particles, and to start clearance by phagocytes and immune reactions by immunocompetent cells.
Reflex mechanisms

A number of reflex mechanisms may help the defence of the respiratory tract (Reynolds, 1997). They are made possible by the presence of irritant and stretch receptors on the mucosa of the airways of the URT and of the largest LRT airways.

Sneezing is a complex reflex starting from the irritant receptors in the nose, usually stimulated 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, that is able to eliminate the potentially harmful inhaled particles.

Cough In the tracheobronchial tree, the cough reflex plays a similar role in eliminating foreign inhaled particles. Dyspnoea can also be considered, at least under certain circumstances, 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 defense mechanism (Knowles et al., 2002). Through ciliary function and mucus secretion with proper salt/water components, the airway epithelial surface is able to act to maintain the mucociliary clearance with a mucus ‘escalator’ from the lowest airways to the top. With a mucus layer
distal to the epithelium containing different types of mucins and a largely prevalent aqueous layer beneath this, 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 underlies the importance of the production and secretion into the airway lumen of two components by the airway epithelia: salt-sensitive defensins and a low-salt liquid able to activate defensins.

**Innate defence molecules**

The epithelial lining fluid in the airways contains a myriad of 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, these innate antimicrobial molecules, although with many differences in site and the cell types producing them,

| Table 2. Key antimicrobial factors in epithelial lining fluid and their activities |
|-----------------|-----------------|-----------------|-----------------|
| **Factor**      | **Type of molecule** | **Cell origin** | **Antimicrobial activities** | **Main immunomodulatory activities** |
| **Defensins**   | Peptides         | Phagocytic cells | BC | Mitogenic |
|                 |                  | Lymphocytes     | BS | Chemotactic |
|                 |                  | Airway epithelial cells | AV | Degranulates MCs |
| **Cathelicidins** | Pro-peptides    | Neutrophils     | BC | Downregulation of |
|                 |                  | Monocytes       | BS | TNF-α |
|                 |                  | Monocytes       | AV | Chemotactic |
|                 |                  | Airway epithelial cells | AF | |
| **SLPI**        | Protein          | Macrophages     | BC | Antiprotease |
|                 |                  | Neutrophils     | BS | Anti-inflammatory |
|                 |                  | Airway epithelial cells | AV | |
| **SP-A, SP-D**  | Lipoproteins     | Alveolar type II cells | BC | Opsonic |
|                 |                  | Club cells (Clara cells) | BS | Modulate leukocyte functions |
| **Lactoferrin** | Glycoprotein     | Neutrophils     | BC | Antioxidant |
|                 |                  | Airway epithelial cells | BS | Binds LPS |
| **Lysozyme**    | Enzyme           | Neutrophils     | BC | Unknown |
| **Lactoperoxidase** | Enzyme         | Airway epithelial cells | BC | Antioxidant? |

BC: bactericidal; BS: bacteriostatic; AV: antiviral; AF: antifungal; AP: antiparasitic; MC: mast cell; TNF: tumour necrosis factor; SLPI: secretory leukocyte peptidase inhibitor; SP: surfactant protein; LPS: lipopolysaccharide.
secretory stimuli, and direct and indirect activities (table 2), provide a highly evolutionarily conserved, powerful screen against infections in the naïve host. They also trigger more specific and targeted immune reactions taking place into the airways and in the alveolar structures. In addition, the same molecules have a role as immune modulators, 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 receptors (e.g. Toll-like receptors, NOD-like receptors, scavenger receptors, etc.) on phagocytes, namely macrophages and neutrophils, as well as on 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 complement system, 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. In the normal individual, the vast majority of cells recovered through bronchoalveolar lavage (BAL) are alveolar macrophages. 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. These may be non-immune or immune, i.e. specific immunoglobulins originated by previous immunisation of the host against the pathogen. Opsonins facilitate alveolar macrophage phagocytosis and subsequent bacterial clearance by the intracellular killing systems. The size of the bacterial inoculum, virulence and resistance, and possibly deficits of local immunity mechanisms in the host, may cause the failure, at least in a first round, of host defences. This will cause recruitment of additional phagocytes, such as neutrophils, at sites of infection, and sustain an immune and inflammatory reaction.

Acquired immune reactions with immunoglobulin, 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)
- free immunocompetent cells 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, immunisation can occur at a distant site (e.g. gastrointestinal mucosa) and, by the recirculation of lymphocytes, protection can be provided in the respiratory system. Acquired immune reactions start also in the lung with the interaction between antigens and antigen-presenting cells. In the lung, at least two types of antigen-presenting cell 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 alveolar macrophages the ability to process microbial proteins into small peptide fragments that are then transported on the cell surface together with major histocompatibility complex (MHC) molecules. The complex between the MHC and antigenic epitopes is then presented to T-cells. Antigen presentation is made through the T-cell receptor (TCR) on the T-cell surface.

Antigen presentation initiates the production of immunoenhancing cytokines and chemokines. A part from the interleukins (ILs) and other mediators associated with the
T-helper (Th) type 1 or 2 immune reactions, IL-17 is a pro-inflammatory cytokine mainly produced by T-cells with an important role in induction of a neutrophil-mediated protective immune response against bacteria or fungal pathogens (Matsuzaki et al., 2007; Di Stefano et al., 2009). IL-17 seems to be an example of the crossroads between different host defense mechanisms, as it regulates cell-mediated immunity and induction of antimicrobial peptides, such as defensins. This process of specific immune reaction also promotes adaptive B-cell proliferation and specific immunoglobulin production. The relative proportions of different immunoglobulins in the URT and LRT differ one from each other as well as compared with the blood. Immunoglobulins represent ~10% of total proteins in airway secretions. In the URT, IgA represent the vast majority of this immunoglobulin. Airway IgA is predominantly polymeric: secretory IgA comprises two IgA monomers held together by a joining chain and by another glycoprotein, the secretory component, which is produced by serous and epithelial cells. In contrast with the URT, in the LRT, as detected by BAL, IgG is predominant, representing ~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 figure 1 represents a superb model of how the human body is able to interact efficiently with the external environment in order to preserve its structure and function. Conversely, impairment and/or dysfunction of each of the different components of this system represent the pathogenetic basis for the development of many respiratory disorders. As an example, primary ciliary dyskinesia results in recurrent airway infections, CF is associated with dysfunction of mucociliary clearance and fluid homeostasis, and in chronic colonisation and/or infection of the airways and in inflammatory airway disorders, many different mechanisms undergo changes, enhancement or impairment (Di Stefano et al., 2009; Pignatti et al., 2009).

Further reading

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 aids viral transmission. 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 severe COPD. Cough may also 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 typical patient is middle-aged and female. The cough appears to have no pattern to it but a careful history will often reveal many common features of the presenting complaint. It has been traditional to divide these patients without radiographic abnormalities and no obvious other lung disease into a triad of diagnoses,
namely asthmatic cough, post-nasal drip syndrome (rhinitis) 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 usually 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 post-nasal drip syndrome and reflux cough. Thus, the latter frequently does not conform to the criteria for peptic gastro-oesophageal reflux disease. Because of the commonality of the clinical history in chronic cough (table 2), it has been suggested that there is a single unifying diagnosis of 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 (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 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 (TRP) group (fig. 2). The capsaicin-sensitive ‘hot’ receptor (TRPV1) is upregulated in patients with cough. This is due to pro-inflammatory mediators increasing expression of TRPV1, either in neurones or in other airway tissues. Rather than directly causing a cough, angiotensin-converting enzyme inhibitors alter cough sensitivity by a TRPV1-dependent mechanism, thus explaining the continued irritation long after drug withdrawal. Another TRP receptor, TRPA1, is highly reactive to a

Table 1. Early reports from cough clinics illustrating the variety of cough diagnosis dependent on criteria used

<table>
<thead>
<tr>
<th>Authors</th>
<th>Mean age (years)</th>
<th>Patients (females)</th>
<th>Asthma syndrome</th>
<th>GOR</th>
<th>Rhinitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irwin et al. (1981)</td>
<td>50.3</td>
<td>49 (27)</td>
<td>25</td>
<td>10</td>
<td>29</td>
</tr>
<tr>
<td>Poe et al. (1982)</td>
<td>109 (68)</td>
<td>36</td>
<td>35</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>Poe et al. (1989)</td>
<td>44.8</td>
<td>139 (84)</td>
<td>24</td>
<td>21</td>
<td>41</td>
</tr>
<tr>
<td>Irwin et al. (1990)</td>
<td>102 (59)</td>
<td>102 (59)</td>
<td>25</td>
<td>24</td>
<td>41</td>
</tr>
<tr>
<td>Hoffstein et al. (1994)</td>
<td>47</td>
<td>228 (139)</td>
<td>25</td>
<td>24</td>
<td>41</td>
</tr>
<tr>
<td>O’Connell et al. (1994)</td>
<td>49</td>
<td>87 (63)</td>
<td>6</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Smyrnios et al. (1995)</td>
<td>58</td>
<td>71 (32)</td>
<td>24</td>
<td>15</td>
<td>40</td>
</tr>
<tr>
<td>Mello et al. (1996)</td>
<td>53.1</td>
<td>88 (64)</td>
<td>14</td>
<td>40</td>
<td>38</td>
</tr>
<tr>
<td>Marchesani et al. (1998)</td>
<td>51</td>
<td>92 (72)</td>
<td>14</td>
<td>5</td>
<td>56</td>
</tr>
<tr>
<td>McGarvey et al. (1998)</td>
<td>47.5</td>
<td>43 (29)</td>
<td>23</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Palombini et al. (1999)</td>
<td>57</td>
<td>78 (51)</td>
<td>59</td>
<td>41</td>
<td>58</td>
</tr>
<tr>
<td>Brightling et al. (1999)</td>
<td>91 (0)</td>
<td>31</td>
<td>8</td>
<td>24</td>
<td></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

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

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.issc.info

Table 3. Risk factors for chronic cough

<table>
<thead>
<tr>
<th>Variable</th>
<th>With cough n/N (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>78/1704 (4.6)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>135/2179 (6.2)</td>
<td>1.38 (1.03–1.86)</td>
<td>0.028</td>
</tr>
<tr>
<td>Heartburn</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>148/2990 (4.9)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>65/889 (7.3)</td>
<td>1.51 (1.10–2.06)</td>
<td>0.009</td>
</tr>
<tr>
<td>Regurgitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>158/3314 (4.8)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>54/568 (9.5)</td>
<td>2.10 (1.49–2.92)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IBS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>111/2914 (3.8)</td>
<td>1.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>98/909 (10.8)</td>
<td>3.05 (2.27–4.09)</td>
<td></td>
</tr>
<tr>
<td>BMI category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>74/1547 (4.8)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>72/1448 (5.0)</td>
<td>1.04 (0.74–1.47)</td>
<td>0.86</td>
</tr>
<tr>
<td>Obese</td>
<td>60/776 (7.7)</td>
<td>1.67 (1.15–2.41)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Nonacid reflux symptoms in the form of regurgitation are more closely associated with cough than acid reflux. IBS: irritable bowel syndrome.
wide range of environmental irritants and causes cough in humans. Upregulation of this receptor provides a mechanism for the exquisite hypersensitivity complained of by patients to agonists 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 component of this phenotype of cough hypersensitivity syndrome and, consequently, long-acting β-agonists may be less effective than anti-eosinophilic medication such as leukotriene antagonists. Reflux disease may be very problematical, as much airway reflux is nonacidic and, therefore, not amenable to blockade by proton pump inhibitors. Propomotility agents, such as metoclopramide and domperidone, may be used. Other motility agents, such as erythromycin, azithromycin and magnesium, have also been advocated. Operative treatment via Nissen fundoplication can be effective in intractable coughing. An alternative strategy is to treat the hypersensitivity component with agents such as gabapentin. Finally, the use of central cough suppression in the form of antitussive agents, such as low-dose morphine, can ameliorate cough in a third of patients with otherwise intractable symptoms.

Sputum

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 CF, the increase in sodium reabsorption leads to a reduction in the sol phase of the airway surface liquid. Airway inflammation, particularly that caused by release of enzymes such as myeloperoxidase (which produces the characteristic green colour) and neutral endopeptidase, and by polymorphs, causes alteration of mucin (MUC) gene expression through proteinase-activated receptors. The death of inflammatory cells and bacteria lead to a soup of DNA that cross-links with filamentous actin, producing gelatinous plugs that increase ventilation/perfusion ratio mismatch with resulting systemic hypoxia.

The treatment of mucus hypersecretion 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.

Figure 1. Capsaicin cough challenge in normal subjects, the effect of captopril enhancing cough reflex sensitivity.
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 years showed no effect on decline in lung function or exacerbation rate. In COPD, two agents, azithromycin and roflumilast, have been shown to be efficacious in those with exacerbations of chronic bronchitis.

Perhaps because of the paucity of specific agents for mucus hypersecretion, nonpharmacological therapy in the form of airway clearance techniques is frequently advocated. However, a recent Cochrane review found the quality of randomised studies to be poor and concluded that any benefits achieved may be small (Osadnik et al., 2012).

**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 this is a common presentation of lung cancer, chest radiography is obligatory in patients when presenting with haemoptysis and, in heavy smokers, CT or bronchoscopy is also required. Aspergilloma and TB may similarly cause 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,
Radiographic percutaneous bronchial artery embolisation is the treatment of choice. Vasculitis is a common and frequently missed cause of recurrent haemoptysis and diffuse alveolar haemorrhage. While the systemic connective tissue diseases, such as systemic lupus erythematosus, may produce small-vessel haemoptysis, the commonest cause is microscopic polyangiitis. The perinuclear anti-neutrophil cytoplasmic antibody (MPO ANCA) 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, both congenital and acquired, and including warfarin therapy or thrombocytopenia, will predispose to haemoptysis.

Further reading

Dyspnoea is the major reason for referral for pharmacological treatment and respiratory rehabilitation programmes in patients with 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. More specifically, it has been postulated that dyspnoea arises when there is a conscious awareness of a mismatch between what the brain expects and what it receives in terms of afferent information from the lungs, airways and receptors in the tendons and muscles of the chest wall (fig. 1 and table 1).

Evaluation of dyspnoea during physical tasks

Exertional dyspnoea can be easily defined as ‘the perception of respiratory discomfort that occurs for an activity level that does not normally lead to breathing difficulty’ (Killian et al., 1995). It follows that the intensity 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 when climbing stairs). The Medical Research Council (MRC) dyspnoea scale can be used for this purpose (table 2), as well as other scales such as the Baseline Dyspnoea Index. Dyspnoea can also be evaluated during a physical task, such as cardiopulmonary exercise testing (CPET). For this purpose, the 10-point Borg scale can be used (table 2). 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’. Using the Borg scale, subjects rate the magnitude of their perceived breathing discomfort during exercise. Though

**Key points**

- Dyspnoea is a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity.
- The mechanisms of dyspnoea are complex and multifactorial: there is no unique central or peripheral source of this symptom.
- The sense of heightened inspiratory effort is an integral component of exertional dyspnoea and is pervasive across health and disease.
- The NVD theory of dyspnoea states that the symptom arises when there is a disparity between the central reflex drive (efferent discharge) and the simultaneous afferent feedback from a multitude of peripheral sensory receptors throughout the respiratory system. The feedback system provides information about the extent and appropriateness of the mechanical response to central drive.
- Despite the diversity of causes, the similarity of described experiences of dyspnoea suggests common underlying mechanisms.
somewhat less popular, the visual analogue scale (VAS) is another dyspnoea measuring instrument with proven construct validity during CPET. Both the VAS and Borg scale have been shown to provide similar scores during CPET, and to be reliable and reproducible over time in healthy subjects, and in patients with asthma and COPD undergoing CPET.

Physiology

The recent American Thoracic Society statement has emphasised the multidimensional nature of dyspnoea in the sensory–perceptual (intensity and quality), affective distress and impact domains. 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 interneurons to the sensory/association cortex, which is informed of the increased motor drive to increase ventilation. Volitional respiratory effort in healthy subjects is harmoniously matched with the appropriate increase in flow or volume displacement via concurrent afferent proprioceptive information transmitted via vagal, glossopharyngeal, spinal and phrenic nerves. This information is conveyed to the medulla and central cortex, where it is integrated. The result is a harmonious neuromechanical coupling with avoidance of respiratory discomfort or distress. Reproduced and modified from Scano et al. (2010) with permission from the publisher.
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 ($P_{Imax}$). In healthy subjects, volitional respiratory effort is matched by lung/chest wall displacement (i.e. change in tidal volume ($V_T$) as percentage of vital capacity (VC)) 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 with avoidance of respiratory discomfort or distress (fig. 1 and table 1).

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 (carbon dioxide), 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, the intensity of which depends on a mismatching between the level of chemically stimulated drive and ongoing inhibition from pulmonary mechanosensors 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 qualitative descriptor clusters of dyspnoea are commonly selected by patients with COPD during physical activity. The descriptor cluster that alludes to increased respiratory work/effort (‘breathing requires more effort or work’) is commonly selected by patients with COPD. Increased sense of work/effort is related to the increased motor drive to the respiratory muscles and increased central neural drive (due to chemostimulation) as a consequence of progressive metabolic and ventilation/perfusion disruptions during exercise. Therefore, increased perceived work/effort during physical activity, in part, reflects the greater ventilatory demand for a given task compared with health. In addition, contractile muscle effort is increased for any given ventilation because of:

<table>
<thead>
<tr>
<th>Table 1. Putative neurophysiological basis of exertional dyspnoea</th>
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</thead>
<tbody>
<tr>
<td><strong>Central (corollary discharge)</strong></td>
</tr>
<tr>
<td>↑ motor drive (inspiratory effort): cortical</td>
</tr>
<tr>
<td>↑ reflex drive (chemical, neural): medullary</td>
</tr>
<tr>
<td><strong>Peripheral (afferent activity)</strong></td>
</tr>
<tr>
<td>Airway/lung receptors (pulmonary stretch receptors, C-fibres, J-receptors)</td>
</tr>
<tr>
<td>Ventilatory muscle receptors (muscle spindles, Golgi tendon organs, joint receptors, type III and IV mechano- and metaboreceptors in the diaphragm and chest wall muscles)</td>
</tr>
<tr>
<td>Peripheral chemoreceptors</td>
</tr>
<tr>
<td>Locomotor muscles receptors (type III and IV afferents)</td>
</tr>
</tbody>
</table>

The most important receptors (afferences) and efferences to respiratory and locomotor muscles involved in the putative pathogenesis of exertional dyspnoea in cardiopulmonary disease. Please see the main text for more details.
1) the acutely increased intrinsic mechanical (elastic/threshold) loading; and

2) functional respiratory muscle weakness.

These respiratory mechanical/muscular abnormalities are, in part, related to resting and dynamic hyperinflation during exercise, and may lead to either a decrease in $P_{\text{Imax}}$ or a further increase in $P_{\text{oes}}$ as percentage of $P_{\text{Imax}}$. Because of these effects, greater neural drive or electrical activation of the respiratory muscle is required to generate a given force. Furthermore, because of limbic system activation, the corollary discharge may be sensed as abnormal, thus evoking a sensation of distress (fig. 1 and table 1).

The other descriptor cluster alludes to unsatisfied inspiration. Structural abnormalities (chronic bronchitis and emphysema), via their negative physiological consequences, i.e. expiratory flow limitation and dynamic hyperinflation, result in dyspnoea. A patient’s physical activity is indeed characterised by a growing mismatch between increase in central neural output to the respiratory muscles and the blunted respiratory mechanical/muscular response (lung/chest wall displacement). This mismatch, which we call neuroventilatory dissociation (NVD), has been proposed to be, at least in part, the neurophysiological basis of the perceived unsatisfied inspiration. 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

Table 2. The MRC dyspnoea scale and the Borg scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MRC dyspnoea scale</strong></td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td>5</td>
<td>Too breathless to leave the house or breathlessness when dressing or undressing</td>
</tr>
<tr>
<td><strong>Borg scale</strong></td>
<td></td>
</tr>
<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>Very severe breathlessness</td>
</tr>
<tr>
<td>7</td>
<td>Very, very severe (almost maximum)</td>
</tr>
<tr>
<td>8</td>
<td>Maximum</td>
</tr>
<tr>
<td>9</td>
<td>Maximum</td>
</tr>
<tr>
<td>10</td>
<td>Maximum</td>
</tr>
</tbody>
</table>
dyspnoea (fig. 2). In particular, patients experience intolerable dyspnoea during exercise because VT expansion is constrained from below (by the effects of dynamic lung hyperinflation or the already critically reduced resting inspiratory capacity), as there is no space to breathe. This so-called dyspnoea threshold seems to be at the level at which the inspiratory reserve volume (IRV) critically approaches 0.5 L. Once this critical IRV is achieved, further expansion in VT is negated, the effort–volume displacement ratio ($P_{oes}/P_{Imax}$ divided by $VT/VC$) increases sharply and dyspnoea intensity rises steeply to intolerable levels. The data support the central importance of mechanical restriction in causing dyspnoea in COPD patients.

**Neuromuscular disorders** Patients with neuromuscular disorders (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. 3).

**Interstitial lung disease** As in COPD, restrictive dynamic respiratory mechanics limits the ability of patients with interstitial lung disease (ILD) to increase ventilation in response to the increased metabolic demands of physical tasks. One of the characteristic features of ILD is a reduction in lung compliance and lung volumes. This has two major consequences.

1. Greater pressure generation is required by the inspiratory muscles for a given VT.
2. The resting TLC and IRV are often diminished compared with health.

Therefore, VT expansion is constrained from above early in exercise (reflecting the reduced TLC and IRV), which results in greater reliance on increasing 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/unsatisfied inspiration and rapid shallow breathing. Because of increases in both dynamic elastance and efferent respiratory drive, inspiratory difficulty/unsatisfied inspiration may have its neurophysiological basis in the conscious awareness of a dissociation between the increased drive to breathe (and concurrent increased respiratory effort, i.e. $P_{oes}/P_{Imax}$) and the restricted mechanical response of the
respiratory system (i.e. Vt/VC), i.e. the inability to expand Vt 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** 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 time 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 their lungs to the same extent as those obese subjects who deflate their lungs, with both volume subgroups reaching similar dyspnoea scores. In ‘hyperinfilters’, dynamic hyperinflation, along with a decrease in IRV, 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 EELV has three important consequences linked together during exercise:

1) Decrease in expiratory reserve volume
2) Dynamic airway compression
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.

**Effects of interventions on dyspnoea**

Effective improvement in exertional dyspnoea represents one of the most challenging targets of management in patients with cardiopulmonary disease. Traditionally, the approach to improving exertional dyspnoea in all of the major cardiopulmonary diseases involves interventions that:

1) reduce ventilatory demand (by reducing the drive to breathe);
2) improve ventilatory capacity;
3) improve respiratory mechanics (by reducing the mechanical load);
4) increase the functional strength of weakened ventilatory muscles;
5) address the affective dimension of dyspnoea; and
6) any combination of the above.

It is of note that interventions should be selected based on the underlying pathophysiological background of the specific disease under examination and may differ from one disease to another. However, multiple interventions are generally required...
and appear to have additive or synergistic effects.

Some of these interventions include the following.

- Bronchodilators
- Oxygen
- Heliox
- Exercise training
- Biventricular pacing (specific for CHF patients)
- Biofeedback techniques
- NIV
- Lung volume reduction surgery and related endoscopic techniques
- Various combinations of these

All of the above strategies have proven to provide beneficial sensory consequences in a variety of patients with cardiopulmonary diseases.

In selected patients, interventions such as opiates (oral and inhaled) reduce respiratory drive and alter affective components of dyspnoea. Recently, it has been shown that inhaled furosemide may modulate respiratory sensation by altering afferent inputs from vagal receptors within the lungs. Psychological counselling, cognitive/behavioural modification and anxiolytics can have favourable influences on the affective dimension of chronic dyspnoea.

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 and rapid breathing) for exertional dyspnoea in patients with restrictive and obstructive syndromes raises the intriguing possibility that they share some common underlying mechanisms.

Further reading


Chest pain

Matthew Hind

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 the triage of patients attending emergency rooms. Questions are typically asked about the character, location, radiation, severity, exacerbating and relieving factors, and relationship to movement such as breathing or coughing. Objective assessment using a questionnaire, such as the McGill Pain score (Melzack, 1975) 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 neurons synapse with spinothalamic fibres that ascend, cross the spinal cord and terminate in the contralateral ventroposterior thalamic nucleus. Thalamocortical 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 with movement such deep respiration. The pain is often unilateral, reflecting the site of 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. Costochondritis and Tietze’s syndrome are inflammatory

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.
disorders of thoracic joints that present with chest wall 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 scanning. 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 or rib fractures. Contrast CT 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 the evaluation of ‘bony’ pain. MRI examination is of particular use in visualising nerve roots. Direct endoscopic visualisation of either the upper gastrointestinal tract (oesophagogastrroduodenoscopy) or major airways (bronchoscopy) allows epithelial inspection and offers the opportunity for direct microbiological, cytological and histological sampling.

Management of chest pain is clearly influenced by the underlying disease. It is, however, essential to provide adequate analgesia not only to alleviate suffering but prevent secondary complications such as pneumonia. The use of a pain ladder, starting with simple analgesics such as paracetamol and nonsteroidal anti-inflammatory drugs escalating to mild then stronger opiates, follows guidance by the World Health Organisation (WHO) for management of cancer pain but is also extremely useful for noncancer pain. Topical analgesia, such as capsaicin creams or infiltration of local anaesthetic, are particularly useful following thoracic surgery. The use of adjuvants, to calm fear and anxiety, can be considered at each step of the pain ladder. Tricyclic antidepressants together with anticonvulsants can be particularly helpful in neuropathic pain. Nonpharmacological management, such as radiotherapy for painful bony metastasis, can also be extremely useful. It is essential drugs are given ‘by the clock’ rather than ‘on demand’. The three-step approach advocated by WHO of administering the correct drug, at the correct dose, at the correct time is inexpensive and 80–90% effective.

Further reading
Physical examination

Martyn R. Partridge

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.

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 as well as in those with established disease, and we need to bear this list in mind when examining the patient. The patient with COPD 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 and breathlessness

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

Key points

- It is essential to bear in mind that breathlessness can have a variety of causes.
- Physical examination should follow the taking of the medical history and differential diagnoses, and is an opportunity to confirm normality or discover abnormality.
- Physical examination comprises inspection, palpation, auscultation and percussion.
- The respiratory physician must not forget that disease of other systems may also be the cause of the symptoms and that comorbiditiy is common.
Inspection

On inspection, the key points to observe are as follows.

- General appearance (breathlessness or cachexia)
- Respiratory rate
- Appearances of the hand (finger clubbing (fig. 2), tremor, tobacco staining or flapping tremor suggestive of carbon dioxide retention)
- Does the chest wall move symmetrically?
- Are there any chest wall deformities (scoliosis or pectus excavatum) or scars (figs 3 and 4)?
- Are there any abnormal vessels suggestive of superior vena cava obstruction (fig. 5)?
- 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

Remember that inspection of relevance to the respiratory system involves more than inspection of the chest itself, for example, one should note erythema nodosum (fig. 6) or gynaecomastia (fig. 7).

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.

Table 1. Breathlessness: differential diagnosis according to onset

<table>
<thead>
<tr>
<th>Onset</th>
<th>Differential diagnosis</th>
</tr>
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<tbody>
<tr>
<td>Within minutes</td>
<td>Pulmonary embolus</td>
</tr>
<tr>
<td></td>
<td>Pneumothorax</td>
</tr>
<tr>
<td></td>
<td>MI</td>
</tr>
<tr>
<td></td>
<td>Cardiac rhythm disturbance</td>
</tr>
<tr>
<td></td>
<td>Dissecting aneurysm</td>
</tr>
<tr>
<td></td>
<td>Acute asthma</td>
</tr>
<tr>
<td>Over hours or days</td>
<td>Pleural effusion</td>
</tr>
<tr>
<td></td>
<td>LVF (LV dysfunction or valve dysfunction or septal rupture post-MI)</td>
</tr>
<tr>
<td></td>
<td>Asthma</td>
</tr>
<tr>
<td></td>
<td>Blood loss</td>
</tr>
<tr>
<td></td>
<td>Lobar collapse</td>
</tr>
<tr>
<td></td>
<td>Respiratory muscle weakness (Guillain–Barré syndrome)</td>
</tr>
<tr>
<td>Over weeks</td>
<td>Infiltration (malignancy, sarcoidosis, fibrosing alveolitis, extrinsic allergic alveolitis, eosinophilic pneumonia)</td>
</tr>
<tr>
<td></td>
<td>Respiratory muscle weakness (motor neurone disease)</td>
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MI: myocardial infarction; LVF: left ventricular failure; LV: left ventricular; SBE: subacute bacterial endocarditis.
Figure 1. Diagnosis and management of respiratory disease. ACE: angiotensin-converting enzyme; LV: left ventricular; DVT: deep vein thrombosis; FH: family history; VTE: venous thromboembolism.
Determining the position of the trachea by inserting the index and middle fingers in the suprasternal notch.

Examining the cervical and supraclavicular lymph nodes for enlargement.

Assessing vocal fremitus by asking the patient to loudly and deeply repeat the words ‘ninety-nine’ while 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 a stroke from the wrist;
- strike firmly at right angles upon the finger of the other hand, which lies along the intercostal space; and
- do so in a symmetrical manner, systematically comparing both sides of the chest at a point equidistant 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 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 polyphonic and bilateral, as in asthma or COPD, or monophonic and localised, as may be found in cases of lung cancer, 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 a more definite sign; to elicit this, one asks the patient to whisper ‘ninety-nine’ and, when it is present, such as 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, while 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.

Further reading

Ventilation is constrained by the mechanical properties of the airways, lung and chest wall. The latter two determine the volume at which the movement of gas is accomplished at rest and in daily activities such as exercise, phonation, laughing, changes in body posture, etc. However, when cardiopulmonary disease is present, 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 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. Sports like swimming are associated with an increase in TLC as a result of an increase in inspiratory muscle force.

**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.
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 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 and cardiac failure), chest wall stiffness (e.g. neuromuscular diseases, obesity, ascitis and pregnancy) or thoracic space competition (e.g. pleural effusions and pneumothorax).

Measuring TLC is of great importance in clinical practice, as it allows the identification of 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, for the most part, 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 or reduced lung elastic recoil.

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 the chest wall. Additional mechanisms may dynamically contribute to the elevation of 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 not exceed the critical pressure necessary to generate maximal flow, thus allowing EFL to occur late in expiration and at a lower lung volume. Secondly, some airways could close near TLC early in expiration as a result of disease, thus preventing the subtending alveolar units from emptying and contributing to the increase in RV.
In addition, the effects of volume history of the manoeuvre preceding the expiration may 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 airway 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 et al. (1968), the effects of volume history on airway size depend on the mechanical characteristics of the 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.

Figure 3. Effects of deep breath on maximum expiratory flow and residual volume according to the relative hysteresis theory of Froeb et al. (1968). a) Pressure–volume loops of lung parenchyma and airways on inspiration (insp) and expiration (exp). The area inside the loop is called hysteresis. b) Partial and maximal flow–volume loops (dotted and continuous lines, respectively). Upper panels: 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 as the partial manoeuvre. Middle panels: 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 manoeuvre than after a partial manoeuvre. Lower panels: 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.
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 achieved at a higher volume. This is what presumably occurs in chronic airflow obstruction or severe asthma. 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, and the VC measured during a forced expiratory manoeuvre (PVC). 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 performed in a seated or upright position (fig. 1). Its mechanical determinants are the inward elastic recoil of the lung and the opposing outward recoil of the chest wall (fig. 2). In the 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 one 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 and cardiac diseases) or in chest wall elastance (e.g. in chest wall and pleural diseases, respiratory muscle paralysis, and obesity). This is important, as reduced FRC is associated with hypoxaemia and, in obesity, with increased airway responsiveness.

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 allow 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 expense 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 causing dyspnoea together with the increase in EILV near TLC.

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 is >1 Hz.

Conclusions

Measuring lung volumes is now an integrative part of lung function assessment. In addition to assisting 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.

Further reading

Respiratory mechanics

Daniel Navajas and Ramon Farré

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 the inspiratory muscles. The net inward elastic recoil of the total respiratory system ($P_{rs}$), the sum of $P_L$ and $P_{CW}$, tends to return the system to the overall equilibrium volume.

Key points

- $P_{alv}$ is lower and higher than $P_{ao}$ during inspiration and expiration, respectively.
- The lungs exert inward elastic recoil that increases with $V_L$.
- Body plethysmography allows the measurement of both $R_{aw}$ and $V_L$.
- The FOT allows the measurement of respiratory resistance during spontaneous breathing with minimum patient collaboration.
- Respiratory mechanics can be monitored in sedated mechanically ventilated patients performing post-inspiratory and post-expiratory pauses.
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

$$R_{aw} = \frac{P_{mo} - P_{alv}}{V'}$$

where $V'$ is the gas flow. In healthy adults, $R_{aw}$ measured at FRC is $\sim 2$ 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 ($G_{aw}$):

$$G_{aw} = \frac{1}{R_{aw}}$$

Since large lungs have wider airways, the specific airway resistance ($sR_{aw}$) computed as

$$sR_{aw} = R_{aw} \cdot FRC$$

provides a resistance measurement normalised for differences in lung size. Similarly, specific airway conductance ($sG_{aw}$) is defined as

$$sG_{aw} = \frac{G_{aw}}{FRC}$$

**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. $P_{mo}$ 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, 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 ($k$) 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, $P_{alv} \approx P_{mo}$ and

$$k = \frac{P_{alv}}{P_{box}}$$

Therefore,

$$R_{aw} = \frac{P_{alv}}{V'} = \frac{k \cdot P_{box}}{V'}$$

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

![Figure 2. Measurement of $R_{aw}$ by body plethysmography.](image)
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 Raw. An added advantage of this technique is that it provides a FRC measurement for the computation of sRaw. However, the device is bulky and expensive, and is not suited to measurement in supine patients.

Interrupter technique

Raw can also be measured outside the box with a pneumotachograph–shutter system. The subject breathes at rest through the pneumotachograph. 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, Raw can be computed as the ratio between the flow just before occlusion and the Pmo recorded during flow interruption. Raw is usually computed as the mean of flow interruptions performed in several breathings.

The interrupter technique can be implemented in handheld devices and requires only minimal patient cooperation. However, due to progressive equilibration between Pmo and Palv, the computed value of Raw depends on the time lag between the start of occlusion and Pmo measurement. Slow pressure equilibration in patients with airflow obstruction results in an underestimation of Raw.

Forced oscillation technique

In addition to Raw, lung and chest wall tissues also exhibit resistive load because of internal frictional resistance to motion. Resistance of the total respiratory system (Rrs) is the sum of Raw and tissue resistance. The tissue component of Rrs is generally small in comparison with Raw.

Rrs 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. Rrs 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 (Xrs) 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 supine. Changes in Rrs 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 Pl–Vl relationship. Lung deformability is measured as lung compliance (CL), defined as the change in volume divided by the change in pressure:

\[ CL = \frac{\Delta V_l}{\Delta P_l} \]

\( \Delta V_l \) can readily be measured with a spirometer connected to the mouth. The measurement of \( \Delta P_l \) requires the simultaneous recording of Ppl and Palv. Ppl is usually estimated from the oesophageal pressure (Poes) recorded with a small balloon attached to the tip of a catheter introduced through the nose into the lower oesophagus. Palv 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 $CL$ decreasing markedly with volume. $CL$ is habitually computed in the range of tidal volume at rest (between FRC and FRC + 0.5 L). In the normal adult, $CL$ is $≈0.2$ L·hPa$^{-1}$. The elastic behaviour of the lung can also be characterised by lung elastance ($EL$), defined as the reciprocal of $CL$:

$$EL = \frac{1}{CL}$$

Chest wall compliance ($CCW$) is computed as

$$CCW = \frac{AV_L}{AP_{CW}}$$

In healthy subjects, the value of $CCW$ is comparable to that of $CL$. Since the elastic pressure of the respiratory system is $P_{rs} = P_L + P_{CW}$, the compliance of the respiratory system ($CRs$) is related to $CL$ and $CCW$ as

$$\frac{1}{CRs} = \frac{1}{CL} + \frac{1}{CCW}$$

$CRs$ and $CCW$ 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 ($ERS$ and $RS$, respectively) of the respiratory system is

$$P_{ao} = RS \cdot V + ERS \cdot V$$

where $V$ is volume. $RS$ and $ERS$ 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, $RS$ and $ERS$ 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 $P_{h}$, followed by a slow decay to a plateau ($P_{s}$). The sudden decrease in $P_{ao}$ is associated with the resistive load of the airways. Therefore, $ Raw $ is estimated as

$$Raw = \frac{P_{max} - P_{s}}{V'}$$

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 ($P_{max} - P_{s}$).

The additional performance of a post-expiratory pause allows $ERS$ 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 ($P_{Emax}$) is measured at TLC. Maximum inspiratory pressure measurements ($P_{Imax}$) 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.
Further reading

Gas transfer: $TLCO$ and $TLNO$

J. Mike Hughes

Transfer factor of the lung for carbon monoxide

Apart from spirometry, the transfer factor of the lung for carbon monoxide ($TLCO$) is the most frequently performed pulmonary function test. It focuses on the integrity of the alveolar (gas exchanging) part of the lung. $TLCO$ can detect abnormalities limited to the pulmonary microcirculation, the only routine test that can do so. It helps to think of $TLCO$ as a measure of the anatomy of the alveolar region, whereas blood gas measurements ($P_{aO_2}$ and $P_{aCO_2}$) measure a physiological efficiency, which involves airways and larger blood vessels, as well as alveolar structures. For example, $TLCO$ is normal in asthma (alveoli are uninvolved), but the $P_{aO_2}$ may be considerably reduced.

Definition

The transfer factor (called $DLCO$ in North America) measures the surface area available for gas exchange. It is closely related to the oxygen diffusing capacity. $TLCO$ is the quantity of inhaled carbon monoxide absorbed, per unit time and per unit carbon monoxide partial pressure. The pressure gradient is the alveolar–plasma carbon monoxide tension ($PCO$) difference. Carbon monoxide is chosen for alveolar–capillary exchange because, after diffusing into capillary blood, carbon monoxide binds to Hb as carboxy-Hb ($HbCO$), but at an extremely low partial pressure ($PCO$). Plasma $PCO$ is so low that it is not usually measured, but it may reach significant levels in current smokers. Carbon monoxide uptake is independent of blood flow, but it is dependent on the number of Hb-binding sites, i.e. on capillary volume, as well as molecular diffusion across the alveolar–capillary membranes. ‘Transfer’ is the better term, because chemical reaction as well as ‘diffusion’ is involved.

Technique

Nearly all clinical laboratories use the single-breath technique of Ogilvie et al. (1957). The $TLCO$ is measured during a 10-s breath-hold at maximal inspiration (this volume is the TLC). Breath-holding at TLC optimises the distribution of the inhaled marker gases (helium (or another insoluble gas such as methane ($CH_4$)) and carbon monoxide), and makes $TLCO$ independent of ventilation distribution. The breathing manoeuvre is shown in figure 1. The subject is asked to:

- exhale slowly to residual volume;
- make a signal;
- inspire rapidly to full inflation;
- hold their breath.

The breath-hold is assisted by automatic closure of the inspiratory and expiratory valves for a pre-set time (9–11 s), after which

Key points

- $TLCO$ measures alveolar function.
- $TLCO$ is the product of $KCO$ and $VA$.
- $KCO$ (or $TL/VA$) is the more specific index of alveolar integrity.
- $KCO$ is low in emphysema and fibrosis.
- $KCO$ is high in extrapulmonary restriction.
exhalation occurs rapidly (there is no need for a forced expiration) and an alveolar sample is taken, from which water vapour and carbon dioxide are absorbed before helium and carbon monoxide concentrations are analysed. The effective breath-hold time is calculated according to Jones et al. (1961) (fig. 1).

Calculation of the Tlco

The key point is that the Tlco is the product of two measurements, the alveolar volume (VA) and the rate of alveolar uptake of carbon monoxide, given by the slope (kco) of alveolar uptake of CO (fig. 2), equivalent to the transfer coefficient of the lung for carbon monoxide (Kco). During the breath-hold at maximal inspiration, VA should equal TLC minus the anatomical dead space (97–98% of the TLC). In practice, VA in normal subjects is 93.5% of TLC ± 6.6% (Roberts et al., 1990). The 10-s breath-hold is insufficient time for complete gas mixing; in airflow obstruction, the measured VA may be much less than 80% of the actual TLC (measured by multi-breath gas dilution or plethysmography).

The kco is the rate of alveolar uptake of carbon monoxide 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*), Kco/Pb* = kco (min⁻¹.kPa⁻¹). The final step in the calculation of Tlco is the multiplication of kco by VA (in mmol: 1 mmol = 22.4 mL standard temperature, pressure and dry).

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**Figure 1. Tlco set-up and breathing protocol.** The breath-hold time is set automatically, and is calculated from 0.33 × inspired time to the time after 1 L of expiration. FACO: alveolar carbon monoxide fraction; FAre: alveolar helium fraction; RV: residual volume.
The next step is the division of $T_{LCO}$ by $V_A$ in L (body temperature, pressure, saturated at 37°C, not mmol):

$$\frac{T_{LCO}}{V_A} = K_{CO} \text{ (mmol·min}^{-1}·\text{kPa}^{-1})$$

but the units only differ from $k^{\text{CO}}$ by a constant factor except for small variations in $P_{O_2}$, ($K_{CO}/k^{\text{CO}} \sim 37$). Thus, $T_{LCO}/V_A (=K_{CO})$ remains, in essence, the rate constant for alveolar carbon monoxide uptake. This terminology is confusing (Hughes et al., 2012) because the impression is given that $T_{LCO}/V_A (=K_{CO})$ ‘corrects’ the $T_{LCO}$ for variations in $V_A$. Unfortunately, this is not the case, and with normal lung structure $K_{CO}$ at 50%, TLC predicted (as % of $K_{CO}$ at predicted TLC) is 150% not the 100% required by an accurate volume ‘correction’.

If $V_A$ remains constant, $T_{LCO}$ and $K_{CO}$ will change equally (as % predicted). There are formulae to correct $T_{LCO}$ for anaemia, so the Hb level should always be known. Smoking raises plasma $P_{CO}$ (a ‘back pressure’ effect) and produces HbCO, displacing HbO₂ (an ‘anaemia’ effect), so smoking should be prohibited for 12–24 h before testing. Oxygen breathing with an increase in alveolar oxygen tension ($P_{AO_2}$) reduces $T_{LCO}$ and $K_{CO}$ by competitive antagonism between oxygen and carbon monoxide; it is the basis of the Roughton–Forster equation which partitions $1/T_{LCO}$ (transfer resistance) into $1/D_M$ (alveolar–capillary membrane diffusion resistance) and $1/0V_{c}$ (transfer resistance of red cells).

**Figure 2.** $T_{LCO}$: carbon monoxide and helium analysis. Carbon monoxide and helium concentrations versus breath-hold time to illustrate the origin and calculation of the two components (slope of the transfer coefficient of the lung for CO ($k_{CO}$) and alveolar volume ($V_A$)) from which $T_{LCO}$ is derived. $CO(i)$ and $CO(t)$ are carbon monoxide concentrations inspired ($i$) and after exhalation (with dead space discard) at time $t$ after breath-hold (the same for $He(i)$ and $He(t)$). $CO(a)$ is the calculated alveolar concentration at breath-hold start before alveolar uptake has begun. $V_i$: inspired volume. $V_{Danat}$: anatomic dead space.
When VA is reduced and lung structure (or the remaining lung structure) is normal, \( \text{TlCO} \) and \( \text{KCO} \) change in opposite directions (table 1) if the cause is:

- reduced alveolar expansion, e.g. extrapulmonary restriction, or
- a reduction in aerated alveolar units, e.g. pneumonectomy or consolidation or atelectasis.

Other causes of a reduced VA are: 1) diffuse alveolar damage (emphysema or fibrosis) (\( \text{TlCO} \) and \( \text{KCO} \) both reduced), and 2) airflow obstruction (VA low due to poor gas mixing), where \( \text{TlCO} \) and \( \text{KCO} \) are variable, being low in emphysema and normal or high in asthma.

**Implications of \( \text{KCO} \times \text{VA} = \text{TlCO} \)**

Transfer coefficient of the lung \( \text{Tl/VA} \) does not correct \( \text{TlCO} \) for a low VA because \( \text{Tl/VA} \) often rises when VA falls. \( \text{Tl/VA} \) is equivalent to \( \text{KCO} \), the rate constant for alveolar uptake of CO.

The same \( \text{TlCO} \) (say 60% predicted) can arise from different combinations of \( \text{KCO} \) and VA, such as: 1) high \( \text{KCO} \) and low VA (extrapulmonary restriction); 2) low \( \text{KCO} \) and normal VA (pulmonary vasculopathy); or 3) low-ish \( \text{KCO} \) and low-ish VA (fibrosis) (table 2).

**Transfer factor of the lung for nitric oxide**

The transfer factor of the lung for nitric oxide (\( \text{TlNO} \)) was introduced into clinical medicine by Guenard et al. (1987) and Borland et al. (1989). The methodology and calculations are the same as the \( \text{TlCO} \), and both tests can be performed simultaneously in one single-breath manoeuvre. The rate of alveolar uptake of nitric oxide (\( \text{KNO} \)) is 4–5 times faster than \( \text{KCO} \), so the breath-hold time may have to be reduced to 5–6 s unless a very sensitive nitric oxide analyser is used. The faster uptake of

### Table 1. Physiological influences on the \( \text{TlCO} \) and the \( \text{KCO} \)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>( \text{TlCO} ) % pred</th>
<th>( \text{KCO} ) % pred</th>
<th>( \text{VA} ) % pred</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac output increase</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{PAO}_2 ) increase</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{VA} \downarrow ) (reduced alveolar expansion)</td>
<td>↓</td>
<td>↑↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{VA} \downarrow ) (reduction in no. of aerated units)</td>
<td>↓</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( \text{PAO}_2 \): alveolar oxygen tension.

### Table 2. Different combinations of \( \text{KCO} \) and \( \text{VA} \) but a similar \( \text{TlCO} \)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>( \text{TlCO} ) % pred</th>
<th>( \text{KCO} ) % pred</th>
<th>( \text{VA} ) % pred</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspiratory muscle weakness</td>
<td>59</td>
<td>120</td>
<td>50</td>
<td>Lack of alveolar expansion</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>58</td>
<td>111</td>
<td>51</td>
<td>Localised loss of lung units</td>
</tr>
<tr>
<td>Diffuse interstitial lung disease</td>
<td>54</td>
<td>84</td>
<td>66</td>
<td>Alveolar capillary damage (± loss of units)</td>
</tr>
<tr>
<td>Emphysema</td>
<td>54</td>
<td>59</td>
<td>91</td>
<td>Alveolar capillary damage (FEV1/FVC ratio reduced)</td>
</tr>
<tr>
<td>Idiopathic PH</td>
<td>56</td>
<td>58</td>
<td>96</td>
<td>Microvascular damage (FEV1/FVC ratio normal)</td>
</tr>
</tbody>
</table>

% pred: % predicted; PH: pulmonary hypertension; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; Reproduced and modified from Hughes et al. (2012).
Nitric oxide is due to a two-fold (versus carbon monoxide) increase in diffusivity through the alveolar–capillary membranes, and a faster reaction with red blood cell Hb than carbon monoxide. The $\text{TLNO}/\text{TLCO}$ and $\text{KNO}/\text{KCO}$ ratios (they are identical since $\text{VA}$ is common to both measurements) are 4.3–4.9 in normal subjects. The $\text{TLNO}$ is less sensitive to physiological changes in the pulmonary circulation than the $\text{TLCO}$; the $\text{TLNO}$ is independent of changes in haematocrit and $\text{PAO}_2$. The $\text{TLNO}/\text{TLCO}$ ratio is reduced in alveolar under expansion and may be a marker of extrapulmonary restriction; it is expected to be reduced in chronic heart failure. Further research is needed to see whether the $\text{TLNO}/\text{TLCO}$ ratio has a role in pulmonary function testing (Hughes et al. 2013).

**Further reading**

- Hughes JMB, et al. (2012). Examination of the carbon monoxide diffusing capacity ($\text{DL(CO)}$) in relation to its $\text{KCO}$ and $\text{VA}$ components. *Am J Respir Crit Care Med*; 186: 132–139.
Control of ventilation

Brian J. Whipp† and Susan A. Ward

The ventilatory control system is highly complex, involving:

- transmission of primary humoral stimuli from their sites of generation to the sensing elements;
- integration of chemoreceptor afferent activity within brainstem ‘respiratory centres’;
- generation of respiratory motor-discharge patterns;
- neuromuscular transmission at the respiratory muscles; and
- generation of appropriate pulmonary pressure gradients to produce the required airflow and ventilation.

Consequently, while 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 responses should be made in the context of the entire ‘input–output’ relationship. Individuals with increased airway resistance or impaired respiratory muscle function, for example, may have an abnormally low overall ventilatory carbon dioxide or hypoxic response despite normal chemoreflex responsiveness.

Ventilatory response to inhaled carbon dioxide

The relationship between \( V' E \) and arterial (a) or alveolar (A; typically end-tidal (ET)) carbon dioxide tension (\( PCO_2 \)), 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 carbon dioxide responsiveness. The resulting \( V' E-\text{PETCO}_2 \) relationship is typically linear in healthy, normoxic individuals, with a slope \( (\Delta V' E/\Delta \text{PETCO}_2) \) averaging \( \sim 2-3 \text{ L·min}^{-1}·\text{mmHg}^{-1} \). This slope reflects the carbon dioxide responsiveness of

Key points

- Ventilatory carbon dioxide responsiveness is determined as the slope of the linear iso-oxic \( V' E-\text{PETCO}_2 \) relationship \( (\Delta V' E/\Delta \text{PETCO}_2) \), using steady-state, constant-concentration inspirates or hyperoxic rebreathing. \( \Delta V' E/\Delta \text{PETCO}_2 \) reflects central and, if \( PaO_2 \) is not excessive, also carotid chemoreceptor activity. Being appreciably shorter, the latter test is preferred, although \( \Delta V' E/\Delta \text{PETCO}_2 \) reflects only central chemoreflex activity.

- Ventilatory hypoxic responsiveness is determined from the curvilinear isocapnic \( V' E-\text{PETO}_2 \) response, using steady-state, constant-concentration inspirates or rebreathing. It reflects solely carotid chemoreceptor activity. Expressing \( V' E \) versus \( SaO_2 \) linearises the profile, with the slope \( (\Delta V' E/\Delta SaO_2) \) providing the hypoxic responsiveness index (however, \( PaO_2 \), not \( SaO_2 \), is the actual stimulus). This can also be estimated using the Dejours hypoxia-withdrawal test: abrupt oxygen administration from a prior hypoxic background acutely suppresses carotid-body activity to cause a transient, rapid \( V' E \) decline; the maximum decrease as a fraction of the total hypoxic \( V' E \) providing the hypoxic index.
both the central ‘chemoreceptors’, located predominantly on the ventral medullary surfaces and also, if \( P_aO_2 \) is not excessive, the peripheral chemoreceptors (predominantly, if not exclusively, the carotid bodies in humans).

At \( P_aO_2 \) 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 carbon dioxide responsiveness increases with reductions of \( P_aO_2 \) below normal, \( \Delta V'E/\Delta P_{ETCO_2} \) increases with greater, constant degrees of hypoxaemia and decreases with greater, constant degrees of hyperoxia. This results in a ‘fan’ of hypoxia-dependent carbon dioxide response slopes reflecting altered response ‘sensitivity’ (also termed ‘potentiation’), with little or no change in the extrapolated \( V'E \) intercept on the \( P_{CO_2} \) axis (fig. 1). By contrast, sustained metabolic acidemia or alkalaeemia results in a parallel shift by the carbon dioxide response relationship (i.e. no change in carbon dioxide ‘sensitivity’) with a reduced or increased \( V'E \) intercept, respectively.

The increasing \( \Delta V'E/\Delta P_{ETCO_2} \) with greater levels of simultaneous hypoxia reflects a progressively greater carotid-body response component; it is crucial, therefore, to maintain \( P_aO_2 \) constant (iso-oxic) during the test. Above a \( P_aO_2 \) of ~200 mmHg, the carotid-body component is effectively inactivated and hence the sufficiently hyperoxic carbon dioxide response entirely reflects that of the ‘central’ component. Interpretation depends on the relationships between the typically measured \( P_{ETCO_2} \) (or, less typically, \( P_aCO_2 \) and \( P_{CO_2} \) (and hydrogen ion concentration \([H^+]\)) at each set of chemoreceptors; these relationships depend on factors such as the local-tissue perfusion, carbon dioxide production, carbon dioxide 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 \( (I) P_{CO_2} \) should be used for \( \Delta V'E/\Delta P_{ETCO_2} \) characterisation. Each level is maintained for ~8–10 min, with the average \( V'E \) and \( P_{ETCO_2} \) over the final 2–3 min providing the steady-state values. Consequently, the test is time-consuming, although transiently overshooting \( P_{CO_2} \) beyond the required level can reduce the time required to attain the new \( V'E \) steady state.

This concern is obviated, to a considerable extent, by the rebreathing method of Read et al. (1967), which takes a small fraction of the time to perform while providing effectively the same \( \Delta V'E/\Delta P_{ETCO_2} \) value as the steady-state method. The subject re-breathes from a 6–7-L bag initially containing ~7% carbon dioxide balance oxygen. The high initial \( P_{CO_2} \) is designed to raise \( P_aCO_2 \) rapidly to, or close to, the mixed-venous level, such that the subsequent rebreathing provides an effectively linear increase in \( P_aCO_2 \); the high inspired oxygen tension \( (P_{IO_2}) \) maintains \( P_aO_2 \) 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, reflecting both the transit delay between the lungs and sites of chemoreception and the

![Figure 1. Steady-state ventilatory responses to inhaled \( P_{CO_2} \) at constant oxygen tension \( (P_{IO_2}; \text{solid lines}) \). The dotted line depicts the response to progressively increasing \( P_{CO_2} \) (hyperoxic rebreathing test).](#)
$V^{'E}$ response kinetics. Consequently, as the test is designed to provide a constant rate of change of $P_{CO_2}$ at the chemoreceptor sites, the rate of change of $V^{'E}$ is compared with the rate of change of $PETCO_2$ ($\Delta V^{'E}/\Delta PETCO_2$). This is currently the more common means of assessing carbon dioxide responsiveness, although it is important to recognise that the carbon dioxide responsiveness obtained by this hyperoxic method reflects only central chemoreflex activity.

One must be careful, however, 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 $PCO_2$ and $PaCO_2$.

Beginning at a value below the spontaneous control condition, carbon dioxide responsiveness is not characterised by the extrapolated dashed lines in figure 1. Rather, there is a region of virtual insensitivity to increasing $PCO_2$, 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 $PETCO_2$ 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 $PETCO_2$ between these conditions at resting ventilation can be used as an index of the threshold change. Duffin (2011) has suggested $PETO_2$ values of 150 and 50 mmHg for this assessment.

**Estimation of ventilatory response to hypoxia**

The $V^{'E}$ response to hypoxia, if defined under isocapnic conditions, is considered solely to reflect carotid chemoreceptor activity. Both constant-concentration inspirate and rebreathing techniques have been successfully utilised for the characterisation. The pattern of the $V^{'E}$ response to a step decrease of $PiO_2$ is not monotonic, even with $PETCO_2$ being maintained as 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 (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 carbon dioxide 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 $V^{'E}$–$PaO_2$ relationship over a range of increasingly hypoxic inspirates is curvilinear, with the $V^{'E}$ rate of change approaching infinity at a $PaO_2$ of ~30 mmHg. Naturally, at higher isocapnic $PCO_2$ 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, $PaCO_2$ is allowed to decrease spontaneously as $V^{'E}$ increases (poikilocapnia), then both the peak initial $V^{'E}$ 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 avoiding, by means of a carbon dioxide-absorbing system, the otherwise progressive hypercapnia. The resulting curvilinear response to the progressive isocapnic hypoxia is shown in figure 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 \( V^E - P_{aO2} \) relationship can be transformed into a linear relationship by substituting \( S_{aO2} \) for \( P_{aO2} \) (fig. 2c):

\[
V^E = G \cdot S_{aO2} + V^E(0)
\]

where \( V^E(0) \) is the control \( V^E \) 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 \( S_{aO2} \) in normal subjects. At higher isocapnic levels, \( G \) is increased as a result of the potentiating effect of carbon dioxide on carotid chemosensitivity, which sums with the further central carbon dioxide–H\(^+\) stimulation.

In addition to the ease of measuring \( S_{aO2} \), noninvasively by pulse oximetry, and averting any assumption regarding the difference between \( PET_{CO2} \) and \( P_{aO2} \), the linearity of the \( V^E \) 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 \( P_{aO2} \); \( S_{aO2} \) is merely a practical expedient, with uncertainties regarding the influence of conditions altering haemoglobin affinity for oxygen.

The current degree of a subject’s hypoxic ventilatory drive may be estimated by the hypoxia-withdrawal test of Dejours (1962).

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**Figure 2.** a) \( V^E \) time-course to prolonged isocapnic step-decrease in end-tidal oxygen tension (\( P_{O2} \)). b and c) Ventilatory response to progressive isocapnic hypoxia (in two subjects) as a function, respectively, of end-tidal \( P_{O2} \) and oxygen saturation (\( S_{O2} \)). d) Ventilatory time-course to a hyperoxic step-increase in an exercising hypoxic subject with alveolar proteinosis. \( PET_{CO2} \): end-tidal carbon dioxide tension. b and c) Reproduced from Rebuck et al. (1981) with permission from the publisher. d) Reproduced from Wasserman et al. (1989) with permission from the publisher.
If a particular level of $P_{aO2}$ is established by inhalation of a hypoxic gas mixture, or noting the spontaneous $P_{aO2}$ if the subject is already hypoxaemic (as in figure 2d for an exercising subject with alveolar proteinosis), then the abrupt administration of 100% oxygen will acutely suppress carotid-body hypoxic responsiveness and cause $V'\varphi$ to fall transiently and rapidly. The maximum decrease in $V'\varphi$ as a fraction of the total hypoxic $V'\varphi$ provides the hypoxic index. In addition to the assumption (probably justified in humans) that the consequently high level of oxygen tension ($P_O2$) actually silences the carotid bodies, the validity of the Dejours test (1962) depends upon the $V'\varphi$ decrement reaching its nadir prior to the subsequently increased $P_{aCO2}$ (caused by the reduced $V'\varphi$) influencing central sites of carbon dioxide responsiveness. As the nadir of the response commonly occurs $\sim 20–25$ 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 carbon dioxide 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 carbon dioxide response, and

2) the increase in $V'\varphi$ between the hyperoxic (peripheral chemoreceptors silenced) and the hypoxic (40 mmHg $P_{aO2}$) carbon dioxide response relationship, measured at a standard target level of 40 mmHg $P_{aCO2}$ ($AV_{40}$).

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.

Further reading

Arterial blood gas assessment

Paolo Palange, Alessandro Maria Ferrazza and Josep Roca

The fundamental function of the lung is to contribute to homeostasis by ensuring that pulmonary oxygen uptake ($V'_{O2}$) and carbon dioxide production ($V'CO_2$) match the body’s 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 oxygen ($P_{aO2}$) and carbon dioxide tension ($P_{aCO2}$), and pH in arterial blood. In clinical practice, ABG analysis is needed to assess both 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 (HF) and renal failure). Moreover, ABG analysis is mandatory to establish a diagnosis of respiratory failure.

Modern equipment for performing ABG assessment uses electrodes to measure $P_{aO2}$, $P_{aCO2}$ and pH. Other variables, such as bicarbonates (actual $HCO_3^-$ and standard $HCO_3^-$), base excess (BE) and oxyhaemoglobin saturation ($S_{aO2}$), 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 $P_{aO2}$ and $P_{aCO2}$, while the second step addresses the assessment of A–B status using $P_{aCO2}$, pH and, eventually, $HCO_3^-$ (or BE). If serum electrolytes, and in

Key points

- ABG is mandatory for the diagnosis of respiratory failure and of A–B disorders.
- Pulmonary gas exchange status is best evaluated by the integrated reading of $P_{aO2}$ and $P_{aCO2}$.
- A–B status is best evaluated by the integrated reading of $P_{aCO2}$ and pH, with concomitant measurement of serum electrolytes.
- Mixed A–B disorders are very common in clinical practice.
- The correct interpolation of ABG represents a fundamental step for the diagnosis and treatment of A–B disorders.
- The study of serum chloride is fundamental to further investigate the causes of metabolic disorders affecting A–B equilibrium.
particular chloride, are measured, a further insight into the differential diagnosis of metabolic A–B disorders can be obtained (third step).

**Step 1: evaluation**

Healthy subjects at sea level breathing room air (inspiratory oxygen fraction \( F_{IO2} \) 0.21) show \( PaO_2 \) values close to 90–95 mmHg. \( PaO_2 \) values <80 mmHg are considered arterial hypoxaemia and \( PaO_2 \) <60 mmHg indicates hypoxaemic respiratory failure. Because of the characteristics of the oxyhaemoglobin dissociation curve, a \( PaO_2 \) of 60 mmHg corresponds to a \( SaO_2 \) of 90% and is located at the upper end of the steepest portion of the curve. \( PaO_2 \) values <60 mmHg will have a substantial impact, reducing arterial oxygen content and compromising tissue oxygenation. The accepted reference interval for \( PaCO_2 \) is 35–45 mmHg. By convention, hypercapnic respiratory failure is established at \( PaCO_2 \) >50 mmHg.

Abnormal respiratory gases in arterial blood are generally due to impaired pulmonary gas exchange. Intrapulmonary factors that may cause arterial hypoxemia are listed in table 1. Pulmonary alveolar ventilation \((V')/perfusion \((Q')\) mismatch is the most frequent determinant of hypoxaemia and hypercapnia in the clinical scenario. However, the identification of pulmonary shunt \((Q'\rightarrow Q\rightarrow Q') 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, \( Fio_2 \), \( VO_2 \) and \( V'E \) are also determinants of \( PaO_2 \) and \( PaCO_2 \).

When \( PaCO_2 \) values are close to 40 mmHg, \( PaO_2 \) is an excellent indicator of the efficacy of the lung as an oxygen exchanger, but abnormal \( PaCO_2 \) values (hypercapnia or hypocapnia) may benefit from the integrated reading of \( PaO_2 \) and \( PaCO_2 \) values indicated in table 1. Such an integrated view can be numerically obtained by computing the alveolar–arterial oxygen tension difference \((Pa–aO_2)\) using the simplified formula

\[
PA–aO_2 = ((PB-PH_2O) \cdot F_{IO2} \cdot PaCO_2 / R) - PaO_2
\]

where \( PB \) is barometric pressure, \( PH_2O \) is the partial pressure of water vapour in the airways and \( R \) is the respiratory quotient \((V'CO_2/V'O_2, \sim 0.80 \) at rest).

At sea level, the normal expected \( PA–aO_2 \) value is <15 mmHg in young subjects and <20 mmHg in the elderly. Table 1 shows the contribution of the \( PA–aO_2 \) 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 \( PaO_2 \) should be examined, keeping in mind that in the normal lung \( PA–aO_2 \) widens when breathing additional oxygen. While hypoxaemia due to pulmonary \( V'/Q' \) mismatch 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 \( PA–aO_2 \) is to use the rule of ‘130’. It is assumed that in a healthy subject, at sea level \((FIO_2=0.21)\), the sum of \( PaO_2 \) and \( PaCO_2 \) should be \( \sim 130 \) mmHg. Consequently,

\[ PA–aO_2 = 130 - (PaO_2 + PaCO_2) \]

The following examples illustrate the use of the rule. A patient with \( PaO_2 \) 70 mmHg and

<table>
<thead>
<tr>
<th>Cause</th>
<th>( PaO_2 )</th>
<th>( PaCO_2 )</th>
<th>( PA–aO_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoventilation</td>
<td>↓</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>( V'/Q' ) mismatch</td>
<td>↓</td>
<td>↔ ↔ ↑</td>
<td>↑</td>
</tr>
<tr>
<td>Oxygen diffusion limitation</td>
<td>↓</td>
<td>↔ ↓</td>
<td>↑</td>
</tr>
<tr>
<td>Shunt</td>
<td>↓ ↓</td>
<td>↔ ↓ ↑</td>
<td>↑ ↑</td>
</tr>
</tbody>
</table>

Table 1. \( PA–aO_2 \) in the evaluation of the causes of arterial hypoxaemia
\( P_{aCO_2} \), 60 mmHg \((PA-aO_2, \approx 130-(50+60)=20 \text{ mmHg})\) is hypventilating a lung that is functionally ‘normal’, with a \( PA-aO_2 \) within the reference interval. However, a patient with hypoxaemic respiratory failure and hypocapnia \((P_{aO_2}, 50 \text{ mmHg}, P_{aCO_2}, 20 \text{ mmHg}; PA-aO_2, \approx 130-(50+20)=60 \text{ mmHg})\) shows worse pulmonary oxygen exchange (higher \( PA-aO_2 \)) than a patient with respiratory failure and hypercapnia \((P_{aO_2}, 50 \text{ mmHg}, P_{aCO_2}, 50 \text{ mmHg}; PA-aO_2, \approx 130-(50+50)=30 \text{ mmHg})\). The computation of \( PA-aO_2 \) (and the use of the rule of 130) is not useful clinically when \( FIO_2 \) increases. Calculating the \( P_{aO_2}/FIO_2 \) ratio is recommended to assess the efficacy of the lung as an oxygen exchanger in critical care when comparing ABG measurements taken at different values of \( FIO_2 \). Lung injury is defined as \( P_{aO_2}/FIO_2 \), \( 300 \text{ mmHg} \) while acute respiratory distress syndrome (ARDS) is associated with a \( P_{aO_2}/FIO_2 <200 \text{ mmHg} \) (table 2). Recently, three mutually exclusive categories of ARDS severity based on the degree of hypoxaemia have been proposed:

- **mild** \( (P_{aO_2}/FIO_2 \text{ from } 200 \text{ to } \leq 300 \text{ mmHg}) \)
- **moderate** \( (P_{aO_2}/FIO_2 \text{ from } 100 \text{ to } \leq 200 \text{ mmHg}) \)
- **severe** \( (P_{aO_2}/FIO_2 \leq 100 \text{ mmHg}) \)

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

Arterial pH is highly regulated to be maintained between 7.38 and 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 \( (P_{aCO_2}) \)
- the metabolic component

Hypercapnia (high \( P_{aCO_2} \)) generates respiratory acidosis (low pH) whereas hypocapnia (low \( P_{aCO_2} \)) is associated to respiratory alkalosis (high pH). In simple acute respiratory disorders, for each 10-mmHg variation in \( P_{aCO_2} \), 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 concentration \((\text{[HCO}_3^-]\)) computed through the Henderson–Hasselbalch equation:

\[
pH = 6.1+\log([\text{HCO}_3^-]/0.03 \cdot P_{CO_2})
\]

where \( P_{CO_2} \) is carbon dioxide tension. In the past, the role of simple rules associating changes in \( P_{aCO_2} \) with changes in pH (and \( \text{HCO}_3^- \)) has been emphasised as useful for the diagnosis of simple and mixed A–B disorders. A graphical illustration of this approach is presented 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 COPD patient with an episode of severe exacerbation showing acute hypercapnia leading to respiratory acidosis. The second

### Table 2. Respiratory failure

<table>
<thead>
<tr>
<th>Hypoxaemic respiratory failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P_{aO_2} \leq 60 \text{ mmHg}, P_{aCO_2} \text{ normal or low, at sea-level } (FIO_2 \ 0.21) )</td>
</tr>
<tr>
<td>Hypoxaemia due to pulmonary ( V'A/Q' ) mismatching ( (P_{aO_2} \text{ rises with } FIO_2) )</td>
</tr>
<tr>
<td>Chronic respiratory diseases</td>
</tr>
<tr>
<td>(only pulmonary fibrosis shows oxygen diffusion limitation with ( V'A/Q' ) mismatch)</td>
</tr>
<tr>
<td>Hypoxaemia due to intrapulmonary shunt ( (\text{lung units with } V'A/Q'=0) ) ( P_{aO_2}, \text{ responds to } FIO_2) ) ( P_{aO_2}/FIO_2 \leq 200 )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypercapnic respiratory failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P_{aCO_2} \geq 50 \text{ mmHg and } P_{aO_2} \text{ low, at sea-level } (FIO_2 \ 0.21) )</td>
</tr>
<tr>
<td>‘Normal’ lung ( (PA-aO_2 \text{, gradient preserved}) )</td>
</tr>
<tr>
<td>Reduced ( V'A \text{ due to extrapulmonary factors} )</td>
</tr>
<tr>
<td>Advanced chronic respiratory disease or severe exacerbation</td>
</tr>
<tr>
<td>Hypoxaemia due to pulmonary ( V'A/Q' ) mismatch</td>
</tr>
</tbody>
</table>

ERS Handbook: Respiratory Medicine
example fits any situation leading to hyperventilation and low \( P_{aCO_2} \) that generates respiratory alkalosis (e.g. interstitial oedema in HF). The third row indicates an example of acidosis due to a metabolic disturbance (e.g. exercise-related increase in blood lactate, ketoacidosis, renal failure, etc.). 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), these often evolve to mixed A–B abnormalities.

**Step 3: more on A–B disorders**

To further investigate the causes of metabolic disorders, the measurement of serum electrolytes, and in particular chloride, is of great help. In fact, while respiratory disturbances directly affect pH by modifying \( P_{aCO_2} \), metabolic disturbances can be derived from changes in the net difference between negative and positive charges dissolved in the serum (strong ions and weak acids). An increase in negative charges reduces pH, while a reduction increases pH (fig. 3). The negative charges that strongly influence the A–B equilibrium are chloride and the so-called non-measurable anions (see later). Several types of renal tubular acidosis impair renal chloride excretion, resulting in a net increase in serum chloride concentration and, thus,
in metabolic acidosis. Lower gastrointestinal losses of sodium, potassium and water (diarrhoea) cause an increase in the serum concentration of chloride, thus resulting in hyperchloraemic acidosis. However, reduction of chloride (e.g. loop diuretics) causes metabolic alkalosis. The main mechanism that may cause metabolic alkalosis is the increase in renal ammoniagenesis that stimulates chloride excretion as ammonium chloride. Several factors can increase renal ammoniagenesis: primitive hyperaldosteronism, hypovolaemia (e.g. secondary hyperaldosteronism) and hypokalaemia. In the clinical setting, the causes of metabolic alkalosis can be classified as chloride-responsive or chloride-resistant based on the response to chloride salt administration (table 5). Negative charges other than chloride are usually calculated by the anion gap (AG) formula:

\[ \text{AG} = [\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-]) \]

The AG represents the amount of non-measurable anions (acids), and the normal value is around 12–14 mEq·L⁻¹. The most common acids that cause high-AG metabolic acidosis are lactic acid (lactic acidosis), keto acids (diabetic or alcoholic acidosis) and inorganic acids (renal failure). The reduction in AG due to severe reduction in serum albumin can generate a mild metabolic alkalosis.

### 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 the ABG. As a first step (step 1), the combined reading of \( P_{aO_2} \) and \( P_{aCO_2} \) 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

#### Table 3. Examples of simple A–B disorders

<table>
<thead>
<tr>
<th>pH</th>
<th>( P_{aCO_2} )</th>
<th>([\text{HCO}_3^-])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory acidosis</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Respiratory alkalosis</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

#### Table 4. Respiratory disorders

**Respiratory acidosis**
- Central nervous system depression, neuromuscular disorders
- Chest wall abnormalities
- Lung diseases

**Respiratory alkalosis**
- Anxiety, central nervous system disorders
- Hormones/drugs (catecholamine, progesterone, hyperthyroidism, salicylate)

#### Table 5. Metabolic disorders

<table>
<thead>
<tr>
<th>Metabolic acidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normochloraemic acidosis (or high anion gap acidosis)</td>
</tr>
<tr>
<td>Ketoacidosis</td>
</tr>
<tr>
<td>Lactic acidosis</td>
</tr>
<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>Toxins</td>
</tr>
<tr>
<td>Hyperchloraemic acidosis (or normal anion gap acidosis)</td>
</tr>
<tr>
<td>Extra-renal loss of sodium</td>
</tr>
<tr>
<td>Renal tubular acidosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolic alkalosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloride-responsive type</td>
</tr>
<tr>
<td>Gastric fluid loss</td>
</tr>
<tr>
<td>Volume contraction</td>
</tr>
<tr>
<td>Chloride-resistant type</td>
</tr>
<tr>
<td>Mineral corticoid disorders</td>
</tr>
<tr>
<td>Milk-alkali and Bartter syndromes</td>
</tr>
<tr>
<td>Hypoalbuminaemia</td>
</tr>
</tbody>
</table>
blue circles). As a second step (step 2), the combined reading of $P_aCO_2$ and pH is needed for the correct diagnosis of A–B disorders (red squares). Furthermore, the study of serum electrolytes, particularly serum chloride, may be of great help in the identification of the causes of metabolic disorders (red squares) (step 3).

Further reading

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, gender 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, cardiovascular and pulmonary gas exchange variables during symptom-limited incremental exercise, is considered the gold standard for evaluating the degree and causes of exercise intolerance in disease states (table 1). Moreover, CPET has been extensively used in patients with COPD, CF, interstitial lung diseases (ILDs), pulmonary vascular disorders (PVDs) and CHF.

In COPD and CF, exercise tolerance is mainly limited by pulmonary mechanical 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 and CHF, both circulatory (e.g. reduced adaptation in cardiac output) and pulmonary gas exchange abnormalities contribute to exercise intolerance.

Exercise protocols

**Maximal incremental test** The symptom-limited maximal incremental exercise protocol is recommended as a first step in the evaluation of exercise tolerance. \( V'_{\text{E}} \), heart rate, oxygen uptake (\( V'O_2 \)), carbon dioxide production (\( V'CO_2 \)), and end-tidal oxygen and carbon dioxide tensions are the primary variables measured, typically on a breath-by-breath basis using computerised systems. Additional required measurements include ECG, blood pressure, dyspnoea, leg discomfort, exercise-related arterial oxygen desaturation and spirometry with flow–volume loop recording. 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 and severe aortic stenosis represent absolute contraindications to CPET. Resting lung function measurements and ECG are usually obtained before CPET. Cycle and treadmill exercise have been used interchangeably, although the former is largely used 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 W 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 used to determine the appropriate work rate for an endurance protocol.

**Constant work rate (CWR) tests**, on a cycle ergometer or on a treadmill, are used 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 \(h_L\)) results in steady states either being delayed or not attained at all.

**Walking tests**, such as the 6-min walking test, have been increasingly used for the assessment of exercise tolerance in chronic lung diseases. The object of this test is to walk as far as possible in 6 min. The test should be performed indoors along a 30-m flat, straight corridor; encouragement significantly increases the distance walked. Measurements of \(S_{\text{pO}}\), heart rate and exertional symptoms are recommended during this test.

**Indications for CPET**

In patients with lung diseases, exercise testing is mainly used 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**

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

**Lactate threshold** \(h_L\) is the highest \(V'O_2\) at which the arterial lactate concentration 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.

**Oxygen pulse** The oxygen pulse is the product of the stroke volume and the difference between the arterial oxygen content \((CaO_2)\) and the mixed venous oxygen content \((CvO_2)\). Given the Fick equation

\[
V'O_2 = \text{cardiac output} \times (CaO_2 - CvO_2)
\]

the oxygen pulse can be calculated as:

\[
\text{Oxygen pulse} = \frac{V'O_2}{\text{heart rate}}
\]

In patients with ILD, the oxygen 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 \(CaO_2\). In PVD, the oxygen pulse is characteristically low at peak exercise and may not increase during incremental exercise, reflecting the abnormal cardiac output adaptation.
Heart rate reserve (HRR) The peak heart rate (HRpeak) achieved in a symptom-limited exercise test decreases with age. The most commonly used equation to predict HRpeak is

\[ \text{HRpeak, pred} = 200 - \text{age} \]

HRR is defined as the difference between HRpeak, pred and HRpeak. In healthy individuals, HRR is virtually zero; a high HRR is usually observed in patients with COPD, CF and ILD.

\[ V'E = V'CO_2 \]

Although it is conventional to express the ventilatory response to exercise relative to \( V'E \), it can be measured as the slope of the \( V'E - V'CO_2 \) relationship (\( \Delta V'E/\Delta V'CO_2 \)) over its linear region, i.e. typically extending from ‘unloaded pedalling’ to the respiratory compensation point. In normal individuals, \( \Delta V'E/\Delta V'CO_2 \) values of around 23–25 have been reported.

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

Breathing reserve (BR) provides an index of the proximity of the ventilation at the limit of tolerance (\( V'E_{\text{max}} \)) to the maximal voluntary ventilation (MVV):

\[ \text{MVV} = \text{resting FEV1} \times 40 \]

BR can be defined as \( V'E_{\text{max}} \) as a percentage of MVV:

\[ \text{BR} = 1 - V'E_{\text{max}}/\text{MVV} \]

In COPD, CF and ILD, BR is usually reduced or absent at peak CPET exercise (fig.1). Analysis of 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 oxygen desaturation During exercise, \( S_pO_2 \), is normally maintained in the region of around 97–98%. However, arterial oxygen desaturation can be observed in patients with moderate–severe ILD and in patients with primary pulmonary hypertension.

Tolerable limit of exercise and ‘isotime’ measurements Tlim is the tolerable limit of exercise, expressed as function of time measured during CWR protocols. In clinical practice, high-intensity (around 70–80% of maximal work rate) CWR protocols are used for the evaluation of interventions. In
addition to \( T_{\text{lim}} \), measurement of pertinent physiological variables (e.g. \( V'_{\text{E}} \), inspiratory capacity and dyspnoea) at a standardised time (isotime) are obtained.

**CPET response patterns**

**Ventilatory Response** In normal individuals during incremental exercise, \( V'_{\text{E}} \) increases linearly relative to work rate or \( V'_\text{O}_2 \). At some point, \( V'_{\text{E}} \) begins to increase more steeply in response to the development of lactic acidosis, to maintain acid–base homeostasis (normal individual in fig. 1). The ventilatory response to exercise in patients with lung disorders is increased (COPD patient in fig. 1). Conventionally, the ratio of \( V'_{\text{E}} \) 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 \( V'_{\text{E}}/\text{MVV} \) exceeds 85%. In lung diseases, the increase in \( V'_{\text{E}}/\text{MVV} \) may reflect a reduction in MVV or an increase in \( V'_{\text{E}} \). The ventilatory response during exercise is influenced by metabolic rate (\( V'_{\text{CO}_2} \)), \( P_{\text{aCO}_2} \) and the physiological dead space fraction of the tidal volume (\( V'D/V_T \)). The relationship between these variables is described as:

\[
V'_{\text{E}} = (863 \times V'_{\text{CO}_2})/\left(P_{\text{aCO}_2} \times (1-V'D/V_T)\right)
\]

where \( P_{\text{aCO}_2} \) is expressed in Torr. In lung diseases, for a given \( V'_{\text{CO}_2} \) and \( P_{\text{aCO}_2} \), \( V'_{\text{E}} \) is usually increased because of a higher \( V'D/V_T \). \( \Delta V'_{\text{E}}/\Delta V'_{\text{CO}_2} \) or \( V'_{\text{E}}/V'_{\text{CO}_2} @\theta L \) is often used in the functional assessment of patients with lung diseases (e.g. COPD, ILD and PVD) and cardiovascular disorders (e.g. CHF). \( V'_{\text{E}}/V'_{\text{CO}_2} \) is usually increased, particularly in patients with PVD (fig. 2). Another particular behaviour of the \( V'_{\text{E}} \) response during exercise is the cyclic fluctuation of \( V'_{\text{E}} \) and expired gas kinetics, also defined as exertional oscillatory ventilation, which can occur in approximately one-third of patients with CHF. While the origin of such a ventilatory abnormality is still controversial, its clinical relevance in terms of a negative prognosis is well established.

**Pulmonary gas exchange** The efficiency of pulmonary gas exchange can be assessed by studying the magnitude of alveolar–arterial oxygen tension difference (\( P_{\text{A-aO}_2} \)) at rest and during exercise. Normally, \( P_{\text{aO}_2} \) does not decrease during exercise and \( P_{\text{A-aO}_2} \) 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 \( P_{\text{A-aO}_2} \) (>30 Torr) at peak exercise accompanied by arterial oxygen desaturation. These changes reflect regional ventilation–perfusion ratio 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 \( V'_\text{O}_2\max \), reduced \( \theta L \), steeper heart rate–\( V'_\text{O}_2 \) relationship (with a reduced heart rate reserve at peak exercise) and a shallower profile (or even flattening) of the oxygen pulse increase with increasing \( V'_\text{O}_2 \). 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 (table 2).

Several studies have confirmed that \( V'O_2\max \) is superior to other indexes in the risk stratification of patients with end-stage lung diseases; many centres, however, use field tests for prognostic purposes.

**Evaluating the effects of therapeutic interventions**

High-intensity (75–80% of peak work rate) endurance CWR protocols performed on a cycle ergometer or treadmill to \( T_{lim} \) have been successfully used in COPD patients for the evaluation of the effects of therapeutic interventions (e.g. bronchodilators, oxygen, heliox and rehabilitation). These types of protocols have a greater power to discriminate therapy-induced changes in COPD patients, with a higher fractional improvement in exercise tolerance compared with incremental CPET. However, it should be recognised that the hyperbolic profile of the relationship between the power output and exercise duration \( (T_{lim}) \) (the ‘power–duration curve’) during CWR tests is responsible for a considerable proportion of variability in the improvement magnitude of \( T_{lim} \). That is, \( T_{lim} \) is influenced by the pre-intervention work rate and exercise duration and their relative positioning on the power–duration profile. Without knowledge of these aspects, any change in \( T_{lim} \) to a single CWR bout must be cautiously interpreted in terms of realistic physiological benefits obtained from the intervention.

**Further reading**


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**Table 2. CPET prognostic indices**

<table>
<thead>
<tr>
<th></th>
<th>COPD</th>
<th>ILD</th>
<th>CF</th>
<th>PVD</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V'O_2\max )↓</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>( V'\text{E}/V'\text{CO}_2 )↑</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Arterial oxygen desaturation</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exertional oscillatory ventilation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>++</td>
</tr>
</tbody>
</table>
As early as 1859, Sir Henry Hyde Salter described ‘bronchial sensibility’ in patients with asthma. Later, in 1945, Tiffenau suggested that measuring changes in expiratory flow after inhaling acetylcholine or isoproterenol could be helpful in assessing patients with airways disease. Ultimately, these observations led to the concept of bronchial hyperresponsiveness (BHR), which is defined as ‘an increase in the ease and degree of airflow limitations in response to bronchoconstrictor stimuli in vivo’ (Sterk, 1996).

BHR is assessed by bronchial provocation testing (BPT), which may be performed with several different aims in mind: it may be done as part of research or in the clinical setting, and with several different chemical substances; it may test specific bronchial responsiveness to an allergen (allergen BPT), or nonspecific bronchial responsiveness by BPT to histamine or methacholine, as well as several other different substances (table 1).

Methods of BPT

BPT can be divided into direct and indirect methods (Pauwels et al., 1988). Methacholine and histamine BPT represent direct methods, using a transmitter (methacholine) or a mediator (histamine) substance as test agents. Indirect methods include exercise testing (which may also be regarded as BPT, but which otherwise is regarded to come outside the present topic), inhaled adenosine monophosphate (AMP), inhaled mannitol and eucapnic voluntary hyperpnoea (EVH) tests. The indirect tests have their effect through causing mediator or transmitter release from inflammatory cells and nerves.

Previously, BPT was performed qualitatively using a 10-fold increase in concentration of the test substance (Aas, 1970), whereas during the last 25 years, a doubling of the concentration/dose of the test substance has been used (Cockcroft et al., 1977a).

Taking bronchial provocation with methacholine as an example, figure 1 shows the reduction in FEV₁ caused by inhaling...
doubling doses, with interpolation on the $x$-axis to determine the provocative concentration of methacholine causing a 20% decrease in FEV$_1$ (PC$_{20}$) (Cockcroft et al., 1977a). Later, a simplification of the test was introduced by inhaling single doubling doses of methacholine, determining the provocative dose of the test agent causing a 20% decrease in FEV$_1$ (PD$_{20}$) (Yan et al., 1983).

The test is performed under standardised conditions, with specified nebulisation rates for the tidal breathing method (PC$_{20}$), inhaling the test agent for 2 min, measuring FEV$_1$ and then inhaling the doubled concentration. The test is stopped when FEV$_1$ is reduced by $\geq 20\%$ and the PC$_{20}$/PD$_{20}$ determined by interpolating the semilogarithmic dose–response curve (fig. 1).

When determining bronchial responsiveness by measuring PD$_{20}$, the cumulated dose inhaled is determined. This is done by inhaling doubling doses of the test substance. The most often-used delivery device is an inspiration-triggered nebuliser enabling inhalation by controlled tidal ventilation, such as the Spira nebuliser (Spira Respiratory Care Centre, Hämeenlinna, Finland) (Nieminen et al., 1988) or the Aerosol Provocation System (Jaeger, Würzburg, Germany). Alternatively, a handheld DeVilbiss nebuliser has been used (DeVilbiss Healthcare, Somerset, PA, USA) (Cockcroft et al., 1977a). A joint Task Force of the European Respiratory Society and American Thoracic Society is presently revising the recommendations for bronchial challenges, including methacholine and histamine BPT. Recommendations given here may be superseded by new recommendations from that Task Force.

Determinations of PC$_{20}$ or PD$_{20}$ are used both for BPT with methacholine and histamine, as well as with AMP, and may be used for allergen BPT. BPT with mannitol was recently developed and launched commercially by inhaling cumulative doses through a powder inhaler. Here, a 15% reduction in FEV$_1$ (PD$_{15}$) is used as cut-off (Brannan et al., 2005).

In EVH, the subject inhales dry air with 4.9% carbon dioxide for 6 min at a preferred ventilation rate of 85% of maximum voluntary ventilation (MMV), which is often calculated as FEV$_1 \times 30$, but a ventilation rate as low as

<table>
<thead>
<tr>
<th>Bronchial responsiveness</th>
<th>BPT substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific</td>
<td>Allergen BPT</td>
</tr>
<tr>
<td>Nonspecific</td>
<td>Methacholine</td>
</tr>
<tr>
<td></td>
<td>Histamine</td>
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<tr>
<td>Direct</td>
<td>Exercise test</td>
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<tr>
<td>Indirect</td>
<td>Exercise test while inhaling dry or cold air</td>
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<tr>
<td></td>
<td>Inhaled AMP</td>
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<td></td>
<td>Inhaled mannitol</td>
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<td>EVH</td>
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Table 1. Different types of bronchial responsiveness assessed by different types of BPT

![Figure 1. Determination of PC$_{20}$ by interpolation on the logarithmic $x$-axis.](image-url)
65% of MVV (FEV1 × 22) is acceptable (Rosenthal et al., 1984). A reduction in FEV1 ≥ 10% is taken as a positive test. EVH testing has been shown to be particularly sensitive for asthmatic athletes, particularly endurance athletes (Stadelmann et al., 2011; Cockcroft et al., 1977b).

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 recently out of fear of worsening the asthma after such BPT. A long-lasting worsening of nonspecific BHR after performing an allergen BPT has been demonstrated (Cockcroft et al., 1977b). Thus, allergen BPT is now mostly a tool in research projects and not used in clinical practice.

However, different measures of nonspecific BHR are often used, both in a research context and a clinical setting. With the diagnosis asthma in mind, direct measures of BHR 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 bronchial responsiveness was found to be more sensitive, but less specific, for discriminating asthmatic from healthy subjects (Crockcroft et al., 1977a). Compared with exercise testing, methacholine BPT was more sensitive, but markedly less specific, for discriminating between asthma and other chronic lung diseases. When adding cold air inhalation to the exercise, sensitivity comparable to methacholine was reached, while maintaining the specificity (Carlsen et al., 1998).

In addition, other differences are found between direct and indirect BPT. Indirect bronchial responsiveness is rapidly influenced by treatment with inhaled steroids, with the first effects appearing after 1 week (Henriksen et al., 1983), whereas methacholine BPT needs several months of inhaled steroid treatment to show an effect (Essen-Zandvliet et al., 1992).

Results of BPT may be used to monitor the effect of treatment in asthma. It has been shown that methacholine 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 methacholine BPT, as compared with follow-up based upon clinical symptoms and lung function measurements, it was shown that follow-up by methacholine BPT improved asthma control and had a positive effect upon airway remodelling as assessed by bronchial biopsies (Sont et al., 1999). Thus, BPT with various substances and performed in a standardised measure is probably, at the present time, the best tool for monitoring asthma patients.

Methacholine BPT (PD20) also has a role in predicting later active asthma, as shown by follow-up in a birth cohort study from 10 to 16 years of age (Riiser et al., 2012).

Further reading

Sputum and exhaled breath analysis

Noninvasive techniques such as induced sputum and exhaled breath analysis have been successfully proven to reveal inflammatory status and to find indicators of airway oxidative stress involved in the pathogenesis of lung diseases. These techniques allow longitudinal sampling of inflammatory biomarkers in the lung of 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, 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 ultrasonically nebulised saline solution (isotonic or hypertonic) over different time periods and subsequent expectoration of secretions. The subject is asked to inhale 200 mg salbutamol before induction, and FEV1 is monitored before and after each inhalation to either prevent or detect possible bronchoconstriction.

After collection, the sputum sample is processed within 2 h according to a standardised method with mucolytic agents (dithiothreitol) and centrifugation is required to separate sputum cells from the fluid phase, which is stored at -80°C for soluble mediator evaluation. If the soluble mediators are affected by mucolytic agents, sputum should be processed with phosphate buffer alone.

Safety issues Sputum induction is a simple, safe and well-tolerated procedure even in patients with severe lung diseases and exacerbations. It is recommended that experienced personnel apply standard operating procedures taking into consideration the degree of airway obstruction, use a modified protocol for subjects with severe airway obstruction, and assess lung function and symptoms during

Key points

- Sputum and exhaled breath analysis are useful noninvasive tools to appraise airway inflammation, particularly in a longitudinal sense.
- Eosinophils are the most significant sputum biomarkers for the evaluation of airway inflammation.
- Many inflammatory mediators can be measured in the fluid phase of sputum but their usefulness remains at research level.
- Nitric oxide is the most reliable exhaled biomarker to assess eosinophilic airway inflammation. Other exhaled biomarkers need further validation and a clear demonstration of their utility in the diagnosis and/or follow-up of airway diseases.
the procedure. Sputum induction is considered to be safe if the fall in FEV₁ is within 5% of baseline after waiting for 15 min. If a FEV₁ fall >20% occurs, the inhalation must be stopped. 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. The cut-off for sputum eosinophils varies from >2 or >3% according to different authors and European Respiratory Society (ERS) guidelines.

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

In up to 40% of subjects with chronic cough, a sputum eosinophil count >3% is seen. These subjects with cough, sputum eosinophilia and no lung function alterations receive the diagnosis of eosinophilic bronchitis, and have an objective response to corticosteroid treatment.

In COPD, neutrophils are usually increased and they are associated with reduced FEV₁, suggesting that neutrophilic airway inflammation is functionally relevant. A cut-off for sputum neutrophilia should take into account age, since neutrophils accumulate in the airways with ageing. Sputum eosinophilia could be present in subjects with COPD and usually predicts a response to corticosteroid therapy.

In figure 1, three representative examples of induced sputum are shown.

Many inflammatory mediators can be measured in the fluid phase of sputum. These mediators are granulocyte proteins, leakage markers, cytokines and chemokines, eicosanoids, and proteases. Unlike sputum cells, up to now, no determination of sputum soluble mediators has entered routine evaluation of airway inflammation. Recently, the application of new techniques, such as RT-PCR, in situ hybridisation, proteomics, etc., has allowed a wider approach to the study of sputum soluble...
mediators in order to generate a disease associated pattern of mediators.

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

**Reproducibility and validity** Sputum induction is a reproducible, sensitive and valid method. A standardised methodology of sputum induction and processing was issued in 2002 by an ERS Task Force in order to provide guidance for the reproducibility of the results obtained.

Exhaled breath

Measuring biomarkers in breath is useful for monitoring airway inflammation and

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Asthma</th>
<th>COPD</th>
<th>CF</th>
<th>Sarcoïdosis</th>
</tr>
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<tbody>
<tr>
<td><strong>Cellular phase</strong></td>
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<tr>
<td>TCC</td>
<td>↑</td>
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<tr>
<td>Eosinophils</td>
<td>↑</td>
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<td>Neutrophils</td>
<td>↑</td>
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<td>Lymphocytes</td>
<td></td>
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<td></td>
<td>↑</td>
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<tr>
<td>CD8⁺</td>
<td></td>
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<td>↑</td>
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<tr>
<td>CD4⁺</td>
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<tr>
<td><strong>Fluid phase</strong></td>
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<tr>
<td>ECP</td>
<td>IL-8</td>
<td>IL-8</td>
<td>MMP-9</td>
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<td>MPO</td>
<td>IL-6</td>
<td>IL-17</td>
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<tr>
<td>Albumin</td>
<td>TNF-α</td>
<td>IL-23</td>
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<tr>
<td>Fibrinogen</td>
<td>IL-10</td>
<td>NE</td>
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<tr>
<td>Nonkinase plasminogen activator</td>
<td>IL-17</td>
<td>Leptin</td>
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<tr>
<td>Plasminogen activator</td>
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<td>Neurokinin A</td>
<td>MPO</td>
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<td>IL-5</td>
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<td>IL-13</td>
<td>ECP</td>
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<tr>
<td>Cys-LTs</td>
<td>EPO</td>
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<tr>
<td>8-isoprostane</td>
<td>LTB₄</td>
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<tr>
<td>MMP-9/TIMP ratio</td>
<td>GRO-α</td>
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</tr>
<tr>
<td>VEGF</td>
<td>MCP-1</td>
<td>GM-CSF</td>
<td>MMP-1</td>
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<td>MMP-8</td>
<td>MMP-9</td>
<td>MMP-12</td>
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<tr>
<td></td>
<td>Hyaluronan</td>
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</tbody>
</table>

↑: increased level; TCC: total cell count; ECP: eosinophil cationic protein; MPO: myeloperoxidase; IL: interleukin; Cys-LT: cysteinyl leukotriene; MMP: matrix metalloproteinase; TIMP: tissue inhibitor of metalloproteinases; VEGF: vascular endothelial growth factor; TNF: tumour necrosis factor; HNL: human neutrophil lipocalin; NE: neutrophil elastase; EPO: eosinophil peroxidase; LT: leukotriene; GRO: growth related oncogene; MCP: monocyte chemotactic protein; GM-CSF: granulocyte–macrophage colony-stimulating factor.
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 the gas phase out of the nearly water-saturated exhalate, and water-soluble volatiles that are exhaled and absorbed into the condensing breath are the main components of EBC.

Breath samples include:

- end-exhaled air, which represents the alveolar air
- mixed exhaled air, which represents the gas mixture coming from the dead space of the bronchial tree and the alveolar gas-exchange space

**Sample collection and analysis** Exhaled breath analysis is completely noninvasive, and is suitable for longitudinal studies and for monitoring the response to pharmacological therapy.

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.

The exhaled gases analysed include:

- exhaled nitric oxide fraction (FeNO), which is a marker of airway inflammation
- carbon monoxide, a marker of inflammation and oxidative stress
- ethane, a marker of lipid peroxidation

For gas analysis, chemiluminescent or electrochemical methods and gas chromatography are the most sensitive methodologies used.

Figure 2 shows two commercially available portable FeNO analysers.

Furthermore, an increase in breath temperature can also be evaluated with a high-accuracy thermometer, which is associated with airway inflammation and remodelling.

Figure 2. Two commercially available portable FeNO analysers. a) Niox Mino (Aerocrine AB, Uppsala, Sweden). b) Quark NObreath (Cosmed, Rome, Italy). Images courtesy of the manufacturers.

Exhaled breath can be condensed through cooling devices, resulting in 1–2 mL EBC over 10 min of tidal breathing. This procedure is noninvasive, simple and easy to perform in patients of any age. In-house and commercially manufactured condensers are available. For pH evaluation, argon deaeration of the EBC sample is needed.

The analysis of EBC is usually performed by immunoassays, mass spectrometry, high-performance liquid chromatography (HPLC), nuclear magnetic resonance, luminometry, spectrophotometry and pH measurement.

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

**Validity** FeNO is the most reliable exhaled marker and is clinically used to assess eosinophilic airway inflammation. It is also useful for assessing adherence to inhaled steroid therapy and the need for further anti-inflammatory treatment in asthma, for differential diagnosis of cough, and for differentiating asthma from COPD. The role of FeNO in COPD is less clear. Smoking reduces FeNO levels, causing misleading results.

Imunoassays 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 found yet. However, the use of dilution markers can be avoided by: 1) testing for multiple biomarkers and calculating ratios among them; and 2) identifying 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:

- flow and time dependence
- influence of respiratory patterns
- origin of markers in EBC
- possible nasal, saliva and sputum contamination

New methodologies (HPLC/mass spectrometry, proteomics, metabolomics, etc.) able to define patterns of exhaled biomarkers specific for distinct airway diseases are under evaluation. Volatile organic compounds (VOCs) (carbon monoxide, ethane, pentane, etc.), in particular, are currently studied for their role in airway inflammation and oxidative stress.

The latest achievements in standardisation and validation of exhaled breath analysis have been presented in American Thoracic Society/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.

Further reading

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 or diffuse lung disease, and in patients with persistent infection or local pulmonary infiltrates (table 1).

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 bodies
- Palliation of endobronchial airway obstruction by tumour ablation or insertion of stents
- 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
- 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.

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**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, and more recently in asthma and emphysema.
The oropharynx is anaesthetised with 4% lidocaine spray 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 sedation (fig. 2). The choice of sedative drugs varies with local practice. Midazolam at a dose of 2–5 mg administered intravenously is more commonly used and has the advantage of amnesic properties in addition to its sedative effect. Alternative agents are opiates, such as fentanyl or alfentanil, which also have antitussive properties. A number of institutions are now switching to nurse-administered sedation and using low-dose propofol infusions as a very short-acting general anaesthetic.

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. During bronchoscopy, the trachea, bronchi and airways down to the subsegmental level are carefully inspected for the presence of mucosal abnormalities, secretions, anatomical variants, malacia (degree of collapse of trachea and main bronchi in expiration) and endobronchial lesions (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 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 or cytofix 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)** 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** is used to obtain parenchymal lung tissue for the evaluation of diffuse lung diseases. It is particularly useful when a bronchocentric component is visible on CT scans. The closed biopsy forceps are advanced into a specific bronchial segment until they meet 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 be placed in cytofix 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 \( \sim 2\% \). Mortality from the procedure is \(< 0.02\%\).

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 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 BAL, 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 (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. Its use for other disease, such as sarcoidosis and TB, is increasing.

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.

Cryoprobes may also utilise to obtain better tissue samples either endobronchially or for transbronchial lung biopsy. Patients need to be intubated with an endotracheal tube or laryngeal mask. The cryoprobe is passed through the instrument channel of the bronchoscope and applied to the tissue to be biopsied. The freezing effects cause the tissue to become adherent and gentle traction is applied to tear off a piece of the frozen tissue. The probe and bronchoscope need to be removed from the airway, and the piece of tissue thawed and placed in formalin. It is not possible to remove the probe through the instrument channel of the bronchoscope when there is tissue adherent to the tip, hence the need to intubate the patient. It is still possible to perform the procedure under sedation. If transbronchial lung biopsy is performed with cryoprobes, it is essential to use fluoroscopy in order to minimise the risk of a pneumothorax.

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 that 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 of 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 while maintaining the catheter in the appropriate position. The catheter can then subsequently be loaded with a remote device that 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 intrabronchial valves, can be used for bronchoscopic volume reduction. Other developments include airway stents, biological polymers, endobronchial coils and thermal vapour. Bronchial thermoplasty, 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.

Further reading
- Bronchoscopy International. www.bronchoscopy.org
- Interventional Bronchoscopy. www.interventionalbronchoscopy.co.uk
Bronchoalveolar lavage

Patricia L. Haslam

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) and American Thoracic Society (ATS), 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 HRCT patterns are often sufficiently diagnostic to avoid the need for BAL or lung biopsy. An ATS/ERS consensus terminology for the idiopathic interstitial pneumonias published in 2002 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 exclude a diagnosis.

How to obtain a sample

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

For both research and routine applications, a standardised BAL procedure must be followed in order to minimise variability due to the unknown dilution factor during lavage.
Table 1. A guide to main types of BAL inflammatory cells and other cytological features in lower respiratory diseases

<table>
<thead>
<tr>
<th>Predominant BAL inflammatory cell types increased compared with normal range*</th>
<th>Other characteristic cytological features</th>
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<tbody>
<tr>
<td><strong>Lower respiratory tract infections</strong></td>
<td></td>
</tr>
<tr>
<td>Community-acquired; nosocomial pneumonia</td>
<td>Neutrophils very high in bacterial pneumonias</td>
</tr>
<tr>
<td>Opportunistic infections in AIDS; organ transplant recipients and patients on chemotherapy</td>
<td>Neutrophils often moderately increased</td>
</tr>
<tr>
<td><strong>Thoracic malignancies</strong></td>
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<tr>
<td>Adenocarcinoma or bronchoalveolar cell carcinoma</td>
<td>Not of diagnostic value</td>
</tr>
<tr>
<td>Metastatic or lymphangitic spread from nonpulmonary tumours</td>
<td>Not of diagnostic value</td>
</tr>
<tr>
<td>B-cell lymphomas</td>
<td>Lymphocytes often strikingly increased</td>
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<tr>
<td>Hodgkin’s lymphoma</td>
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<tr>
<td><strong>Rare lung diseases</strong></td>
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</tr>
<tr>
<td>Alveolar lipoproteinosis</td>
<td>Not of diagnostic value</td>
</tr>
<tr>
<td>Pulmonary haemosiderosis</td>
<td>Mainly macrophages containing particles similar to those in smoking but orange-brown</td>
</tr>
<tr>
<td>Pulmonary Langerhans cell histiocytosis</td>
<td>Mainly macrophages containing smoking-related particles</td>
</tr>
<tr>
<td><strong>Fibrosing mineral dust diseases</strong></td>
<td></td>
</tr>
<tr>
<td>Asbestosis</td>
<td>Moderate increases in neutrophils with or without increased eosinophils or lymphocytes</td>
</tr>
<tr>
<td>Talc pneumoconiosis</td>
<td>Insufficient information</td>
</tr>
</tbody>
</table>
Table 1. Continued

<table>
<thead>
<tr>
<th>Hard metal lung disease/giant cell interstitial pneumonia</th>
<th>Mild increases in neutrophils with or without increased eosinophils or lymphocytes</th>
<th>Refractile particles of hard metal in macrophages plus giant cells if also giant cell interstitial pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug-induced lung diseases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone-induced pneumonitis</td>
<td>Lymphocytes increased</td>
<td>Large phospholipid inclusions in macrophages</td>
</tr>
<tr>
<td>Acute alveolar haemorrhage</td>
<td>Not of diagnostic value</td>
<td>Numerous erythrocytes and ‘bloody’ fluid</td>
</tr>
<tr>
<td>Drug-induced eosinophilic pneumonia</td>
<td>Eosinophils very high</td>
<td></td>
</tr>
<tr>
<td><strong>Other pulmonary eosinophilias</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic eosinophilic pneumonia</td>
<td>Eosinophils very high</td>
<td></td>
</tr>
<tr>
<td>Allergic diseases: asthma; Churg–Strauss syndrome; bronchopulmonary aspergillosis</td>
<td>Mild to moderate increases in eosinophils plus lymphocytes</td>
<td></td>
</tr>
<tr>
<td>Parasitic infections: schistosomiasis; <em>Strongyloides</em></td>
<td>Eosinophils often high</td>
<td></td>
</tr>
<tr>
<td><strong>Acute respiratory distress syndrome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Idiopathic interstitial pneumonias</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic pulmonary fibrosis</td>
<td>Moderate increases in neutrophils with or without increased eosinophils</td>
<td></td>
</tr>
<tr>
<td>Nonspecific interstitial pneumonitis</td>
<td>Mild increases in lymphocytes plus neutrophils with or without increased eosinophils</td>
<td></td>
</tr>
<tr>
<td>Cryptogenic organising pneumonia</td>
<td>Moderate increases in lymphocytes plus neutrophils</td>
<td></td>
</tr>
<tr>
<td>Lymphoid interstitial pneumonia</td>
<td>Increases in lymphocytes</td>
<td></td>
</tr>
<tr>
<td>Respiratory bronchiolitis-associated ILD</td>
<td>Mainly macrophages containing smoking particles plus a few neutrophils</td>
<td></td>
</tr>
<tr>
<td>Desquamative interstitial pneumonia</td>
<td>Macrophages containing smoking particles plus moderate increases in neutrophils with or without increased eosinophils or lymphocytes</td>
<td></td>
</tr>
<tr>
<td>Acute interstitial pneumonia</td>
<td>Neutrophils very high</td>
<td></td>
</tr>
</tbody>
</table>
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 has long promoted BAL standardisation in a series of European guidelines. In 1999, the ERS published consensus guidelines recommending a standardised BAL procedure to use in adults based on the most comprehensive review of sources of variability for measurement of BAL components yet undertaken. The aim of using optimal BAL standardisation to minimise variability is to improve the reliability of quantitative measurements of all components. Minimising variability is an essential scientific requirement for research. However, a 2012 ATS clinical practice guideline on the clinical utility of BAL in ILD, recommends that ‘the BAL target site be chosen on the basis of an HRCT performed before the procedure, rather than choosing a traditional BAL site.’ This did not achieve full consensus because of the disadvantage that it would reduce BAL standardisation before it is known whether moving away from a standard BAL site would change diagnostic interpretation. To avoid compromising BAL standardisation, more research is needed into ILDs to compare lavages from both the standard BAL site and the site selected on the basis of HRCT, to conclude whether there is any clinical advantage to be gained. For now, the established standardised BAL procedure should also continue to be employed in patients with diffuse bilateral lung diseases. The standard site is also required to study healthy controls or patients with apparently ‘normal’ lungs, and to reduce variability for research. The site recommendation differs for patients with localised lung diseases such as some malignancies or infections, where BAL is targeted to the site of maximal involvement.

A protocol using the European recommended standard BAL procedure is as follows.

1) Perform BAL under local anaesthesia using fibroptic bronchoscopy as part of pre-treatment assessment.
2) Proceed initially as for routine fibreoptic bronchoscopy:
- generally semisupine 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).

7) Record the lavage site, total BAL fluid introduction volume and number of aliquots, and the total recovery volume.

8) Immediately send the BAL sample to the laboratory to enable processing to commence within 1 h because BAL cells deteriorate rapidly in saline.

9) Also send a patient protocol with age, sex, provisional diagnosis and other factors that influence BAL findings including smoking history (current, ex- or nonsmoker), current medications and associated diseases.

10) If biopsies are needed, perform these after BAL to avoid contamination of BAL with blood or bronchial tissue debris.

BAL is safe and side-effects are low, the same 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 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 pH 7.2–7.4 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. a milky appearance suggestive of alveolar lipoproteinosis or a very bloody appearance 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 and 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 at a 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 it in a small
volume (1–2 mL) to achieve a more concentrated suspension. Perform a total cell count, and calculate the number of cells per mL and total in the original BAL fluid.

6) Adjust the volume of the cell suspension to a standard $1.5 \times 10^6$ cells·mL$^{-1}$ to make cytocentrifuge slide preparations. Use 100-μL aliquots ($1.5 \times 10^2$ cells) per slide (spin at $90 \times g$ 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 air-dried preparations can be delayed for $\geq 24$ 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–Grünwald–Giemsa-stained cytocentrifuge slide preparations by light microscopy. First, low-power magnification ($\times 10$ and $\times 25$ objective lenses) is used to search the entire preparation and semi-quantitatively grade (on a scale from 0 to 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 ($\times 40$ or $\times 60$ 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 $\geq 400$ 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 $>5\%$ 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 birefringent 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 *P. 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 normal ranges that can be employed for differential BAL cell counts are shown in table 2. Smoking-related inclusions are frequent in macrophages from smokers.

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

Although this section describes BAL procedures, it would be incomplete without a summary of 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.

### Further reading


<table>
<thead>
<tr>
<th>Cell type</th>
<th>Nonsmokers</th>
<th>Smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophages</td>
<td>≥ 80</td>
<td>≥ 90</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>≤ 20</td>
<td>≤ 10</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>≤ 3</td>
<td>≤ 4</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>≤ 0.5</td>
<td>≤ 3</td>
</tr>
<tr>
<td>Mast cells</td>
<td>≤ 0.5</td>
<td>≤ 0.5</td>
</tr>
<tr>
<td>Plasma cells</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ciliated or squamous epithelial cells</td>
<td>≤ 5</td>
<td>≤ 5</td>
</tr>
</tbody>
</table>

Cata are presented as % total cells.
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 and pleura or for diagnosis of mediastinal masses, especially those located in the anterior mediastinum.

**Contraindications**

Absolute contraindications are:
- contralateral pneumonectomy
- bleeding disorders
- an uncooperative patient
- uncontrollable cough
- suspected arteriovenous malformation or hydatid cyst

Relative contraindications that may increase the risk of complications are:
- respiratory failure
- severe COPD
- pulmonary arterial hypertension
- 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, CT has become the most common means of guidance. Although performing a CT scan is more time-consuming, it has several advantages:
- It helps determine the safest needle trajectory avoiding vascular structures, fissures, bullae and necrotic areas of the tumour;
- It allows an approach to lesions not visible on fluoroscopy, such as small lesions; and
- It avoids 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 a guidance system when the lesion is in contact with the thoracic wall.

**Key points**

- PFNB is indicated when a cytohistological diagnosis of a peripheral lung lesion is required.
- PFNB may also be indicated for diagnosis of mediastinal mass and expansive lesions of the pleura and chest wall.
- The most common guidance system for PFNB is CT; 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%).
**Type of needle** Commercially available needles are either:

1. aspiration needles that yield material satisfactory for cytological evaluation (Chiba, Franseen, Westcott or Nordenstrom); or

2. histology needles that yield a tissue core (Trucut, Menghini or Silverman).

Needle diameter should be $<20$ Gauge and generally 20–22 Gauge needles are utilised. The evidence is currently insufficient to support a difference between cytology needles and core-needle biopsy in identifying lung malignancies. Histology needles have a higher specificity to diagnose benign lesions and the use of a core-biopsy needle is recommended when either a benign lesion or a malignancy other than cancer (i.e. lymphoma) is suspected.

**Results**

The reported sensitivity of PFNB ranges from 60% to 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 non-diagnostic PFNB does not rule out the possibility of malignancy. Recent papers report the feasibility of PFNB for obtaining lung tumour samples suitable for gene mutation analysis (i.e. epidermal growth factor receptor).

**Complications**

The most frequently reported complication is minor pneumothorax, with an average incidence of $\sim 25\%$ (range 4–42%). Major pneumothorax, requiring chest tube drainage, occurs in $\sim 6\%$ of cases. Haemoptysis occurs in 5–10% of cases and is generally mild and self-limiting. Rare complications include air embolism (0.07%), haemothorax, empyema, tumour implantation along the needle tract and haemopericardium.

**Further reading**

Thoracoscopy was first used more than 100 years 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 in TB. 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. Other terms used are ‘pleuroscopy’, ‘thoracoscopy for chest physicians’ and ‘local anaesthetic thoracoscopy’. Surgical thoracoscopy is better described as video-assisted thoracic surgery (VATS) which is performed in an operating room under general anaesthesia with selective intubation, whereas medical thoracoscopy can be performed under local anaesthetic or conscious sedation in an endoscopy suite using non-disposable rigid or semi-rigid (semi-flexible) instruments. It is therefore considerably less invasive, less cumbersome to the patient, and less expensive.

Nevertheless, 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, and as such should be part of specialist pleural disease services. 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.

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 non-disposable 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.
There are two different techniques of diagnostic and therapeutic thoracoscopy, as performed by the pneumologist. One, very similar to the technique first described by Jacobaeus for diagnostic purposes, uses a single entry with a rigid, usually 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-rigid pleuroscope, which has the advantage that handling is very simple, similar to a flexible bronchovideoscope (fig. 2).

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 pulmonary perforations, can be avoided by using safe points of entry.
and a cautious biopsy technique. Reported mortality rates are very low (<0.001). 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. 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. 3). Biopsies can be taken under direct visual control not only of the costal pleura, but also of the visceral and diaphragmatic pleura.

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, including for hormone receptor determination in breast cancer, as well as a more precise staging.

An additional advantage is that the diagnostic procedure can easily be combined with the therapeutic procedure of talc poudrage which is, at present, the most successful conservative pleurodesis method.

In tuberculous pleural effusion, MT/P has a high diagnostic sensitivity of almost 100% (fig. 4). It provides a bacteriological confirmation of the diagnosis of TB much more often and, thus, the possibility to perform susceptibility tests, which may have a considerable impact on the correct treatment and final outcome in patients with drug resistances. In parapneumonic pleural effusion and 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.

For those who are familiar with the technique, other (mainly diagnostic) indications are biopsies from the

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**Figure 3.** The different biopsy techniques used in the diagnosis of malignant pleural effusions and their sensitivity expressed in percentages (cytological and histological results combined). Prospective intra-patient comparison (n=208). Reproduced from Loddenkemper (1998).

**Figure 4.** The different biopsy techniques used in the diagnosis of tuberculous pleural effusions and their sensitivity expressed in percentages (cytological and histological results combined). Prospective intra-patient comparison (n=100). Reproduced from Loddenkemper (1998).
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.

Further reading

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 seventh to eighth 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 aspirated. Then, 20–60 mL of

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.
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

**Table 1. Thoracentesis set**

<table>
<thead>
<tr>
<th>Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Povidone–iodine solution or alcohol</td>
</tr>
<tr>
<td>Sterile drapes, gloves and gauzes</td>
</tr>
<tr>
<td>Abbocath-type needle catheters</td>
</tr>
<tr>
<td>Local anaesthesia</td>
</tr>
<tr>
<td>Syringes</td>
</tr>
<tr>
<td>Three-way stopcock</td>
</tr>
<tr>
<td>Aspiration set (if therapeutic)</td>
</tr>
<tr>
<td>Adhesive strips</td>
</tr>
<tr>
<td>Instrumentation table</td>
</tr>
</tbody>
</table>
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 as follows.

- **Pneumothorax** 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** 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** can be prevented by avoiding the lower rim of the upper rib and by excluding coagulopathies.
- **Haemopneumothorax** is rare when the aforementioned technique is observed and the patient has no bleeding disorder.

**Re-expansion pulmonary oedema** This can be prevented by removing less than 1–1.5 L of pleural fluid.

**Additional recommendations**

1. The region from the midclavicular 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.

**Further reading**

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, the following discussion will be limited to the effects on interventional bronchoscopy of pulmonary function tests.

In addition, interventional bronchoscopy will be 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).

Over the past few decades, the literature on interventional bronchoscopy has mainly focused on the ‘technicality’ of the various procedures; data pertaining to 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 with 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 is 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 has to be reduced by $\geq 50\%$ in order to cause breathing impairment, a clinical observation that recently has been corroborated by a fluid dynamic 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. 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 (area under the receiver operating curve $\leq 0.52$).

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 COPD 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
- symptoms of UAS occur earlier during exercise

The most commonly used quantitative criteria to detect UAS include

- maximal expiratory flow at 50% FVC (MEF$_{50\%}$/maximal inspiratory flow at 50% FVC (MIF$_{50\%}$) $< 0.30$ for intrathoracic and $> 1$ for extrathoracic stenosis
- FEV$_1$/MEF $> 10 \, \text{mL}\cdot\text{L}^{-1}\cdot\text{min}^{-1}$
- MIF$_{50\%} < 100 \, \text{L}\cdot\text{min}^{-1}$
- FEV$_1$/FEV$_{0.5} > 1.5$

The visual criteria are the presence of a plateau, biphasic shape, or oscillations in
the inspiratory or expiratory curves. However, the absence of a good correlation between the severity of UAS as determined by flow–volume loop analysis and breathing symptoms or radiological assessment of UAS points to the need for a method that can detect and document UAS in patients at risk. Forced oscillation tests at different breathing flow rates provide an accurate and reproducible measure of UAS, namely flow dependence of resistance, as documented in a comparative prospective cohort analysis of 10 normal subjects, 10 COPD patients and 10 patients suffering from tracheal stenosis, before and after airway stenting (Verbanck et al., 2010).

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, 1288 mL for peak expiratory flow (PEF) and 550 mL for FEV1 after stenting in nine patients. Gelb 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 (448 mL), PEF (920 mL·s⁻¹), MEF25–75% (470 mL·s⁻¹) and forced inspiratory volume in 1 s (310 mL) after stenting in a total of 24 patients. Improvements were more pronounced 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 +470 mL, FVC +620 mL and PEF +79 L·min⁻¹) and after tracheal laser debulking and/or stenting for inoperable malignant thyroid disease (FEV1 +540 mL, FVC +730 mL and PEF +96 L·min⁻¹) (figs 4 and 5). Oviatt et al. (2011) showed significant improvements in 6-min walk distance (99.7 m), FEV1 (448 mL) and FVC (416 mL) 30 days after bronchoscopic treatment for malignant airway obstruction.

Ernst et al. (2007) showed improvements in some but not all patients stented for severe tracheomalacia, in terms of respiratory symptoms, quality of life, and 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. Amjadi et al. (2008) and Oviatt et al. (2011) also documented significant and objective improvements in quality of life scores. Data on physiological effects of repermeabilisation techniques without additional stenting are even more scarce: objective improvements in pulmonary function were seen in 58% of patients after cryotherapeutic debulking of central airways,
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 multisite). 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 multisite, 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 on 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 of UAS. However, as a screening tool in a general population, these aberrations show a poor accuracy in predicting UAS. Forced oscillation tests may prove to be more accurate in detecting and document UAS. In extremely symptomatic, almost suffocating patients, immediate intervention with repermeabilisation/stenting is warranted. In nonlife-threatening cases, pre-intervention pulmonary function testing may yield useful information on the type, site and extent of the stenosis, whereas post-procedure 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 multisite, 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 are an invaluable tool in the armamentarium of modern pulmonology.
Further reading

Chest X-ray and fluoroscopy

Walter De Wever

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. Its lower sensitivity demands greater accuracy in interpretation. This greater accuracy can be achieved by following a standardised and systemic approach to a complete review of a chest radiograph. Technical factors and the position of the patient should also be considered when a chest radiograph is reported. Comparing prior films with recent ones is mandatory for the evaluation of pulmonary diseases.

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 is not rotated; and
• the scapulae are 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 posteroanterior (PA) radiograph is possible and that lung markings behind the heart are clearly visible. The exposure should be as short as possible, consistent with the production of adequate contrast. A high kilovoltage 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, anteroposterior (AP) upright or supine projections offer alternative but considerably less satisfactory views. The AP projection is of inferior quality because of the shorter focal distance, the greater magnification of the heart and, often, the restricted ability of these patients to suspend respiration or achieve full

Key points

• Chest radiography is the first step in radiological diagnosis of chest diseases.
• Although it is a common technique, achieving high image quality is challenging and depends on getting several factors right.
• The move from film to digital imaging offers exciting opportunities to improve image consistency and data management.

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inspiration. Based on a review of the literature and the recommendations of the American College of Radiology and the American Thoracic Society, recommendations on the use of chest radiographs are summarised in table 2.

<table>
<thead>
<tr>
<th>Radiographic appearance</th>
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</thead>
<tbody>
<tr>
<td>Frontal view (PA view)</td>
</tr>
<tr>
<td>Area from the lower cervical spine to below the costophrenic angles</td>
</tr>
<tr>
<td>Sternotclavicular joints symmetrical about the midline</td>
</tr>
<tr>
<td>Shadows of the scapulae away from the lung field</td>
</tr>
<tr>
<td>Lateral view</td>
</tr>
<tr>
<td>Soft tissues of the axillae should be included</td>
</tr>
<tr>
<td>Respiration</td>
</tr>
<tr>
<td>End of normal inspiration</td>
</tr>
<tr>
<td>Positioning of the patient</td>
</tr>
<tr>
<td>Erect position</td>
</tr>
<tr>
<td>Very ill patients: horizontal or semierect PA position</td>
</tr>
<tr>
<td>Film exposure factors</td>
</tr>
<tr>
<td>High kilovoltage</td>
</tr>
<tr>
<td>Focus: film distance</td>
</tr>
<tr>
<td>Must be kept constant for any particular department</td>
</tr>
<tr>
<td>150–180 cm</td>
</tr>
</tbody>
</table>

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 the 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 the 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 the 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, CT 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 performed 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 interpretation of a bedside radiograph requires extensive radiological experience to avoid misinterpretation of pleural and pulmonary disease. In addition, bedside radiography is an irreplaceable tool for detecting the malposition of tubes and lines and to identify associated complications. 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 is the common name for different technologies that are characterised by a direct readout matrix that covers the whole exposure area. Conversion of X-ray intensity into electrical signals can either be direct (selenium-based systems) or indirect (scintillator/photodiode systems). Advantages of digital radiography 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. Digital radiography 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, represents the logical culmination of the

Figure 1. a) PA chest radiograph. Normal lungs are visible as black fields (air) (*) with superposition of multiple white linear structures (vessels and walls of airways). The lung hila 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 of 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 <0.5. The bony components of the chest visible on the frontal view are: the ribs (+), the manubrium sternum (8), the clavicles (9), the scapulae (10) and the vertebral bodies on the midline. The diaphragm (11) is sharply delineated and 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).
extensive research that is continuing in this area.

New developments in chest radiography

With the introduction of digital radiography, development of new techniques became possible. These techniques are dual energy, temporal subtraction, rib suppression technique and digital tomosynthesis.

Dual energy involves weighted subtraction of low- and high-energy images, and results in images representing bone structures or soft tissue. This technique can improve the detection of small, noncalcified pulmonary nodules and the detection of calcified chest lesions. Disadvantages of this technique are the higher radiation dose compared with standard digital radiography, the reduced signal to noise ratio and the need for additional hardware to perform this technique.

Temporal subtraction involves subtraction of a current image from a prior image of the same patient. With this technique, the detection of pathological changes over time becomes easier. Sophisticated algorithms are needed to eliminate detection errors caused by differences in matching the projections of the two examinations.

Rib suppression technique This is a processing technique that suppress ribs in the image. Advantages of this technique over dual energy are:

- no need for an additional radiation dose or specialised equipment
- noise levels are not increased

Eliminating ribs has already shown to be effective in detection of lung lesions.

Digital tomosynthesis is a method of producing coronal cross section images using a digital detector and a chest X-ray system with a moving X-ray tube. This technique can improve the detection of pulmonary nodules by producing cross-section images without overprojection of the ribs or overlying vascular structures.

Chest fluoroscopy

Chest fluoroscopy was a popular procedure a generation ago. Patients were examined fluoroscopically in various projections and multiple spot radiographs were obtained.

<table>
<thead>
<tr>
<th>Table 2. Recommendations for the use of chest radiography</th>
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<tbody>
<tr>
<td><strong>Indications</strong></td>
</tr>
<tr>
<td>Signs and symptoms related to the respiratory and cardiovascular system</td>
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<tr>
<td>Follow-up of previously diagnosed thoracic disease for evaluation of improvement resolution, or progression</td>
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<tr>
<td>Staging of intrathoracic and extrathoracic tumours</td>
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<tr>
<td>Pre-operative assessment of patients scheduled for intrathoracic surgery</td>
</tr>
<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>
</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>
</tr>
<tr>
<td><strong>No indications</strong></td>
</tr>
<tr>
<td>Routine screening of unselected populations</td>
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<tr>
<td>Routine pre-natal chest radiographs for the detection of unsuspected disease</td>
</tr>
<tr>
<td>Routine radiographs solely because of hospital admission</td>
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<tr>
<td>Mandated radiographs for employment</td>
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<tr>
<td>Repeated radiograph examinations after admission to a long-term facility</td>
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</table>
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.

Dose and image quality in chest radiography

The radiation dose to the patient for chest radiography is relatively low but because of its frequent use, the collective dose can be considerable. The effective dose of a PA chest radiograph is about 0.02 mSv, which is about 0.5% that of a CT scan of the chest. The effective dose related to the lateral chest image is approximately two times higher compared with the dose of a PA projection. Studies indicate that dose reduction in PA chest images to at least 50% of commonly applied dose levels does not affect diagnosis in lung fields; however, dose reduction in the mediastinum, upper abdomen and retrocardiac areas appears to directly deteriorate diagnosis.

Further reading

Lung CT and MRI

Johny A. Verschakelen

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

Except for visualisation of the heart and great vessels, MRI of the chest is less frequently used in daily clinical practice, but in selected cases, this imaging technique can sometimes add information to what is seen on CT.

Computed tomography

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, todays scanners have multiple rows (multislice, multirow or multidetector row CT). This allows for a fast simultaneous acquisition of multiple images in the scan plane with one rotation of the X-ray tube around the patient. In this way, very good blood vessel opacification becomes possible using a limited amount of contrast (fig. 1). Spiral CT also offers flexible image reconstruction options, such as reconstructing images at various image thicknesses and two- 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 highly detailed images. It is used when detailed information on 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

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.
images may be somewhat reduced when multislice acquisition is used, the overall amount of information obtained is usually larger. Indeed, instead of a small number of axial slices with an image gap in between, a continuous dataset is obtained that allows the production of additional slices in different imaging planes. For this reason, this technique is currently 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 may be the increased radiation dose. However, 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.

In addition, new reconstruction algorithms, such as iterative reconstruction, that allow further dose reduction without important loss in image quality are being developed.

Low-dose CT has been used in several lung cancer screening trials to examine whether any survival benefit can be found in patients with screen-detected cancers compared with the unscreened. The initial data from one trial showed a 20.3% reduction in lung cancer mortality among participants in the CT arm of the study. However, other articles have presented conflicting predictions of survival benefit and debate over the clinical utility of CT screening for lung cancer is ongoing. As mentioned earlier, a CT of the chest is usually performed when the chest X-ray is abnormal or suspicious for the presence of pathology, although there are certainly indications for doing this examination even when the chest X-ray 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 into 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 that are available at the time of the CT examination. Particularly, diffuse and interstitial lung diseases are often very difficult to diagnose when the interpretation is only based on the CT presentation. Ideally, cooperation should be established between the clinician who is responsible for the patient, the radiologist and, when pathological information is present or probably required, the pathologist.

Continuous efforts are made to improve image quality and the diagnostic performance of CT imaging of the lung. Dual-energy CT scanning is helpful to study pulmonary perfusion in patients with pulmonary embolism (fig. 1). A further increase in the number of detector rows is feasible and may reduce acquisition time and, hence, image quality. Automated and semiautomated software packages will help to interpret the CT images.

### Magnetic resonance imaging

Like CT, MRI produces multiplanar cross-sectional images, but allows for a greater
tissue characterisation because it has a better contrast resolution than CT (fig. 2). It also has the benefit of not using ionising radiation.

In MRI, tissue protons are exposed to a strong external magnetic field and realign along the plane of the magnetic gradient. From this position they are then 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 along the magnetic field is installed, signal detection can be confined to a pre-selected body plane. Processing of these data then yields a sectional image of the plane of interest.

Today, MRI has an established role in the imaging of the heart and the great thoracic vessels. For the chest wall, diaphragm, mediastinum and lung, MRI was, for many years, considered a useful ‘problem-solving’ technique in specific instances, in addition to CT. These instances included the identification of tumour invasion in the chest wall and mediastinal structures, the differentiation between solid and vascular hilar masses, the assessment of diaphragmatic abnormalities,

**Figure 1. Dual-energy multislice spiral CT acquisition technique in a patient with pulmonary embolism. a) An enhancement defect is seen in a small branch of the right pulmonary artery (arrow). b) The perfusion scan shows a triangular area of decreased lung perfusion (arrows).**

<table>
<thead>
<tr>
<th>Abnormal chest X-ray</th>
</tr>
</thead>
<tbody>
<tr>
<td>Further evaluations of a chest wall, pleural, mediastinal or lung abnormality seen on a chest X-ray</td>
</tr>
<tr>
<td>Rule out or confirm a lesion seen on a chest X-ray</td>
</tr>
<tr>
<td>Lung cancer staging and follow-up</td>
</tr>
<tr>
<td>Assessment of thoracic vascular lesions</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Normal chest X-ray</th>
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<tbody>
<tr>
<td>Detection of diffuse lung disease</td>
</tr>
<tr>
<td>Detection of pulmonary metastases from a known extrathoracic tumour</td>
</tr>
<tr>
<td>Demonstration of pulmonary embolism</td>
</tr>
<tr>
<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>
</tr>
</tbody>
</table>

**Table 2. Indications for CT of the chest**

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and the study and follow-up of mediastinal lymphoma during treatment. As mentioned earlier, nowadays most centres use multidetector spiral CT for thoracic imaging, including the areas thought previously to be the domain of problem-solving MRI.

Although it has become clear now that MRI will always be second to CT when it comes to the visualisation of pulmonary structure, disease and patterns with high spatial resolution, the many research and development efforts that have been made during recent years have resulted in new and valuable applications that are very promising, and that could once be implemented in the clinical practice. There has been much interest in the role of MRI in the diagnosis of pulmonary embolism as a radiation-free alternative to CT. Some 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 representing underperfused lung tissue on gadolinium-enhanced MRI. In addition, imaging of pulmonary ventilation by MRI has become possible. Hyperpolarised helium-3 gas has been used successfully to demonstrate perfusion changes in patients with asthma, COPD and CF, and hyperpolarised xenon-129, fluorine and oxygen-enhanced lung MRI are methods of gas imaging that have opened the field of imaging pulmonary ventilation by MRI. Diffusion-weighted magnetic resonance is another interesting application. This technique provides a measurement that reflects the random Brownian motion of water protons in biological tissue. This motion causes magnetic resonant 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.

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

Further reading

High-resolution computed tomography (HRCT) is a CT acquisition and reconstruction technique that produces highly detailed images. It differs from ‘classical’ CT by the fact that thin slices (0.5–1 mm) are generated and that high-frequency reconstruction algorithms are used to improve image detail. As thin slices are necessary, the technique is also called thin-slice CT. Before the introduction of spiral CT, these thin slices were obtained by the ‘incremental’ acquisition technique in which 1-mm slices were produced with an image interval of 10 mm. Today, most institutions have spiral CT scanners and use multislice acquisition to obtain a continuous dataset of the entire chest that allows generation of a large number of adjacent thin slices. In this way, more information is obtained than with the incremental acquisition technique. In addition, images in other imaging planes and special reconstructions like maximal- and minimal-intensity projections (MIP and MinIP, respectively) can be made.

Because of the important image gap that existed when only incremental acquisition could be used – giving information about a small but well and equally distributed sample of the lung – the HRCT technique was (and still is) predominantly used to study diffuse and interstitial lung disease (DILD). It should be emphasised, however, that with the multislice spiral CT technique, thin and highly detailed images of the lung can be reconstructed from almost every CT examination.

HRCT and DILD

Since its introduction into clinical practice, the use of HRCT has constantly increased. This is related not only to the fact that this technique provides important morphological information on the lung parenchyma (it offers the highest image detail of the lung) but also because it helps to better understand the clinical and pathological course of some diseases, which has even resulted in the formulation CT classifications to categorise disease. HRCT is also partly responsible for the radical change in the diagnostic work-up of DILDs that has occurred the last 10 years. The historical gold standard of histologic diagnosis has been replaced by an integrative approach of clinical, radiological and, when necessary, pathologic data during multidisciplinary discussions. HRCT and
histology are nowadays often considered as ‘silver’ standards. This does not mean that lung biopsy is less important but implicates that the multidisciplinary discussion defines in which cases a lung biopsy will very likely give more (or important additional) information than CT and in which cases a biopsy is not needed.

There are several reasons why HRCT plays an important role in this multidisciplinary discussion.

• Some DILDs can have a typical HRCT pattern and when this disease presents with such a pattern, HRCT may be very accurate in the diagnosis, i.e. HRCT may have a high positive predictive value (PPV). Idiopathic pulmonary fibrosis (IPF) is such a disease (fig. 1). The PPV of HRCT in IPF patients is >90% when a typical appearance pattern (predominant cystic, irregular linear pattern, traction bronchiectasis and no predominant ground-glass opacity) is combined with a typical distribution pattern (subpleural and basal lung). Unfortunately, a typical HRCT pattern of IPF is only seen in less than half of cases. In that situation, a part of the multidisciplinary discussion will be related to the question of whether the combination of HRCT with the clinical data is sufficient for diagnosis or whether an additional lung biopsy is necessary. Table 1 gives a list of diseases in which CT can be diagnostic when a typical pattern is present.
• If it is decided that a lung biopsy is necessary, HRCT can help to determine the best location for taking the lung sample by suggesting the most likely areas of active disease and avoiding the areas of (nonspecific) terminal fibrosis.
• The information provided by HRCT and histology is very often complementary. While histology provides a microscopic view of a small part of the lung, HRCT gives a ‘sub-macroscopic’ or sub-millimetre view of the entire lung. Combination of this information can indeed result in a single diagnosis. It should be emphasised, however, that in some patients with DILD, multiple

Table 1. Diseases that can present with a typical HRCT pattern

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<th>Disease</th>
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<td>Sarcoidosis</td>
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<td>Langerhans’ cell histiocytosis</td>
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<td>Hypersensitivity pneumonitis</td>
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<td>Lymphangitic spread of cancer</td>
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<td>Silicosis and coalminers’ pneumoconiosis</td>
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<td>Lymphangiomyomatosis</td>
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<td>Cryptogenic organising pneumonia</td>
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pathologic and/or HRCT patterns can be seen simultaneously. In that situation, multidisciplinary discussion should determine the clinical significance of these individual patterns.

- HRCT can be helpful during follow-up of disease and in this way contribute to the diagnosis by providing information about speed of disease progression. HRCT also plays a role in patients with acute exacerbation of DILD and in the differential diagnosis with infection, left heart failure or other causes of acute lung disease.

HRCT and focal lung disease

As mentioned earlier, HRCT obtained by the incremental method was not suitable for the study of localised and focal lung abnormalities because of the image gap. The introduction of multislice spiral CT has made it possible to choose the slice thickness after the examination and highly detailed thin slices of the entire chest can be produced instead of, or in addition to, the thicker slices. In this way, it is possible to obtain not only additional detailed information of the focal lung lesion but also of the entire lung. Lymphangitic spread (fig. 2), lung perfusion defects in patients with pulmonary embolism, tumour extension into the surrounding lung, early pulmonary oedema and early small airway infection are examples of disorders that can be better appreciated on thin slices than on thick slices.

Figure 2. Patient with breast cancer developing lymphangitic spread of cancer. a, b) The first CT examination a) axial and b) coronal view shows a normal lung parenchyma. c, d) The second CT examination 6 months later shows a linear pattern in the right lower lobe caused by thickening of the interlobular septa together with the development of a pleural effusion. c) Axial view and d) coronal view.
HRCT technique

The basic HRCT examination contains continuous axial 1-mm slices of the entire chest obtained with a multislice spiral CT scan at breath hold after deep inspiration. From these data, additional coronal reconstructions are usually made, as these are not only helpful to study the cranio-caudal distribution of disease but often allow better visualisation of the presence and distribution of linear opacities. If desired, these CT data can also be used to calculate MIPs, which can be helpful to study small lesions and their relation to the pulmonary lobule, and MinIPs, which may be helpful to study low-attenuation lung disease. Expiratory HRCT (stopping breathing after deep expiration) should be performed when small airway narrowing is suspected. This expiratory HRCT can be obtained by the incremental method, in which 1-mm slices are produced with a larger image interval (20–30 mm), or by low-dose spiral CT. A lower radiation dose is used in this technique. Finally, it may be necessary to add a few slices in the prone body position. These are performed in patients suspected of having early DILD when supine CT shows minimal changes in the posterior and basal parts of the lung, areas that are often first involved in DILD but also often show a gravity-related perfusion increase. Prone CT scans are mostly able to differentiate between these entities as gravity-related changes will disappear in the prone body position. Administration of intravenous contrast is not necessary.

HRCT in the diagnosis of diffuse lung disease

As mentioned earlier, HRCT plays an important role in the process of making the diagnosis of diffuse lung disease. Interpreting a HRCT image of the lungs of a patient suspected of having DILD is a stepwise process. First, it is important to decide whether the lung changes are indeed resulting from a diffuse lung disease, i.e. a disease that is diffusely spread over an important part of the lung and shows CT changes that are composed in a repeating arrangement (pattern). If it very likely is a diffuse lung disease, the disease pattern should be determined: how does the disease appear, i.e. what is the appearance pattern (nodular or linear, increased or decreased attenuation), and where are the abnormalities located, i.e. what is the distribution pattern (which lung areas are involved and how does disease relate to the pulmonary lobule)? The disease pattern can be very typical (table 1) but is often atypical and a differential diagnosis list should be proposed. In both cases, it is important to have a multidisciplinary discussion in which the HRCT findings are correlated with the clinical findings. HRCT can then be helpful in the decision of whether a lung biopsy is necessary or not and, if so, of the best site to take the biopsy. Finally, the integration of the clinical, HRCT and pathological data may result in an assumed diagnosis or a differential diagnosis list, or the disease may be considered as unclassifiable.

Further reading

Nuclear medicine of the lung

Antonio Palla and Duccio Volterrani

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

Diagnosis of pulmonary embolism

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

PLS has been proven to be useful for:

- diagnosis of pulmonary embolism
- 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 are typically multiple, wedge-shaped and often bilateral. PLS has a sensitivity of 100%: 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 it is cumbersome, time consuming and poorly available. Nowadays, VLS is only indicated in some individual patients with pulmonary embolism, 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; this method has made it possible to obtain a diagnostic accuracy similar to that shown by angio-CT. PLS also plays a leading role in the follow-up of patients with pulmonary embolism, as it helps to monitor the efficacy of treatment in the first few days, it allows prompt detection of early and late recurrences and evolution towards pulmonary hypertension, and it may differentiate between thromboembolic pulmonary hypertension and other types of pulmonary hypertension.

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.
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 ‘panda’ 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. In addition, gallium scintigraphy is indicated in investigating metabolic activity in pulmonary infections and the efficacy of proper therapy. In the diagnosis of pulmonary TB, 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 the efficacy of chemotherapy in lymphomatous diseases and may help differentiate post-actinic fibrosis from residual tumour foci when a lung density persists after radiotherapy.

Lung cancer

PET is a nuclear medicine technique that produces a three-dimensional image 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 increasing specificity compared with PET alone. The most frequently used tracer is 2-[18F]-fluoro-2-deoxy-D-glucose (FDG), a glucose analogue, the tissue concentration of which is directly related to 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 amount potentially present if the tracer had been evenly distributed in the body.

FDG-PET has proven useful in:
- diagnosing and staging lung cancer
- monitoring the efficacy of treatment
- defining the biological target volume for radiation treatment planning

Figure 1. Solitary pulmonary nodule as it appears on a) chest CT, b) PET/CT and c) FDG-PET.
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 imaged by FDG-PET.

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 the 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. However, a positive finding should not preclude mediastinoscopy. Moreover, the addition of FDG-PET to the standard workup can prevent unnecessary thoracotomies and change the 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 MRI 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.

Further reading

Transthoracic ultrasound

Florian von Groote-Bidlingmaier, Coenraad F.N. Koegelenberg and Chris T. Bolliger

Key points

- Transthoracic ultrasound can be performed with the most basic ultrasound equipment and allows for immediate and mobile assessment of patients with a wide variety of respiratory diseases.

- The major indications for the use of transthoracic ultrasound are the description of pleural effusions, pleural thickening, diaphragmatic dysfunction, and chest wall and pleural tumours.

- Other applications of transthoracic ultrasound include the diagnosis of a pneumothorax, pulmonary consolidation, tumours, interstitial syndromes and pulmonary embolism.

- Furthermore, ultrasound is ideal to guide thoracentesis, drainage of effusions and other thoracic interventions, and is particularly useful in intensive care units where radiographic equipment is unavailable.

- Major advantages of the technique 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 section.

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).

Special attention must be paid to patient positioning. The posterior chest is ideally scanned in the sitting position whereas the anterior and lateral chest are best examined in the supine or lateral decubitus position.

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 ultrasound is called the ‘lung sliding’ sign.

Ultrasound 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 or A-lines (fig. 1).

Chest wall pathology

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

Pleural pathology

Transthoracic ultrasound is most commonly used to investigate pleural effusions, and is more sensitive than decubitus radiographs at demonstrating minimal or loculated effusions. The ultrasound appearance of a pleural effusion depends on its nature and chronicity.

Figure 1. The typical appearance of a normal chest on ultrasound. 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 ultrasound). Reverberation artefacts beneath the pleural lines imply an underlying air-filled lung. P: pleura; L: lung; R: reverberation artefact.

Figure 2. a) Example of an anechoic pleural effusion. 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 in b), which is classified as complex septated. Multiple septa form many compartments in the same effusion. PE: pleural effusion; L: lung; S: septum.
Four appearances based on the internal echogenicity are recognised:

- anechoic
- complex but nonseptated
- complex and septated
- homogenously echogenic

Transudates are invariably anechoic, nonseptated and free flowing, whereas complex, septated or echogenic effusions are usually exudates. Malignant effusions are 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

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 Diacon et al. (2005) with permission from the publisher.
- **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
- **large** if the space is bigger than a two-probe range

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

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. (2009) found that pleural thickening ≥1 cm, pleural nodularity and diaphragmatic thickening ≥7 mm were highly suggestive of malignant disease. In their study, ultrasound correctly identified 73% of malignant effusions.

The detection of a pneumothorax by means of ultrasound requires a greater deal of expertise than the detection of pleural fluid. A recent meta-analysis concluded that bedside ultrasonography had a higher sensitivity and similar specificity for the diagnosis of a pneumothorax when compared with chest radiography. The absence of normal lung sliding, the loss of comet-tail artefacts and exaggerated horizontal reverberation artefacts are reliable signs of the presence of a pneumothorax. Ultrasound is also the ideal tool to screen for a post-procedural pneumothorax after transthoracic procedures and transbronchial biopsy.

**Pulmonary pathology**

A lung tumour abutting the pleura will be detectable by ultrasound (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.

Ultrasound can detect pneumonic consolidations provided they have contact with the pleura. Early pneumonic consolidation may appear very similar to the diffusely echogenic tissue-like texture of the liver. Both air and fluid bronchograms are usually seen within the consolidated lung. Noninfective causes of consolidations with similar appearance on ultrasound include pulmonary infarction, haemorrhage and bronchoalveolar carcinoma. Consolidation can be differentiated from an interstitial syndrome, for which long, laser-like vertical hyperechoic lines, called B-lines, are pathognomonic. Interstitial syndromes may include pulmonary oedema, interstitial pneumonia or diffuse parenchymal lung disease.

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.

Another indication for the use of transthoracic ultrasound is the assessment
of pulmonary and pleural-based cysts, which commonly appear as large, round anechoic lesions.

**Conclusion**

The value of ultrasound 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.

**Further reading**

Acute lung injury (ALI) and its most severe manifestation, acute respiratory distress syndrome (ARDS), are defined by physiological criteria (i.e. ratio of $P_{aO_2}$ to inspiratory oxygen fraction ($F_{IO_2}$) $\leq 300$ mmHg for ALI and $\leq 200$ mmHg for ARDS, independent of positive end-expiratory pressure (PEEP)) and by 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 be evaluated by CT 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 manifestations, triggering systemic inflammatory response syndrome, or in extremis multiple organ dysfunction syndrome.

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, such as aspiration, barotraumas, nosocomial infections and oxygen toxicity, has to be avoided. 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 PEEP to reduce the amount of nonaerated atelectatic lung.

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

- Tidal volume $6 \text{ mL} \cdot \text{kg}^{-1}$ ideal body weight.
- Plateau pressure $<30 \text{ cmH}_2\text{O}$, peak pressure $<35 \text{ cmH}_2\text{O}$.
- 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 ($>15 \text{ cmH}_2\text{O}$) 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. Estimating the transpulmonary pressure by means of oesophageal pressure measurement might help to find the ideal PEEP level. Alternative methods of ventilation 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 (vv-ECMO), which improves both oxygenation and carbon dioxide removal, and allows a highly protective low tidal volume ventilation. Recently, the CESAR trial provides the first evidence that vv-ECMO is superior to conventional treatment in the most severe forms of ARDS. Moreover, a pumpless extracorporeal lung assist was developed using arterio-venous bypass, in which a gas exchange membrane is integrated (interventional lung assist). Interventional lung assist provides effective carbon dioxide elimination and a moderate improvement in oxygenation, and therefore allows a more protective mechanical ventilation.

Concerning pharmacological treatments of ALI/ARDS, inhaled nitric oxide has not been found to be particularly effective and there is no clear convincing data to support the

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![Figure 1. Current definition of ALI/ARDS and the Berlin definition of ARDS based on $P_aO_2/F_iO_2$ criteria.](image)
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.

Further reading

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, and the respiratory controllers in the central nervous system (CNS) linked to respiratory muscles through spinal and peripheral nerves.

When respiratory failure 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 (fig. 1).

The diagnosis of respiratory failure is not clinical but based on arterial gas assessment: it is defined by a $P_{aO_2}$, $< 60$ mmHg and/or $P_{aCO_2}$, $> 45$ mmHg. These values are not rigid; they must serve as a general guide in combination with the patient’s history and clinical evaluation. Respiratory failure may be acute, chronic or acute on chronic, with clinical presentation being quite different between these types.

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

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

Four pathophysiological mechanisms are responsible for hypoxaemic respiratory failure:

- ventilation/perfusion ($V'/Q'$) ratio inequalities;
- shunt;
- diffusion impairment; and
- hypoventilation.

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

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**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.

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Figure 1. Types of respiratory failure. The respiratory system can be considered as consisting of two parts: the lung and the pump. Reproduced and modified from Roussos et al. (2003).
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-COPD diseases may lead to hypoxaemic ARF, which is defined as a $P_aO_2$/inspiratory oxygen fraction ($FIO_2$) ratio $\leq 300$ (table 1).

Hypoxaemia is treated with an increase in $FIO_2$ (the lower the $V'/Q'$, the less the effect) and by recruiting airspaces with assisted ventilation. Airspace de-recruitment occurs when the transpulmonary pressure falls below the airspace collapsing or closing pressure, and when the transpulmonary pressure applied during inspiration fails to exceed the airspace opening pressure. Accordingly, airspace opening can be facilitated by increasing the transpulmonary pressure applied at the end of expiration (CPAP or positive end-expiratory pressure (PEEP)) and at the end of inspiration (inspiratory positive airway pressure).

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

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

Hypercapnic respiratory failure may be the result of CNS depression, functional or mechanical defects of the chest wall, an 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 respiratory failure may occur either acutely, insidiously or acutely upon a chronic carbon dioxide retention. In all of these conditions, the pathophysiological common mechanism

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<td>Alveolar haemorrhage</td>
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<td>Atelectasis</td>
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<td>ALI: acute lung injury.</td>
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<th>Table 2. Causes of acute hypercapnia</th>
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<td>Cardiogenic and noncardiogenic oedema</td>
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<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Upper airway obstruction</td>
</tr>
<tr>
<td>Bronchiectasis</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Other causes</strong></td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Circulatory shock</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>ALS: amyotrophic lateral sclerosis.</td>
</tr>
</tbody>
</table>
is reduced alveolar ventilation for a given value of carbon dioxide production.

Acute exacerbations of COPD (AECOPD) are periods of acute worsening that greatly affect the health status of patients, with an increase in hospital admission and mortality. Estimates of in-patient mortality range from 4% to 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 respiratory failure 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 of $V/Q'$ 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 $V^E$ may result in expiratory flow limitation, dynamic hyperinflation and related intrinsic 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 volume ($V_A$) 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, carbon dioxide retention and acidaemia may occur. Dyspnoea, right ventricular failure and encephalopathy characterise severe AECOPD complicated by ARF. Arterial pH reflects the acute worsening of $V_A$ and, regardless of the chronic $P_{aCO2}$ 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

Figure 2. Schematic representation of the sequence of responsible mechanisms that lead to acute-on-chronic respiratory failure in COPD patients. $t_{tot}$: total respiratory cycle time; $t_i$: inspiratory time; $t_e$: expiratory time; $R_{aw}$: airway resistance; $E_{Ldyn}$: dynamic elastance of the lung; PEEPi: intrinsic PEEP. Reproduced and modified from Roussos et al. (2003).
acute-on-chronic respiratory failure in COPD patients.

Besides medical treatment of the underlying disease, oxygen supplementation and, eventually, ventilator assistance are appropriate therapy for acute-on-chronic respiratory failure. The goal of assisted ventilation (either invasive or noninvasive) during AECOPD is to unload the respiratory muscles and to reduce carbon dioxide by increasing $V_a$, thereby stabilising arterial pH until the underlying problem can be reversed.

**Further reading**

NIV is a key management tool in patients with acute hypercapnic respiratory failure, and meta-analyses confirm it markedly reduces mortality and morbidity in acidic hypercapnic exacerbations of COPD (Lightowler et al., 2003; Keenan et al., 2003). NIV may also be used in other causes of acute ventilatory failure, such as neuromuscular disease and bronchiectasis, but these have not been subject to large randomised controlled trials (RCTs). A more limited role in hypoxaemic respiratory failure is described here. Levels of evidence to support NIV use in acute respiratory failure are shown in table 1.

NIV in acute exacerbations of COPD

NIV reduces endotracheal intubation rate, and decreases intensive care unit (ICU) and hospital duration of stay in acute acidotic exacerbations of COPD; therefore, it should be available in all respiratory centres that admit COPD patients with exacerbations. In a RCT (Plant et al., 2000) carried out on a general respiratory ward NIV halved mortality from 20% to 10%, compared with standard COPD care. In patients already intubated, prompt extubation onto NIV reduces the duration of ventilation and ICU stay, and increases survival (tables 2 and 3). This is largely due to the fact that endotracheal tube-related nosocomial infections are reduced. Patients are also able to eat and drink normally and mobilise quicker. Most studies show improvements in arterial blood gases over the first hour of therapy and fall in carbon dioxide tension and respiratory rate have been shown to predict the success of therapy. Dyspnoea may decrease more rapidly with NIV than with conventional therapy (Bott et al., 1993).

Indications NIV should be used in tachypnoeic, dyspnoeic acute COPD patients with a pH <7.35 and $P_{aCO_2}$ >45 mmHg (6.0 kPa). In severe acidic exacerbations (pH <7.30), the risk of NIV failure and need for intubation is higher but, providing patients are carefully monitored, NIV in a high-dependency unit or ICU may

Key points

- NIV is the gold standard therapy in acute dyspnoic COPD patients with a pH <7.35 and $P_{aCO_2}$ >45 mmHg (6.0 kPa) and has been shown to halve mortality in this situation.
- Patients with an acute exacerbation of COPD and pH <7.30 being treated with NIV should be managed in a high-dependency or ICU area as they are at risk of deterioration and requirement for invasive ventilation.
- In acute hypoxaemic respiratory failure, NIV and entrained oxygen therapy may be tried initially but if improvement in arterial blood gas tensions and dyspnoea do not occur rapidly, urgent consideration should be given to progression to invasive ventilation.
- A combination of NIV and cough assistance with insufflation–exsufflation may be helpful in neuromuscular patients with acute chest infection and reduced cough efficacy.
be tried first, as a failed trial of NIV leading to endotracheal intubation does not lead to higher mortality. Relative contraindications to NIV include mental obtundation due to severe hypercapnia, poor cough and bulbar function, upper airway obstruction, multiple comorbidities, and a very high severity score.

Practicalities of ventilator settings

Bilevel positive pressure devices are most commonly used together with full face mask to obviate leaks from the mouth. Inspiratory positive airway pressure (IPAP) is set to control $P_{aCO_2}$ and reduce the work of breathing; expiratory positive airway pressure (EPAP) is set to overcome episodes of upper airway obstruction and recruit alveoli. A back-up rate a few breaths below the patient’s spontaneous breathing rate is usually chosen. Oxygen therapy should be entrained into the circuit as proximally as possible to the mask in order to titrate to the prescribed $S_{aO_2}$, (e.g. 88–92%). ‘Intelligent’ ventilators that add either an assured tidal volume or minute volume may be helpful in some patients but have not yet been shown to be superior to expert ventilator set-up. Careful attention to mask fit is important as this helps encourage adherence to therapy. Before initiating NIV, advance planning should take place to clarify whether progression to endotracheal intubation is indicated and in accordance with the patient’s wishes and best interests, in the event of NIV failure. An ERS Task Force survey (Nava et al., 2007) showed that NIV was the ceiling of care in 31% of patients with acute exacerbations of COPD admitted to high-dependency units. As pointed out by Demoule et al. (2004), survival in patients with NIV as a ceiling of care is 50–60% for the episode, but one year after admission falls to 30%.

NIV in other causes of hypercapnic respiratory failure

NIV is used in acute hypercapnic exacerbations of CF and bronchiectasis. It may be helpful when combined with intensive physiotherapy and other airway clearance techniques (Demoule et al., 2004) and, indeed, may allow physiotherapy sessions to be extended when these are carried out in patients simultaneously using NIV. In one study (Hodson et al., 1991), NIV was used to bridge CF patients to transplantation.

NIV may also be used to reduce the work of breathing and improve arterial blood gas tensions in patients with respiratory muscle weakness due to neuromuscular conditions such as Duchenne muscular dystrophy, spinal muscular atrophy, myopathies and motor neurone disease. In these situations, if cough peak flow is $<160\text{ L-min}^{-1}$, augmentation of secretion clearance with mechanical insufflation–exsufflation is likely to reduce the risk of intubation.

There are no RCTs of NIV in acute ventilatory failure in patients with obesity hypoventilation syndrome. However, nonrandomised comparisons suggest that NIV is more effective than CPAP in patients with significant hypercapnia and superior to endotracheal intubation in those without major comorbidity. EPAP should be titrated to control the OSA/hypopnoea component and IPAP to control $P_{aCO_2}$.

Table 1. Levels of evidence for use of NIV in acute respiratory failure

<table>
<thead>
<tr>
<th>Strong evidence (level A)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute exacerbations of COPD</td>
<td></td>
</tr>
<tr>
<td>To facilitate weaning of COPD</td>
<td></td>
</tr>
<tr>
<td>Acute cardiogenic pulmonary oedema (cf. CPAP)</td>
<td></td>
</tr>
<tr>
<td>Immunocompromised patients</td>
<td></td>
</tr>
<tr>
<td>Reasonable evidence (level B)</td>
<td></td>
</tr>
<tr>
<td>Post-operative respiratory failure</td>
<td></td>
</tr>
<tr>
<td>‘Do not intubate’ patients</td>
<td></td>
</tr>
<tr>
<td>Upper airway obstruction, OSA, obesity, hypoventilation</td>
<td></td>
</tr>
<tr>
<td>CF, asthma</td>
<td></td>
</tr>
<tr>
<td>Case series/reports</td>
<td></td>
</tr>
<tr>
<td>Restrictive disorders</td>
<td></td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
<td></td>
</tr>
</tbody>
</table>

ERS Handbook: Respiratory Medicine
NIV in acute hypoxaemic respiratory failure

Acute hypoxaemic respiratory failure (AHRF) occurs in a multiplicity of disorders including pneumonia, acute cardiogenic pulmonary oedema, acute lung injury, acute respiratory distress syndrome, and following immunosuppression, trauma and noxious gas inhalation. As the underlying pathophysiological mechanisms of ventilation–perfusion mismatch, shunt and diffusion difficulties differ from hypoventilation in acute ventilatory failure, one can predict that success rates with NIV will be lower. While ventilatory support is used to reduce the work of breathing, improve $P_aCO_2$, control and recruit alveoli, it also buys time for other definitive therapies to take effect. Buying time may be more swiftly effective in, for example, acute pulmonary oedema, where diuretic and vasodilator therapy may be added, or pneumonia, where antibiotics can be introduced, compared with acute lung injury, where there is no specific therapy.

In several RCTs of patients with AHRF of mixed aetiology, NIV reduced the need for intubation, ICU stay and mortality (Wysocki et al., 1995; Antonelli et al., 1998). However, results are less clear-cut in pneumonia, where one study (Confalonieri et al., 1999) showed a subgroup of patients with COPD and community-acquired pneumonia (CAP) experienced less intubation than the pneumonia group as a whole, and a further study (Jolliet et al., 2001) suggests that those with severe CAP experienced a higher intubation rate and longer ICU stay. In highly infectious causes of pneumonia (e.g. severe acute respiratory syndrome and pandemic influenza), special measures are required when using NIV. Although NIV is categorised as an aerosol-generating procedure by some authorities, recent work (Simonds et al., 2010) suggests it mainly generates large droplets (>10 μm in

<table>
<thead>
<tr>
<th>Table 2. Meta-analysis of NIV in acute COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>Treatment failure</td>
</tr>
<tr>
<td>Mortality</td>
</tr>
<tr>
<td>Intubation</td>
</tr>
<tr>
<td>Complications</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Table 3. Meta-analysis of NIV in acute COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>Length of hospital stay days</td>
</tr>
<tr>
<td>Trials in ICUs</td>
</tr>
<tr>
<td>Trials in wards</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Respiratory rate at 1 h breaths min$^{-1}$</td>
</tr>
<tr>
<td>pH at 1 h</td>
</tr>
<tr>
<td>$P_aCO_2$ at 1 h kPa</td>
</tr>
<tr>
<td>$P_aO_2$ at 1 h kPa</td>
</tr>
</tbody>
</table>

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diameter). However, special precautions should be taken, including using personal protective equipment, a high-efficiency N95 microbial filter between the mask and exhalation valve, low pressures, and close attention to mask fit.

In acute cardiogenic pulmonary oedema, there have been several meta-analyses (Winck et al., 2006; Masip et al., 2005; Peter et al., 2006) and a recent large RCT (Crane et al., 2004). Results suggest that use of NIV and CPAP can reduce breathlessness and improve arterial blood gas tensions, and in the meta-analyses, NIV did reduce intubation; however, in the large RCT, which contained more patients than were included in the meta-analyses, there was no difference in mortality at 7 days between oxygen therapy, NIV and CPAP, and no differences in outcomes when NIV and CPAP were compared. A consensus is that medical therapy with nitrates is crucial first-line treatment, with the addition of CPAP in those with marked respiratory distress and NIV for those who are hypercapnic due to high work of breathing and/or concomitant COPD or neuromuscular disorder.

In all the causes of AHF discussed here, NIV with entrained oxygen therapy may be tried initially but close monitoring is required and, if arterial blood gas tensions and dyspnoea are not relieved within the first hour of therapy or the patient’s condition rapidly deteriorates, progression to use of invasive ventilation should be urgently considered.

Further reading


Acute oxygen therapy

Acute oxygen therapy

Acute oxygen therapy is indicated to improve oxygen delivery in situations of cardiac and respiratory arrest, acute severe hypotension, low cardiac output states in the presence of metabolic acidosis and when $S_aO_2$ is $<90\%$. In respiratory conditions, oxygen therapy is prescribed to correct hypoxaemia, rather than to reduce breathlessness, and so should always be titrated to $S_aO_2$ or blood gas measurements. In acutely ill patients, high-concentration oxygen therapy should be prescribed to correct $S_aO_2$ to 94–98\%. In those with hypercapnic respiratory failure or at risk of ventilatory decompensation (e.g. severe COPD, neuromuscular disease, obesity hypoventilation syndrome and chest wall disorders), 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. Indeed, in acute hypercapnic ventilatory failure, ventilatory support is usually the treatment of choice.

Key points

- Oxygen therapy is prescribed to correct hypoxaemia and should thus be titrated to $S_aO_2$.
- In acutely hypoxaemic patients, oxygen should be delivered to correct $S_aO_2$ to 94–98\%.
- In those with hypercapnic respiratory failure or at risk of ventilatory decompensation, a target of $S_aO_2$ of 88–92\% should be the aim.

Long-term oxygen therapy

Chronic hypoxaemia occurs either due to ventilation–perfusion mismatch, alveolar hypoventilation or diffusion problems in chronic lung disease; in some conditions (e.g. COPD), all factors may be present. Long-term oxygen therapy (LTOT) is used to correct hypoxaemia diurnally and nocturnally in the majority of patients. In COPD, LTOT increases survival, reduces polycythaemia and, in some patients, may improve sleep quality and/or neuropsychiatric symptoms. In individuals with chronic ventilatory failure due, for example,

Table 1. Assessment for LTOT

<table>
<thead>
<tr>
<th>Consider assessment in</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with FEV₁ $&lt;30%$ predicted</td>
<td></td>
</tr>
<tr>
<td>Patients with cyanosis</td>
<td></td>
</tr>
<tr>
<td>Patients with polycythaemia</td>
<td></td>
</tr>
<tr>
<td>Patients with peripheral oedema</td>
<td></td>
</tr>
<tr>
<td>Patients with raised jugular venous pressure</td>
<td></td>
</tr>
<tr>
<td>Patients with $S_aO_2$, on air $\leq 92%$</td>
<td></td>
</tr>
</tbody>
</table>
to chest wall disease, first-line treatment is assisted ventilation (e.g. NIV).

Patients should be assessed for LTOT in the presence of the features shown in Table 1.

LTOT is prescribed for >15 h a day, e.g. via concentrator, to correct $S_\text{a}O_2$ to $\geq 90\%$ in those patients listed in Table 2.

Ambulatory oxygen therapy is added to correct hypoxaemia on exercise. In sedentary patients using LTOT, ambulatory oxygen is usually prescribed at the same flow rate as in 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, aiming to correct $S_\text{a}O_2$ to $>90\%$, reduce dyspnoea and increase exercise tolerance. There is no evidence to support the routine use of short-burst oxygen therapy in COPD but it may be prescribed to palliate symptoms in end-stage disease. The evidence to support the use of short-burst oxygen in advanced cancer is minimal but it may be helpful in some individuals as part of a comprehensive supportive care plan.

### Oxygen delivery systems

Oxygen can be delivered by oxygen cylinder, concentrator or liquid oxygen device. LTOT is more cost effectively delivered in the home by a concentrator. The advantages and disadvantages of the different systems are shown in Table 3. LTOT patients should be regularly assessed (at least once a year) to check the suitability of flow rates, adherence to therapy and safety.

#### Table 2: Criteria for LTOT in steady-state patients

| Chronic hypoxaemia ($P_\text{a}O_2 < 7.3$ kPa on air) | $P_\text{a}O_2 < 8.0$ kPa on air in addition to pulmonary hypertension, secondary polycythaemia, right heart failure or nocturnal desaturation |

#### Table 3: Comparison of oxygen delivery devices

<table>
<thead>
<tr>
<th>Delivery system</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compressed oxygen cylinder</td>
<td>Easily available</td>
<td>Frequent refills required</td>
</tr>
<tr>
<td></td>
<td>No power required</td>
<td>High long-term cost</td>
</tr>
<tr>
<td></td>
<td>Economical in the short term</td>
<td>Fire risk</td>
</tr>
<tr>
<td>Home concentrator</td>
<td>Permanent source</td>
<td>Power required</td>
</tr>
<tr>
<td></td>
<td>No need for refills</td>
<td>Needs servicing and spare parts</td>
</tr>
<tr>
<td></td>
<td>Economical in the long term</td>
<td></td>
</tr>
<tr>
<td>Liquid oxygen</td>
<td>Small and portable</td>
<td>Refills required</td>
</tr>
<tr>
<td></td>
<td>No need for power</td>
<td>High cost</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not widely available</td>
</tr>
<tr>
<td>Portable concentrator</td>
<td>Small and portable</td>
<td>High cost</td>
</tr>
<tr>
<td></td>
<td>No need for refills</td>
<td>Limited battery life</td>
</tr>
<tr>
<td></td>
<td>Can be powered by car battery</td>
<td>Cannot deliver high flow</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulsed or demand flow, so unsuitable for use during sleep</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F_\text{i}O_2$ during pulsed flow will vary according to pulse duration,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>trigger sensitivity and oxygen concentration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>delivered</td>
</tr>
</tbody>
</table>

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Entrainment of oxygen therapy into NIV and CPAP circuits

In patients receiving acute or long-term therapy with NIV or CPAP, additional oxygen therapy may be required to correct $\text{SaO}_2$. Oxygen can be entrained into the circuit via a T-piece or through the mask. It is important to note that the more proximal the entrainment (e.g. ventilator side of exhalation port), the greater the inspiratory oxygen fraction ($F_{\text{I,O}_2}$) achieved. In addition, $F_{\text{I,O}_2}$ is likely to be lower than that achieved by delivering a similar oxygen flow rate without NIV/CPAP and difficult to predict accurately, as increases in inspiratory positive airway pressure may reduce $F_{\text{I,O}_2}$.

Further reading


Assessment for anaesthesia/
surgery

Macé M. Schuurmans, Chris T. Bolliger† and Annette Boehler

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 outcome and to identify patients where surgery may be prohibitive.

Pre-operative evaluation for lung resection evaluates to what 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
- emergency procedures

Definite risk factors include:

- COPD
- CHF
- diminished general health status (American Society of Anesthesiologists (ASA) class ≥2 (table 1))
- malnutrition (serum albumin <35 mg·L⁻¹)
- use of pancuronium as a neuromuscular blocker

Probable risk factors include:

- OSA
- general anaesthesia (when compared with spinal or epidural anaesthesia)
- pulmonary hypertension
- abnormal chest radiograph
- cigarette use within previous 8 weeks
- 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 later). Pulmonary function tests should also be performed in patients with unexplained dyspnoea or exercise intolerance, and when 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, and peak flows >80% of the predicted value or the patient’s 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.

Key points

- A careful history and physical examination is necessary to assess the risk of post-operative pulmonary complications
- Pulmonary function testing is not routine except in the case of evaluation for lung resection
- A number of strategies are available to reduce the risk of complications

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Patients with high risk (surgery-specific risk factor plus one or more definite risk factors) will benefit from the following 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
- 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
- regional anaesthesia (nerve block) in very high-risk patients
- avoid pancuronium

Post-operative interventions:
- deep-breathing exercises or incentive spirometry
- epidural analgesia instead of parenteral opioids, selective use of nasogastric tube if post-operative nausea or vomiting, inability to tolerate oral intake, or symptomatic abdominal distension

Cardiac evaluation:
- history, physical examination and resting ECG are frequently required for the initial estimate of the peri-operative cardiac risk
- the inability to climb two flights of stairs or run a short distance indicates poor functional capacity and is associated with an increased incidence of postoperative cardiac events
- 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. Clinical evaluation should focus on respiratory and cardiovascular pathology. Air flow limitation should be optimised before further evaluation, and cardiac disease

### Table 1. 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. Reproduced and modified from Koegelenberg et al. (2008) with permission from the publisher.
identified and managed either medically or surgically. Initial pulmonary function evaluation should include at least FEV1, FVC and TLCO. Values >80% predicted 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 maximal oxygen uptake ($V'_\text{O}_\text{max}$) $>$20 mL·kg$^{-1}$·min$^{-1}$ (or >75% pred) tolerate pulmonary resection up to a 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 of FEV1, TLCO and $V'_\text{O}_\text{max}$ (‘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:

1. anatomical calculation
2. quantitative CT
3. 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 ppoFEV1 is estimated to be equal to the pre-operative FEV1 × ((19-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 based on 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 are marginally less accurate than perfusion scans. The advantage of this method is the availability of the information, as most lung resection candidates invariably have a pre-operative chest CT and modern software simplifies the three-dimensional reconstruction for the calculation of the relative volume of lung to be resected.

Simple stair climbing as a low-cost alternative to assess exercise capacity and operative risk is increasingly being used. A number of recent studies have shown that the ability to climb an elevation $>$22 m is correlated with a favourable surgical outcome for lung resection surgery. Patients unable to reach this elevation then require more sophisticated ergometric evaluation. Adding a time component to the evaluation of the stair climbing test appears to quantify the overall exercise performance more precisely: data from one recent study assessing additionally speed of ascent during stair climbing showed that patients reaching or passing the 20-m elevation mark within 80 s all had formal exercise tests permitting resection up to the extent of a pneumonectomy.

Cardiac assessment: low risk or treated patient

![Figure 1. Algorithm for assessment of cardiopulmonary reserve before lung resection in lung cancer patients. Reproduced and modified from Brunelli et al. (2009).](image-url)
Lung volume reduction surgery for end-stage emphysema has partly redefined the limits of lung resection. Traditional cut-off limits are too prohibitive for these patients, as resection of largely nonfunctional emphysematous tissue leads to improved lung mechanics, improving the overall outcome. The latter is also partly true for moderate-to-severe COPD patients undergoing surgery for lung cancer. Patients with either ppoFEV1 or ppoTLCO <40% pred, or both parameters between 30% and 40% pred can undergo extensive resections such as lobectomy or even pneumonectomy with reasonable safety (mortality of 13.5%) if they have a ppo\(\text{V}O_2\text{max}\) of $>10\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Survival following this strategy appears to be superior than for the nonsurgical strategy.

**Further reading**

Long-term ventilation

Anita K. Simonds

Definition and prevalence

Long-term ventilation (LTV) is a term usually used to describe individuals using either NIV or tracheostomy-delivered ventilation for >3 months on a daily basis in the user’s home or a long-term care facility. Lloyd-Owen et al. (2005) showed a prevalence rate of 6.6 per 100,000 of the population in Europe receiving LTV but there were widely varying practices ranging from a prevalence rate of 17 per 100,000 in France to <1 per 100,000 in Poland. Rates in Denmark, Germany, Spain, the UK and Italy were 9.6, 6.5, 4.1 and 3.9 per 100,000 respectively. Numbers will have grown since 2005, but these data exclude OSA patients using CPAP. There was also a north–south divide with more neuromuscular and chest wall patients receiving LTV in northern Europe and more chronic lung disease patients using LTV in southern Europe. As the prevalence of these conditions does not vary substantially, differences in the pattern of LTV are likely to be historical rather than evidence based.

Key points

- LTV is defined by the requirement for daily ventilatory support for >3 months.
- The majority of LTV recipients use NIV via pressure pre-set ventilators.
- NIV should be started for symptomatic nocturnal hypoventilation or daytime hypercapnia in restrictive disorders.
- NIV extends survival in MND/amyotrophic lateral sclerosis patients.

Pathophysiology

Chronic ventilatory decompensation occurs when the load placed on the respiratory system outstrips its capacity. This occurs in restrictive disorders, such as chest wall and neuromuscular disease, and in chronic lung diseases, such as COPD, CF and bronchiectasis. Disorders of ventilatory drive are less common but LTV is required in patients with congenital central hypoventilation syndrome (CCHS) or other acquired causes of failure of ventilatory drive, such as brain stem cerebrovascular or cervical spinal cord injury events. The clinical course in many patients is punctuated by episodes of acute-on-chronic ventilator failure precipitated by chest infections (e.g. COPD and CF). In others, there is a clear-cut vicious cycle of decline. For example, in chest wall or neuromuscular disease, small lung volumes lead to initially nocturnal hypoventilation and, ultimately, diurnal ventilatory failure if sleep-disordered breathing is not addressed.

Types of LTV

The greatest growth in LTV over the last two decades has been in the use of home NIV. This is virtually all mask ventilation or via oral/nasal interface, as very few patients receive domiciliary negative pressure ventilation (e.g. via cuirass or iron lung). The indications for tracheostomy ventilation are bulbar weakness leading to aspiration, near 24-h ventilator dependence, upper airway lesions, difficulties with NIV, neonatal age range and patient preference.

Ventilators

A survey of LTV in Europe (Lloyd-Owen et al., 2005) showed nearly all patients...
were using positive pressure ventilators (mostly in pressure support mode) with 
<1% using volume ventilators. Dual-mode ventilators are obtainable but, perhaps not 
surprisingly, volume ventilators were most commonly used in neuromuscular and chest 
wall patients, and least frequently used in those with lung disease (COPD/ bronchiectasis). The choice of ventilatory mode and settings should match the 
underlying pathophysiology and be carefully titrated to the patient. Further 
considerations include the age and size of the patient, degree of ventilator dependency, 
and need for oxygen therapy. Humidification is required for nearly all tracheostomy 
patients and is indicated in some patients using long-term NIV (e.g. those with 
recurrent or viscid secretions).

The ventilator care plan should adapt to the patient, as patients with progressive 
disorders will become more ventilator dependent over time and require ventilatory 
support during the day, and/or progress from NIV to tracheostomy ventilation if 
bulbar function worsens; and in children, total ventilatory requirements will change 
with growth.

Tracheostomy

The choice of tracheostomy tube or cannula is dictated by:

- need for mechanical ventilation
- ability of the patient to defend the lower airway (adequate cough and bulbar 
  function)
- temporary or permanent placement
- neck size and anatomy of the patient

The aim is to protect the airway and optimise ventilation while preserving speech 
and swallowing function, and minimising complications related to the tracheostomy 
tube such as sputum plugging, tracheal stenosis and pressure necrosis resulting in 
haemorrhage. Cuffed tracheostomy tubes may reduce aspiration risk in adults but cuff 
pressure should be monitored so that it does not exceed 25 mmHg. Fenestrated 
tubes have a window in the posterior curved region and a removable inner tube. The 
fenestration aids voice production and the inner tube can be removed for cleaning, 
which can be helpful in weaning patients, but long-term use without the inner tube can 
be complicated by granuloma formation. In any patient with a long-term tracheostomy, 
correct size and placement, and regular inspection and bronchoscopy are 
recommended as follow-up.

Chest wall disorders

This group includes patients with scoliosis, old tuberculous lung disease, thoracoplasty 
and chest wall fibrosis. Patients with scoliosis at high risk of ventilatory 
decompensation are shown in table 1.

Neuromuscular disease

Neuromuscular disorders can be grouped into those in which the underlying condition 
is relatively static (e.g. previous poliomyelitis and phrenic nerve injury due to brachial 
neuralgia), those that are slowly progressive (e.g. Duchenne muscular dystrophy (DMD) 
and other myopathies) and those that are rapidly progressive (e.g. motor neurone 
disease and amyotrophic lateral sclerosis). Management plans should therefore take 
into account the natural history of the condition as well as current ventilator needs.

Most neuromuscular patients have normal lungs apart from occasional atelectasis, so 
they are relatively easy to ventilate with low pressures; back-up rates are usually required 
due to profound hypoventilation during REM (rapid eye movement) sleep. Careful 
consideration of the interface is required as individuals may not be able to affix a mask 
easily due to weak muscles of the upper

Table 1. Risk factors for ventilatory decompensation in scoliosis

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital or early-onset scoliosis</td>
</tr>
<tr>
<td>Thoracic curve &gt;100°</td>
</tr>
<tr>
<td>Curve involves high thoracic and cervical vertebrae</td>
</tr>
<tr>
<td>Paralytic aetiology e.g. due to neuromuscular weakness</td>
</tr>
<tr>
<td>Vital capacity &lt;50% predicted</td>
</tr>
<tr>
<td>Comorbidity e.g. COPD, morbid obesity</td>
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</tbody>
</table>
limb, and mid-facial hypoplasia may occur in children and young patients who start NIV before facial skeletal growth is complete. Near-100% 5-year survival has been reported in previous polio patients receiving NIV. In DMD patients, the use of NIV has extended median survival from 18 to 29 years (Eagle et al., 2002; Simonds, 2006) and many young males with DMD are now surviving into their 30s and 40s.

In severe conditions such as Type 1 spinal muscular atrophy, where survival is poor, NIV may be used with the goal of palliating symptoms and allowing home discharge, rather than extending life expectancy.

Bourke et al. (2006) showed in a randomised trial of NIV in motor neurone disease (MND) (amyotrophic lateral sclerosis) that overall survival increased by ~7 months. This improvement was predominantly seen in patients with mild-to-moderate bulbar weakness and quality of life improvements were mainly seen in this group too. However, sleep-related symptoms improved, even in patients with severe bulbar disease. Although it is often reported that NIV cannot be used in MND patients with severe bulbar disease, this belief is overplayed, and a trial is recommended in all MND patients who wish to try NIV. Tracheostomy ventilation may be the only solution to aspiration pneumonia but in some bulbar patients, the combination of NIV, a cough assist device and percutaneous gastrostomy (PEG) feeding works as effectively.

Ventilatory support should be initiated in patients once daytime hypercapnia or symptomatic nocturnal hypoventilation is identified.

**Spinal cord injury**

Individuals with high spinal cord injury or bulbar lesions with no independent ventilatory capacity and an inability to clear secretions will usually require tracheostomy ventilation, but a proportion of quadriplegic patients with minimal ventilatory reserve may be managed by a combination of NIV and cough assist devices. As in other neuromuscular conditions, some patients may be able to augment spontaneous vital capacity by glossopharyngeal ‘frog’ breathing. Phrenic nerve pacing has a role in high spinal cord injury patients and central hypoventilation syndromes, but may need to be supplemented with other forms of ventilatory support and can only be effective if phrenic nerve integrity is maintained.

**Central hypoventilation**

CCHS affects ~1 in 200,000 and is due to mutations in the **PHOX2B** gene. More severe cases experience life-threatening episodes of apnoea or hypoventilation in the first months of life, complicated by other features of autonomic dysregulation such as cardiac arrhythmias or Hirschsprung’s disease. In early infancy, use of ventilation via tracheostomy is recommended to optimise oxygenation and cognitive function. Transition to NIV may be possible later in childhood. Diaphragm pacing has been used in some CCHS children but often has to be combined with invasive ventilation or NIV. Other genetic syndromes associated with hypoventilation include Arnold–Chiari malformation and inborn errors of metabolism such as pyruvate dehydrogenase deficiency.

The obesity hypoventilation syndrome is a form of acquired hypoventilation and is defined by daytime PaCO₂ >45 mmHg (6.0 kPa) in the presence of a BMI >30 kg·m⁻². Obesity hypoventilation patients with mild hypercapnia (PaCO₂ <53 mmHg) with or without OSA may be successfully managed with CPAP therapy. More marked hypercapnia, acute acidic ventilatory decompensation or failure to control sleep-disordered breathing with CPAP are indications for nocturnal NIV (Veale, 2008).

**Chronic obstructive pulmonary disease**

Although numerous selected series of hypercapnic COPD patients have shown physiological advantages of LTV, there is a dearth of adequately powered randomised controlled trials. Several are currently in progress. Meanwhile, McEvoy et al. (2009) randomised 144 COPD patients with FEV₁ <1.5 L or 50% predicted and stable PaCO₂
45 mmHg to receive NIV plus long-term oxygen therapy (LTOT) or LTOT alone. The NIV group had an improvement in survival using an adjusted Cox model but there were no gains in quality of life. It may be that particular subgroups of COPD patients – those with less emphysema and a greater degree of nocturnal hypoventilation, and those with recurrent hypercapnic exacerbations or additional OSA – benefit most, but this remains to be seen.

Pragmatically, current indications for LTV in COPD patients are chronic symptomatic hypercapnia, poor tolerance of LTOT leading to worsening carbon dioxide retention and recurrent admissions for acute-on-chronic hypercapnic respiratory failure responding to acute NIV.

There is a debate on the use of a high-intensity ventilatory approach in COPD patients (high pressure and controlled ventilation). This has been shown to reduce hypercapnia and improve exercise ability (Windisch et al., 2005) but may be less easy to tolerate than lower pressures for some patients.

**CF and bronchiectasis**

Nocturnal NIV can reduce symptoms, including breathlessness, and improve nocturnal oxygenation, sleep quality, peak exercise level and quality of life in chronically hypercapnic adult patients with CF (Young et al., 2008). Fauroux et al. (2008) has also shown stabilisation of lung function in younger CF patients treated for 1 year with nocturnal NIV. Use during physiotherapy can also prove beneficial. Effects on survival are less clear, other than in the situation where NIV is used to ‘bridge’ patients to transplantation.

Case–control studies of patients with bronchiectasis show improvements in oxygenation compared to LTOT alone and, in some groups, the frequency of infective exacerbations may be reduced. Both CF and idiopathic bronchiectasis patients experience ventilation/perfusion mismatch and diffusion problems, and so are likely to require a combination of NIV and LTOT, judged by overnight monitoring of $S_aO_2$ and $P_{aCO_2}$.

**Discharge planning and follow-up**

Planning for discharge in patients receiving tracheostomy ventilation is necessarily more complex than in those using NIV. The key components of a successful discharge plan are listed in table 2.

**Table 2. Discharge planning for home ventilator patients**

| Stability and motivation of patient |
| Competency training of patient, family and carers |
| Arrangements for servicing and emergency back-up of ventilator equipment, including suction machines, cough assist devices and oxygen concentrator if required |
| Supply of disposables e.g. masks, suction catheters, ventilator circuits, filters |
| Liaison with all members of care team (home and hospital) |
| Follow-up assessments/appointments planned |
| Written guides to management of common problems e.g. chest infection |
| Suitable modifications to home environment |
| Risk management plan e.g. battery packs to cover power failure, smaller size tracheostomy tube if difficulties with tube replacement, low and high pressure and disconnection alarms |
| Anticipatory care plan detailing agreed actions in event of chest infection, hospital admission, and preferences regarding resuscitation status and intensive care unit admission |

Further reading

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. Therefore, recent guidelines confirm that microbiological tests such as Gram stains and cultures are not recommended as routine tests in the primary care setting. Nevertheless, an aetiological diagnosis, of both bacteria and viruses and mixtures of these in community-acquired pneumonia (CAP) or lower respiratory tract infections (LRTIs), may be helpful in guiding treatment, particularly in the more severely ill or hospitalised 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, urinary antigen and particularly nucleic acid amplification (NAA) tests, that produce results within 30 min or 4–5 h, microbiological information is becoming clinically useful (table 1).

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 of pneumonia (based on the Fine Severity Index) and blood culture positivity rate. Two sets of blood cultures should be performed in all patients with CAP who require hospitalisation; they should be obtained as early as possible in the disease and before any antibiotic treatment is started. If blood cultures are positive, *Streptococcus pneumoniae* is identified in ~60% and *Haemophilus influenzae* in 2–13%. Despite their low sensitivity, blood cultures in CAP are considered the gold standard for diagnosis of pneumonia 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. 

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**Key points**

For the aetiological diagnosis of LRTIs:

- Gram stain and culture of sputum are valuable in hospitalised patients, if of good quality, 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.
Table 1. Diagnostic approach for the most common specific agents in LRTIs

<table>
<thead>
<tr>
<th>Pathogen (or genus)</th>
<th>Specimen</th>
<th>Rapid tests</th>
<th>Conventional tests</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Blood</td>
<td>Blood culture</td>
<td></td>
<td>Positive in 4–18% of cases when collected within 4 days</td>
</tr>
<tr>
<td>Sputum</td>
<td>Gram stain</td>
<td>Culture</td>
<td></td>
<td>Only purulent samples acceptable; can be obtained in 35–40% of patients; informative if ≥90% Gram positive, diplococcic most relevant if Gram stain is informative</td>
</tr>
<tr>
<td>BAL, PSB</td>
<td>Gram stain</td>
<td>Culture</td>
<td></td>
<td>Quantitative cultures</td>
</tr>
<tr>
<td>Pleural exudates, TNA</td>
<td>Gram stain</td>
<td>Culture</td>
<td></td>
<td>Very specific; only considered if less invasive methods nondiagnostic</td>
</tr>
<tr>
<td>Urine</td>
<td>Antigen test</td>
<td></td>
<td></td>
<td>Sensitivity 50–80% of bacteraemic cases; lacks specificity in children; more evaluation necessary</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>Blood</td>
<td>Blood culture</td>
<td></td>
<td>Less frequently positive than for <em>S. pneumoniae</em></td>
</tr>
<tr>
<td>Respiratory specimens</td>
<td>Gram stain</td>
<td>Culture</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Legionella spp.</em></td>
<td>Urine</td>
<td>Antigen test</td>
<td></td>
<td>Sensitivity 66–95%</td>
</tr>
<tr>
<td>Respiratory specimens</td>
<td>NAA</td>
<td>Culture</td>
<td></td>
<td>Culture on appropriate media; late results</td>
</tr>
<tr>
<td>Serum</td>
<td>IgM and IgG serology</td>
<td></td>
<td></td>
<td>Acute and convalescent specimens; retrospective diagnosis</td>
</tr>
<tr>
<td><em>Chlamydophila pneumoniae, Mycoplasma pneumoniae</em></td>
<td>Respiratory specimens</td>
<td>NAA</td>
<td>Culture</td>
<td>Culture on appropriate medium; low sensitivity</td>
</tr>
<tr>
<td>Serum</td>
<td>IgM and IgG serology</td>
<td></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, NAA</td>
<td>Virus isolation</td>
<td>Requirement for appropriate infrastructure; isolation less sensitive than NAA</td>
</tr>
</tbody>
</table>

NAA tests are not generally available yet and are not US Food and Drug Administration approved. BAL: bronchoalveolar lavage; PSB: protected specimen brush; TNA: transthoracic needle aspiration.
To be of value for microbial diagnosis and early guidance of 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 per field) should not be examined further. It may be difficult to obtain good-quality, purulent sputum. Many LRTI or pneumonia patients, 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, which are the gold standard. The study by Anevlavis et al. (2009) is the first reporting information concerning operating characteristics and the diagnostic value of sputum Gram staining in 1390 patients with bacteraemic CAP. The sensitivity of sputum Gram stain was 82% for pneumococcal pneumonia and 79% for H. influenzae pneumonia, with specificities ranging from 93% to 96%. Data from this study suggest that a properly collected and read Gram stain provides a simple, readily available, rapid and inexpensive test result, and can be a dependable test for the early aetiological diagnosis of bacterial pneumonia. 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 has been shown to have a sensitivity of 65–100% and a specificity of >90% in adult CAP; however, weak positive results should be interpreted with caution. There is a relationship 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 conclusive results of a sputum Gram stain are unavailable.

The urinary antigen test may also be applied to pleural fluid and serum samples with a sensitivity of 50% in bacteraemic patients and 40% in nonbacteraemic patients. In a retrospective study, a rapid immunochromatographic test (ICT) was performed on pleural fluid samples from 34 patients with pneumonia due to S. pneumoniae, and a number of control patients with effusions of non-pneumococcal origin or pneumonia of unknown aetiology. Data on blood cultures, pleural fluid cultures and urinary antigen tests were recorded. The ICT result was positive in 70.6% with pneumococcal pneumonia and negative in 93.3% of patients without pneumococcal pneumonia. The sensitivity of the pleural ICT is higher than that obtained for blood and pleural fluid cultures, but lower than the detection of pneumococcal antigen in urine samples. However, in some patients with pneumococcal pneumonia and a negative urinary antigen test result, a positive pleural fluid antigen test was detected. The ICT
performed on pleural fluid samples therefore augments the standard diagnostic methods of blood and pleural fluid cultures, even in the case of prior antibiotic therapy, and enhances the urinary antigen assay. Vaccination does not result in a positive urinary antigen test. The immuno-

chromatographic urinary antigen test for S. pneumoniae is therefore useful for the aetiological 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 pneumophila serogroup 1 infection. Although >50 Legionella spp. have been identified, >90% of the isolates associated with legionnaires’ disease are L. pneumophila and up to 84% of these are L. pneumophila serogroup 1. 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. L. pneumophila serogroup 1 urinary antigen detection is frequently the first positive laboratory test in this infection. The sensitivity of the tests varies between 65% and 70% in unconcentrated urine and increases significantly after concentration of the specimen. In L. pneumophila 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% to 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. 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: human metapneumovirus, the novel coronaviruses NL63 and 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% to >90% depending on the virus, the patient population studied and the sampling method used. For respiratory infections due to viruses, the optimal specimen is the nasopharyngeal aspirate. Alternatively, oro- or nasopharyngeal swabs can be obtained. A few studies comparing the respective efficacies of two structurally different swabs have been performed and conclude that nylon flocked swabs appear to be more efficient than rayon swabs, yielding significantly more total respiratory epithelial cells and more infected respiratory epithelial cells, which is likely to have a greater effect on diagnostic sensitivity both for antigen- and for PCR-based tests. For the detection of influenza virus infections, the sensitivity of immunofluorescence can be increased by inoculation of appropriate cells with clinical sample followed by immunofluorescence after 48 h. Several common respiratory viruses can be detected simultaneously by the use of pooled monoclonal antibodies. The sensitivity and positive predictive value of the DIF test is lower in adults and older people than in children. Rapid methods for the detection of influenza virus 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, particularly Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella infections and respiratory viruses. It should be remembered that the most reliable serologic evidence of an ongoing infection is based on a four-fold increase in the titre of IgG (or IgG and 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 titres have no diagnostic meaning for an acute infection since the moment of the seroconversion is unknown and necessarily took place sometime before the illness under observation started.

The sensitivity and specificity of serological 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. Since IgM detection in the acute phase shows a moderate sensitivity, provided a specific test is used, further research is needed to better define the role of IgM serology: a combination of IgM antibody detection and PCR may be the most sensitive approach for early diagnosis of M. pneumoniae infections, especially in symptomatic children. It is critically important for current and future investigators to recognise the urgent need for the adoption of a more unified and consistent diagnostic approach. A common set of recommendations should be developed.

Legionella antibody tests also have a sensitivity of only 61–64%, depending on the assay applied, and 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 four-fold IgG antibody increase is detected by EIA in approximately 80–90% of patients at only 20–30 days after the onset of disease.

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

NAA tests

The newest approach in the diagnosis of respiratory tract infections is the detection of microbial nucleic acids by NAA tests. Culture procedures for viruses and fastidious bacteria, M. pneumoniae, C. pneumoniae, L. pneumophila and Bordetella pertussis, which do not normally colonise the human respiratory tract, are too insensitive and too slow to be therapeutically relevant, and these pathogens therefore should be detected using NAA tests, 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, and rhino-, metapneumo- or coronaviruses) and/or to some population groups, e.g. children, adults or the elderly. Great variations occur as a function of time, place and the age-groups studied as well as in the diagnostic
gold standard test used, varying between viral culture and serology. Although the role of some new viruses is becoming clearer in specific patient populations, more studies are needed to identify the clinical relevance of some others, such as the bocavirus. All these studies were performed with traditional NAA tests 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 NAA tests offer a solution. To cover the wide spectrum of aetiological respiratory agents, a number of uni- and/or multiplex reactions are performed simultaneously. Both in-house and commercially available multiplex NAA tests 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 aetiological 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 immuno-compromised hosts. Respiratory infections are more common in solid organ recipients, particularly in lung transplant recipients. Infections are especially dangerous prior to engraftment and during the 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.

NAA tests 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 NAA tests). Very rapid chromatographic tests are also available for RSV, which can be performed 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 aetiological 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. Serological diagnosis of those cases that remain undetected by the NAA tests is of no clinical use, as it is available only after many days or even weeks.

**Further reading**

Upper respiratory tract infections

Gernot Rohde

Prevalence

Upper respiratory tract infections (URTIs) usually occur during the cold months, mainly due to overcrowding inside buildings. The mean frequency is two to four episodes annually for adults. In children it is higher. Antigenic variation of hundreds of respiratory viruses allows repeated circulation in the community.

Spectrum

The upper respiratory tract comprises the airways above the vocal cords and consists of the nose, paranasal sinuses, pharynx and larynx. The most prevalent illness is the common cold (rhinosinusitis), followed by sinusitis, pharyngitis/tonsillitis and laryngitis (table 1).

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

Transmission and predisposition

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

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 parainfluenza viruses, human

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 parainfluenza viruses, 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.
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* and *Mycoplasma*). *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* can be the bacterial cause of rhinosinusitis. *Bordetella pertussis* or *Bordetella parapertussis* are the cause of whooping cough associated with laryngotracheitis.

**Complications**

URTIs usually are self-limiting and 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 (Hib), 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 (table 1) are sufficient. Additional diagnostic investigations should only be performed in special circumstances. These include suspicion of:

- 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 hepatosplenomegalgy and lymphocytosis; perform mononucleosis spot test in blood)

<table>
<thead>
<tr>
<th>Upper respiratory tract infection</th>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common cold</strong></td>
<td>Nasal congestion, mucopurulent nasal discharge, sneezing, sore throat, halitosis</td>
<td>Low-grade fever, nasal vocal tone, inflamed nasal mucosa</td>
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<td><strong>Sinusitis</strong></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>
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<td><strong>Pharyngitis</strong></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, scarlatiniform rash, pharyngeal or palatal vesicles and ulcers (herpangina), tonsillar hypertrophy</td>
</tr>
<tr>
<td><strong>Laryngitis</strong></td>
<td>Hoarseness, voicelessness, dry cough, odynophagia or dysphagia, halitosis</td>
<td>Low-grade fever, cervical lymphadenopathy, inspiratory stridor, tachypnoea</td>
</tr>
</tbody>
</table>

**Table 1. Signs and symptoms**

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</tr>
</tbody>
</table>
Pertussis (perform serology or PCR on respiratory specimens, mostly nasopharyngeal swab)

**Differential diagnosis**

**Influenza** viruses can cause mild URTIs but also systemic disease. The definition of influenza-like illness is fever >38.5°C and one of the following:

- cough
- sore throat
- headache
- 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 can clinically present as laryngopharyngitis and/or tracheobronchitis. History and oesophagogastroduodenoscopy in more severe cases should be performed.

**Granulomatosis with polyangiitis** (Wegener’s) 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 for 10 days)
- bacterial sinusitis, usually a sinusitis not resolving within 7 days (aminopenicillin with or without a β-lactamase inhibitor, second- or third-generation cephalosporins, macrolides, or trimethoprim-sulfamethoxazole for 7–10 days)
- pertussis (macrolides, alternatively trimethoprim-sulfamethoxazole or doxycycline for 7 days)

Nasal decongestants decrease symptoms in rhinitis and sinusitis, and topical nasal steroids improve sinusitis. Confirmed cases of influenza can be considered for therapy with neuraminidase inhibitors according to Centers for Disease Control and Prevention guidelines. 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 Hib vaccination has practically eradicated Hib as a cause of URTI; a herd effect can be demonstrated, as the introduction of the pneumococcal vaccine in children correlated with significant reduction in invasive pneumococcal disease in adults.

**Further reading**

Infective exacerbations of COPD

Marc Miravitlles

The American Thoracic Society/European Respiratory Society Task Force has defined the exacerbation of 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. Patients with more advanced disease may suffer from an increasing number of exacerbations; however, some patients are more prone to suffer from exacerbations irrespective of the severity of airflow impairment – these are the frequent exacerbators, defined as those suffering from at least two exacerbations the previous year. It is estimated that ~30% of patients with moderate-to-severe COPD are frequent exacerbators.

Key points

- Up to 75% of COPD exacerbations are of infective aetiology.
- *Haemophilus influenzae* is the most frequent pathogen causing exacerbations.
- Relapse rate may be as high as 20%.
- Spectrum of antibacterial activity, risk factors for relapse and bacterial resistance to antibiotics are the criteria used for the selection of antibiotics.

Outcomes of exacerbations: risk factors for failure

The failure rate of ambulatory treatment of exacerbations of COPD ranges from 12% to 26%, and failure may lead to hospital admission. COPD severity is associated with a higher rate of severe exacerbation requiring hospitalisation. The mortality of patients admitted to hospital with COPD exacerbation is around 10–14% and the mortality of those admitted to an intensive care unit may be as high as 24%. Hospitalisation has an important impact on COPD patients; it is associated with a higher risk of short- and long-term all-cause mortality at any stage of severity of COPD. 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; this co-infection
has been identified in around 25% of admitted COPD patients with an exacerbation. Interestingly, the symptoms and signs of acute exacerbation in patients with COPD have been replicated experimentally in vivo by infecting subjects with respiratory viruses. This is a demonstration of the pathogenic role of viruses in exacerbations of COPD. Since no effective treatment exists for viral exacerbations, here we will focus on the management of bacterial exacerbations of COPD. The most frequent microorganisms causing exacerbations are presented in Table 2.

The role of bacteria in exacerbations has been a matter of controversy, as 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. In this case, 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 Anthonisen et al. (1987), i.e. increased

| Table 1. Risk factors for failure after ambulatory treatment of exacerbations of COPD |
|---------------------------------|---------------------------------|
| Coexisting cardiopulmonary disease | Increasing number of visits to the GP for respiratory problems (>3 per year) |
| Increasing number of previous exacerbations (>3 per year) | Increasing baseline dyspnoea |
| Severity of FEV₁ impairment (FEV₁ ≤35% predicted) | Use of home oxygen |
| Inadequate antibiotic therapy | GP: general practitioner. |

Table 2. Aetiology of exacerbations of COPD

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

<table>
<thead>
<tr>
<th>Noninfectious exacerbations (20–40% of all exacerbations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Nonpulmonary infections</td>
</tr>
<tr>
<td>Pneumothorax</td>
</tr>
</tbody>
</table>
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 six-fold 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. Other risk factors for infection with Pseudomonas include the presence of bronchiectasis, the previous isolation of Pseudomonas in a given patient and a recent previous courses of antibiotics.

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. To date, the best biomarker available for bacterial exacerbation of COPD is C-reactive protein (CRP), which can be quantified in capillary blood as a point-of-care test even in primary care.

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.

On the other hand, placebo-controlled, randomised clinical trials and large observational studies have demonstrated the efficacy of antibiotics in the treatment of severe hospitalised exacerbation of COPD. Studies are ongoing to determine if patients with clear sputum can be safely treated without antibiotics in the hospital setting.

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 tetracycline, in low-risk patients in countries with a low prevalence of antibiotic resistance, such as the Netherlands, UK and other northern 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 amoxicillin–clavulanate, the respiratory fluoroquinolones (moxifloxacin and levofloxacin) or cephalosporins (cefditoren and 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\(^{-1}\) methylprednisolone or equivalent in a single morning dose for 7–14 days. Treatment for longer than 14 days has not been demonstrated to be more beneficial and increases the likelihood of adverse side-effects. Inhaled bronchodilators, particularly short-acting inhaled \(\beta_2\)-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 the 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 \(\text{PaO}_2 > 8.0 \text{ kPa} \) or \(60 \text{ mmHg}, \text{ or } \text{SaO}_2 > 90\%\). 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 carbon dioxide 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.

### Table 3: Risk classification and suggested antimicrobial therapy

<table>
<thead>
<tr>
<th>FEV(_1) % pred</th>
<th>Most frequent microorganisms</th>
<th>Suggested treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild-to-moderate COPD without risk factors</strong></td>
<td>(&gt;50)</td>
<td><em>Haemophilus influenzae</em>&lt;br&gt; <em>Moraxella catarrhalis</em>&lt;br&gt; <em>Streptococcus pneumoniae</em>&lt;br&gt; <em>Chlamydia pneumoniae</em>&lt;br&gt; <em>Mycoplasma pneumoniae</em></td>
</tr>
<tr>
<td><em><em>Mild-to-moderate COPD with risk factors</em>(^a)</em>*</td>
<td>(&gt;50)</td>
<td><em>Haemophilus influenzae</em>&lt;br&gt; <em>Moraxella catarrhalis</em>&lt;br&gt; PRSP</td>
</tr>
<tr>
<td><strong>Severe COPD</strong></td>
<td>30–50</td>
<td><em>Haemophilus influenzae</em>&lt;br&gt; <em>Moraxella catarrhalis</em>&lt;br&gt; PRSP&lt;br&gt; Enteric Gram-negative bacteria</td>
</tr>
<tr>
<td><strong>Very severe COPD</strong></td>
<td>(&lt;30)</td>
<td><em>Haemophilus influenzae</em>&lt;br&gt; PRSP&lt;br&gt; Enteric Gram-negative bacteria&lt;br&gt; <em>Pseudomonas aeruginosa</em></td>
</tr>
</tbody>
</table>

PRSP: penicillin-resistant *S. pneumoniae*. *\(^a\)*: risk factors are explained in table 1; *\(^b\)*: in the case of intravenous therapy, other antibiotics can be used, such as piperacillin–tazobactam, imipenem or ceftazidime.
Further reading

Pneumonia

Mark Woodhead

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 into groups that can be easily recognised and within which the causative pathogens, and hence the management, are different (table 1).

Community-acquired pneumonia (CAP) is that which occurs in the absence of immune compromise or prior hospital admission within the previous 30 days.

Epidemiology

CAP occurs in between one and 10 per 1000 of the adult population each year. It is more common in children aged <5 years and becomes progressively more common from age 40 years onwards, with a peak in the very elderly. It is more common in those with comorbidity, such as COPD, bronchiectasis, and chronic cardiac and renal disease. It occurs throughout the year with a peak during the winter months.

Nosocomial pneumonia can occur in anyone resident in hospital for ≥48 h. It is especially common in the intensive care unit >48 h after endotracheal intubation (ventilator-associated pneumonia (VAP)) with risk being proportional to the duration of intubation.

Two types of immune dysfunction predispose to pneumonia:

- humoral immune dysfunction, such as immunoglobulin deficiencies; and
- cell-mediated immune function in, for example, 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 nosocomial pneumonia and pneumonia in the immunocompromised.

Key points

- Pneumonia is very common and has 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. Only occasionally do the ‘classical’ features of lung consolidation occur: dullness to percussion, bronchial breathing and enhanced vocal resonance. Chest signs may, however, be absent, making the diagnosis difficult outside hospital. In addition, raised temperature, raised heart and respiratory rates, low blood pressure, and mental confusion may be found.

Clinical features are generally not helpful in predicting the causative organism. The Clinical Pulmonary Infection Score (CPIS) may be useful in nosocomial pneumonia.

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.

A 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. More commonly, 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.

In 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 tests for pneumococcal and *Legionella* antigens 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 nosocomial pneumonia, and especially in VAP, lower respiratory secretions should be sampled either by tracheal aspirate or from bronchoscopic specimens. The latter may also be of value in the immunocompromised.

Differential diagnosis

The differential diagnosis includes acute bronchitis, COPD exacerbation, left ventricular failure, pulmonary embolism, TB, exacerbation of pulmonary fibrosis and rare lung disorders (e.g. pulmonary eosinophilia).

Microbial aetiology and resistance

The same 10 pathogens commonly cause CAP worldwide, 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 and in intravenous drug abusers. Influenza occurs in seasonal outbreaks during the winter months and occasional pandemics. It is the most common viral cause of CAP.

Bacterial antibiotic resistance varies in frequency between countries. Clinically significant resistance to penicillins in *S. pneumoniae* is rare but clinically significant macrolide resistance is more common, especially in Southern Europe (www.earss.rivm.nl).

Table 2. The CURB65 and CRB65 scores

<table>
<thead>
<tr>
<th>Score 1 for each of</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C: mental confusion</td>
<td></td>
</tr>
<tr>
<td>U: blood urea ≥ 7 mmol·L⁻¹</td>
<td></td>
</tr>
<tr>
<td>R: respiratory rate ≥ 30 breaths·min⁻¹</td>
<td></td>
</tr>
<tr>
<td>B: systolic blood pressure &lt; 90 mmHg or diastolic blood pressure ≤ 60 mmHg</td>
<td></td>
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<tr>
<td>65: age ≥ 65 years</td>
<td></td>
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</tbody>
</table>

Mild pneumonia: score of 0–1 (mortality 1.5%); moderate pneumonia: score of 2 (9%); severe pneumonia: score of 3–5 (22%).

Nosocomial pneumonia 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

<table>
<thead>
<tr>
<th>Table 3. European Respiratory Society/European Society for Clinical Microbiology and Infectious Diseases antibiotic guideline options for CAP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outside hospital</strong></td>
</tr>
<tr>
<td><strong>Hospitalised</strong></td>
</tr>
<tr>
<td>Nonsevere</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Severe</td>
</tr>
<tr>
<td>No Pseudomonas risk</td>
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<tr>
<td>Pseudomonas risk</td>
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<td></td>
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</table>

Evidence does not clearly support one regime as better than another so a choice is provided. Decision will depend on local circumstances. *:* gentamicin, tobramycin or amikacin; #: meropenem is preferred.
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 the 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 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 2).

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 be all that is required. In hospital, oxygen at a concentration to maintain $\text{SaO}_2$ (92–95%) should be delivered. If this cannot be achieved, CPAP may be helpful. If there is an unacceptable rise in $\text{PaCO}_2$, then assisted ventilation should be considered. A place for NIV 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 3). Empirical antibiotics for CAP should always include pneumococcal coverage. Treatment for nosocomial pneumonia 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 uncomplicated cases 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.

Further reading

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 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 from 30% to >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 years are less prone to developing HAP than elderly patients; the incidence of HAP may vary between five and 15 episodes per 1000 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 1000 patient-days.

Pathogenesis and risk factors

The understanding of the pathogenesis of HAPs is a fundamental step for the comprehension of the risk factors involved. The main sources of HAP pathogens include:

- healthcare devices
- the environment
- the transfer of microorganisms between the patient and staff or other patients
- oropharyngeal and gastric colonisation, with subsequent aspiration of their contents into the lungs in patients with impaired mechanical, cellular and humoral defences.

**Key points**

- Incidence of hospital-acquired pneumonia 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.

**Table 1. Definitions of HAP**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</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>
</tbody>
</table>
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. 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 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

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**Table 2. Main recommendations for the management of modifiable risk factors for HAP and VAP**

| Host related | Adequate nutrition, enteral feeding via orogastric tubes |
| Device/treatment related | Minimise use of sedatives and paralytics |
| Environment related | Attention to infection-control procedures, *i.e.* staff education, hand washing, patient isolation |

**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
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 CT. The presence of new chest radiographic infiltrates plus one of the three clinical variables (fever \( > 38^\circ C \), leukocytosis or leukopenia and purulent secretions) is sufficient to start antimicrobial treatment.

Concerning the diagnosis of VAP, the lack of accuracy of specific clinical signs of pneumonia led investigators to develop scores to identify respiratory infections. In particular, the Clinical Pulmonary Infection Score (CPIS) is based on six clinical assessments (temperature, blood leukocyte count, volume and purulence of tracheal secretions, chest radiograph infiltrates, tracheal secretions, and \( \text{PaO}_2/\text{FiO}_2 \))

<table>
<thead>
<tr>
<th>Criterion</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tracheal secretions</td>
<td>Absent</td>
<td>No purulent</td>
<td>Abundant and purulent</td>
</tr>
<tr>
<td>Chest radiograph infiltrates</td>
<td>No</td>
<td>Diffuse/patchy</td>
<td>Localised</td>
</tr>
<tr>
<td>Temperature °C</td>
<td>( &gt; 36.5 ) and ( &gt; 38.4 )</td>
<td>( &lt; 38.5 ) or ( &gt; 38.9 )</td>
<td>( &gt; 39 ) or ( &lt; 36 )</td>
</tr>
<tr>
<td>Leukocytes cells ( \cdot \text{mL}^{-1} )</td>
<td>4000 and 11 000</td>
<td>( &lt; 4000 ) or ( &gt; 11 000 )</td>
<td>( &lt; 4000 ) or ( &gt; 11 000 ) + ( \text{band forms} &gt; 50% ) or ( &gt; 500 )</td>
</tr>
<tr>
<td>( \text{PaO}_2/\text{FiO}_2 )</td>
<td>( &gt; 240 ) or ARDS</td>
<td>( &lt; 240 ), no ARDS</td>
<td></td>
</tr>
<tr>
<td>Microbiology ( ^* )</td>
<td>Negative</td>
<td>( \geq 10^3 ) and ( \leq 10^4 )</td>
<td>Positive ( (&gt; 10^4 )</td>
</tr>
</tbody>
</table>

\( \text{FiO}_2 \): inspiratory oxygen fraction; ARDS: acute respiratory distress syndrome. \( ^* \): CPIS is considered positive with a score \( \geq 6 \); \( ^\prime \): tracheal aspirate.

Table 5. Antimicrobial treatment of nosocomial pneumonia

<table>
<thead>
<tr>
<th>Early-onset pneumonia without any additional risk factors ( ^# )</th>
<th>Recommended treatment options</th>
<th>Recommended dosages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminopenicillin plus ( \beta )-lactamase inhibitor</td>
<td>Amoxicillin-clavulanate ( 3 \times 2.2 ) g</td>
<td></td>
</tr>
<tr>
<td>or second/third generation cephalosporin or respiratory</td>
<td>Ampicillin sulbactam ( 3 \times 3 ) g</td>
<td></td>
</tr>
<tr>
<td>fluoroquinolone</td>
<td>Cefuroxime ( 3 \times 1.5 ) g</td>
<td></td>
</tr>
<tr>
<td>Anti-( \text{Pseudomonas} ) ( \beta )-lactams or carbapenems plus fluoroquinolone</td>
<td>Cefotaxime ( 3 \times 2 ) g</td>
<td></td>
</tr>
<tr>
<td>Addition of coverage for MRSA if suspected</td>
<td>Ceftriaxone ( 1 \times 2 ) g</td>
<td></td>
</tr>
<tr>
<td>Piperacillin/tazobactam ( 3 \times 4.5 ) g</td>
<td>Levofloxacin ( 1 \times 750 ) mg</td>
<td></td>
</tr>
<tr>
<td>Ceftazidime ( 3 \times 2 ) g</td>
<td>Moxifloxacin ( 1 \times 400 ) mg</td>
<td></td>
</tr>
</tbody>
</table>

MRSA: methicillin-resistant \( \text{Staphylococcus aureus} \). \( ^\prime \): ertapenem has been suggested; however, its use on a regular basis would lead to a considerable risk of overtreatment.
secretions, oxygenation, pulmonary radiographic findings, and semiquantitative culture of tracheal aspirate), each worth between 0 and 2 points (table 4). A CPIS value ≥ 6 is a threshold to accurately identify patients with pneumonia. However, the value of CPIS still needs to be validated in a large prospective study.

**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 5 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.

**Further reading**

Opportunistic infections in the immunocompromised host

Thomas Fuehner, Mark Greer, Jens Gottlieb and Tobias Welte

Pulmonary diseases remain prevalent among immunodeficient patients, manifesting as infections, malignancy, structural abnormalities such as bronchiectasis or primary ciliary dyskinesia (PCD), and inflammatory dysregulation. The causes of immunodeficiency are considered either primary (congenital) or acquired.

Primary immunodeficiency

Primary immunodeficiency results from either humoral or cellular immunodeficiency, although clinical manifestations commonly result from a combination of both. Disorders of innate immunity commonly alter mononuclear phagocytic activity or the complement system. They have also been implicated in structural defects such as PCD and hereditary splenic deficiency. Cellular defects, typically involving either T-lymphocytes or both T- and B-lymphocytes are common causes of opportunistic infections, such as Pneumocystis jiroveci or cytomegalovirus (CMV) pneumonia. While particularly prevalent among newborns, isolated defects in humoral immunity may be compensated over subsequent months by persisting maternal antibodies. Impaired T-cell or phagocyte function increases the risk of opportunistic infections from particular opportunistic pathogens including Pseudomonas, Burkholderia, P. jiroveci, Aspergillus and CMV. However, the clinical course varies widely, with late presentation in older adults being a not uncommon feature in some syndromes, such as common variable immunodeficiency syndrome (CVID), in which patients are particularly susceptible to encapsulated microorganisms such as Streptococcus pneumoniae or Haemophilus influenzae.

Nontuberculous mycobacterial infections have been described in patients with genetic defects in the interleukin (IL)-12 and interferon (IFN)-γ pathways, as well as in patients with defective regulation of NF-κB (NF-κB essential modifier or NEMO defects).

Acquired immunodeficiency

Acquired immunodeficiencies remain much more prevalent than primary defects and result mainly from the use of cytotoxic medications in chemotherapy, biological treatments and steroids, and radiotherapy.

Key points

- Common causes of acquired immunodeficiency are immunosuppressive medication (corticosteroids, cytotoxic chemotherapy and biologicals), radiation, HIV infection and asplenia.
- The pathogen type depends on the nature of the underlying immune defects.
- Correct assessment of individual risk factors for pneumonia (community versus hospital acquired and immunosuppressed patient) helps to improve treatment.
- Diagnostic and treatment algorithms may help to reduce mortality and the use of antibiotics.
- These algorithms are solely defined for community- and hospital-acquired pneumonia in major guidelines.
HIV infection and transplantation. In each of these patient groups, there is an increased susceptibility to specific groups of pathogens based primarily on the underlying immunological deficit. In comparison to other treatments, less is known about antibody-based treatments directed towards T- and B-cell function or tumour necrosis factor (TNF)-α, and these should be further evaluated when assessing individual patient risk.

**Neutropenia** Infection in neutropenic patients continues to pose major clinical challenges. Host defences are commonly impaired either by the underlying disease in primary deficiencies, or specific treatments or iatrogenic manipulation while hospitalised.

Due to a lack of neutrophil granulocytes, pulmonary infiltrations may be absent or difficult to identify. Current recommendations from the Infectious Disease Work Group of the German Society of Haematology and Oncology reflect this, recommending urgent thoracic CT in all patients with neutropenic fever failing to respond after 3 days of empirical antibiotic treatment (Maschmeyer et al., 2009). Pulmonary infiltrates, where present, require further investigation through bronchoalveolar lavage (BAL). Storage and transport of BAL samples is of critical importance, with 4°C considered the optimal temperature, and testing should ideally begin within 2–3 h of material recovery (Maschmeyer et al., 2009). Diagnostic work-up should include mycobacteria (microscopy, culture and PCR), P. jiroveci (immunofluorescence and PCR), Legionella spp. and galactomannan antigen testing for Aspergillus (Guo et al., 2010). Viral aetiologies should also be considered, particularly common respiratory pathogens, *via* immunofluorescence or PCR. CMV infections, including CMV pneumonia, may be detected *via* CMV antigen in blood, *i.e.* pp65, or CMV DNA, which is currently considered the gold standard (Hodinka, 2003).

The presence of Candida spp. on direct microscopy or even BAL culture requires careful interpretation and is not an automatic indication for treatment. Similar difficulties arise in diagnosing invasive pulmonary aspergillosis. In the absence of a confirmatory biopsy, diagnostic criteria including specific risk factors, CT criteria and corresponding microbiological findings (positive galactomannan antigen test, culture and PCR) are crucial in assisting with decision-making. Current guidelines recommend that all cases of ‘probable’ or ‘proven’ pulmonary aspergillosis be immediately treated (Asciglu et al., 2002).

**Bone marrow transplantation** Patients undergoing allogenic stem-cell or bone marrow transplantation (BMT) are at understandably high risk of neutropenia, and impairment of barrier defences and both cell-mediated and humoral immunity. The degree of neutropenia reflects both the nature and duration of exposure to the precipitating factor. The resulting deficit facilitates even microorganisms with limited pathogenicity in causing serious infections. Patients undergoing allogenic stem-cell transplantation or BMT are subjected to sequential suppression of host defences, predisposing to variation in susceptibility to particular organisms at different phases following transplantation. The greatest infective risk, particularly of opportunistic pneumonias due to *Staphylococcus aureus*, *Pseudomonas aeruginosa*, Enterobacteriaceae, *Aspergillus* spp. or even CMV, occurs within the first few weeks following allogenic stem-cell transplantation.

**Solid organ transplantation** Due to their chronic immunocompromised state, infection represents a lifelong threat to patients after solid organ transplantation and remains a leading cause of early and late mortality. In addition to their direct impact, several studies have linked infection response processes with an increased predisposition to allograft rejection, especially in lung transplantation (LTx) (Fuehner et al., 2012).

While classical symptoms such as fever and cough may be masked in solid organ transplant recipients, this problem is of particular concern in LTx patients. In the early post-transplant phase, such infections
are most commonly bacterial, followed by fungi and then viruses (Kotloff et al., 2011). *P. aeruginosa* is the predominant pathogen, followed closely by *S. aureus*. Common gram-negative organisms causing post-transplant pneumonias include *Klebsiella* and *H. influenzae*.

CMV represents the commonest viral pathogen, occurring in approximately one-third of patients during the first year (Palmer et al., 2010). CMV-naive recipients (R) receiving organs from seropositive donors (D⁺) are at the greatest risk of infection and are predisposed to particularly severe infection. Current guidelines recommend the use of ganciclovir/valganciclovir prophylaxis in D⁺/R- for 6 months following transplant (Kotton et al., 2010).

Community-acquired respiratory viruses consisting mainly of adenovirus and influenza virus along with certain Paramyxoviridae – respiratory syncytial virus (RSV), parainfluenza virus and human metapneumovirus (hMPV) – have gained recognition as pathogens among LTx recipients (Kumar et al., 2010; Gottlieb et al., 2009). While treatment options remain limited, oral ribavirin may improve outcomes in paramyxoviral infections but may not be well tolerated in all patients (Fuehner et al., 2011).

Fungal infections remain a constant, albeit less common, threat and are usually caused by *Aspergillus* or *Candida* species. However, pulmonary candidiasis is rare (Meersseman et al., 2009), particularly among LTx recipients, and detection should be based on culture and histology of bronchial mucosa biopsies rather than BAL findings (Strassburg et al., 2010). Conversely, the presence of *Candida* in blood cultures should be considered significant, with immediate initiation of treatment. BAL analysis may be negative in up to 40% of patients with an invasive aspergillosis. Infections tend to be limited to the airways, with a preponderance towards bronchial anastomoses. Invasive disease at the anastomoses may result in erosion of the pulmonary artery precipitating catastrophic pulmonary haemorrhage. Voriconazole is the first-line treatment of invasive aspergillosis, with echinocandins and parenteral lipid formulations of amphotericin B used as second-line therapy. *Candida* infections generally respond well to fluconazole. In non-*albicans* species, however, fluconazole resistance is becoming increasingly prevalent (Schaberg et al., 2010).

Due to a combination of lifelong cotrimoxazole prophylaxis and low-dose steroid treatment regimes, *P. jiroveci* pneumonia has become rare among adherent patients.

**New immunosuppressive drugs** In recent years, >40 monoclonal antibodies have been licensed for treatment of a wide variety of conditions. Inevitably, subsequent studies have alluded to an increased risk of severe infections in patients receiving antibody-associated immunosuppression (Keyser, 2011). Due to wide variations in immunological interactions, significant variability exists both in the pathogen spectrum and the severity of their effects (Curtis et al., 2011). Their modes of action can be broadly classified into those affecting B-cell function such as rituximab (anti-CD20), those specifically binding T-cells such as alemtuzumab (anti-CD52), co-stimulatory T-cell antibodies such as abatacept, anti-TNF antibodies such as infliximab, adalimumab and certolizumab, and etanercept (anti-soluble TNF receptor) and tocilizumab (anti-IL-6).

**HIV infection** Reduced CD4⁺ cell counts, while not correlating directly, do appear to indicate an increased risk of opportunistic respiratory pathogens in HIV-infected patients. The common bacterial pathogens are *S. pneumoniae* and *Haemophilus* spp. (Benito et al., 2012). Intravenous drug use and smoking appear to increase the pneumonia risk in these patients. Worldwide, *Mycobacterium tuberculosis* is the most important co-infection in HIV-infected patients and significantly influences AIDS-related mortality. *P. jiroveci* is the commonest nonbacterial pathogen. *Nocardia* spp., *Actinomycetes* spp., *Rhodococcus* and *Cryptococcus* are rare opportunistic pulmonary pathogens.
occasionally diagnosed in European patients with poorly treated HIV.

**Asplenia** Antibody production and phagocytosis by splenic macrophages represent a fundamental aspect of defence against encapsulated bacteria. Following splenectomy, patients are at higher risk of infection with S. pneumoniae, Haemophilus spp. and Neisseria meningitidis. Mortality rates from overwhelming post-splenectomy infection (OPSI) are reported to be up to 600 times greater than in the general population. The overall incidence of septicaemia remains low, with an estimated lifetime risk for OPSI of ∼5% (Lynch et al., 1996).

**Further reading**

Pneumonia in the immunocompromised host

Santiago Ewig

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 immnosuppression:

- iatrogenic (through steroidal and nonsteroidal agents)
- neutropenia (usually through antineoplastic chemotherapy)
- haematopoietic 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 constitute 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 and 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 work-up (sputum and blood cultures). A CT scan of the lung (multi-slice scan and HRCT) 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 radiographic presentations, or 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

**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.
relevant pathogens. Occasionally, transbronchial biopsies and/or transbronchial needle aspiration may be rewarding.

**Pneumocystis jirovecii** pneumonia

*P. jirovecii* pneumonia in HIV-infected patients usually occurs in patients with <200 CD4+ helper T-cells per microlitre. It presents with at least one of the following symptoms: fever, cough and dyspnoea on exertion; oral candidiasis is virtually always present. Chest radiography 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 level. 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/primaquine. Adjunctive steroids are indicated in patients with acute respiratory failure.

*P. jirovecii* pneumonia in non-HIV patients differs in that it presents more frequently as an acute-onset pneumonia and tends to be associated with higher mortality.

**Cytomegalovirus pneumonia**

Cytomegalovirus (CMV) pneumonia is defined as pulmonary signs and symptoms and the detection of CMV in pulmonary samples. Nevertheless, patients may shed CMV in the absence of CMV pneumonia. Co-infections with other opportunistic pathogens are frequently encountered. After introduction of CMV prophylaxis, the

<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 (<em>Aspergillus</em> spp.), <em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td>Iatrogenic (anti-TNF-α)</td>
<td>TNF-α</td>
<td><em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td>Neutropenia, HSCT</td>
<td>Neutrophils</td>
<td>Bacteria</td>
</tr>
<tr>
<td>Short duration (&lt;10 days)</td>
<td></td>
<td>Additionally: fungi (<em>Aspergillus</em> spp.)</td>
</tr>
<tr>
<td>Long duration (&gt;10 days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid-organ transplantation</td>
<td>Early (month 1): neutrophils</td>
<td>Bacteria</td>
</tr>
<tr>
<td>Intermediate (months 2–6):</td>
<td>Fungi, viruses, parasites</td>
<td></td>
</tr>
<tr>
<td>macrophages, T-cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late (months &gt;6): depends on</td>
<td></td>
<td>Variable</td>
</tr>
<tr>
<td>extent of immune suppression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV infection</td>
<td>CD4+ T-cell count &gt;500 cells·μL⁻¹</td>
<td>No risk</td>
</tr>
<tr>
<td></td>
<td>CD4+ T-cell count 200–500 cells·μL⁻¹</td>
<td><em>Bacteria, Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td></td>
<td>CD4+ T-cell count &lt;200 cells·μL⁻¹</td>
<td>Additionally: <em>Pneumocystis jirovecii</em></td>
</tr>
<tr>
<td></td>
<td>CD4+ T-cell count &lt;50 cells·μL⁻¹</td>
<td>Additionally: <em>Aspergillus</em> spp., atypical mycobacteria</td>
</tr>
</tbody>
</table>

TNF: tumour necrosis factor.
incidence in allogeneic HSCT is 10–30%, with the highest risk in seropositive recipients, while it is rare in autologous HSCT (<10%). In addition, 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 immunoglobulin. Second-line agents are foscarnet and cidofivir. Antiviral prophylaxis and monitoring are the main preventive strategies.

Tuberculosis

Patients with reduced CD4+ cell counts, and those 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). Anti-TB treatment of pulmonary TB follows the rules of standard treatment (i.e. usually a 2-month regimen consisting of four first-line drugs (isoniazid, rifampicin, ethambutol and pyrazinamide) followed by a 4-month regimen consisting of two drugs (isoniazid and rifampicin)). Testing for drug susceptibility is mandatory and treatment must usually be modified in the presence of resistance. 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 the case of positive skin testing or interferon-γ release assay, receive prophylaxis.

Aspergillus pneumonia

Definite diagnosis of Aspergillus pneumonia 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 (table 2). HRCT is the method of choice to detect Aspergillus pneumonia early in its course. Typical, albeit not specific, signs of Aspergillus pneumonia 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 Aspergillus pneumonia. 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 Aspergillus pneumonia is voriconazole or, alternatively, liposomal amphotericin B. Second-line options include caspofungin and posaconazole. Mortality reaches 50–60%.

### Table 2. Diagnostic criteria for invasive aspergillosis

<table>
<thead>
<tr>
<th>Definitive</th>
<th>Probable</th>
<th>Possible</th>
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<tbody>
<tr>
<td>Histological proof or positive culture from otherwise sterile site</td>
<td>Host factors + CT/tracheobronchitis + mycological criteria</td>
<td>Host factors + CT/tracheobronchitis</td>
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Host factors: several conditions associated with severe immunosuppression; CT: typical (albeit not specific) CT signs (e.g. the halo sign); tracheobronchitis: bronchoscopic visualisation of typical pseudomembranes on the tracheal mucosa (maybe subject to biopsy proof); mycological criteria: e.g. culture positive for Aspergillus, or positive galactomannan test in serum or BAL fluid. Information from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group.
Further reading

Pleural infection

Pleural infection occurs when microorganisms, most commonly bacteria, enter the pleural space. This may be due to direct spread from an underlying pneumonia or may result from blood-borne spread of a systemic bacteraemia. 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 (table 1). Pleural infection is a common and serious medical problem and the incidence is rising despite advances in medical management. It is associated with a mortality rate of 15–20%.

Epidemiology

- Pleural infection is most common in the elderly and children, but can occur at any age
- It is 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. Primary pleural infection is more common than previously thought, either as a result of translocation of bacteria from the oropharynx or as a consequence of bacteraemia from other sites.

Key points

- Pleural infection is common and serious, with a mortality rate of ~15%.
- Blood, in addition to pleural fluid, should always be cultured. A higher microbiological yield is achieved if pleural fluid is sent in both a universal container and blood culture bottles.
- Initial management is with broad-spectrum antibiotics and prompt chest drainage.
- Lung abscess has a 10% mortality rate.
- Invasive procedures are only required when a lung abscess does not respond to prolonged empirical antibiotics or an underlying neoplasm is suspected.

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. This is probably due in part to the differing environment within the pleural cavity, which is more hypoxic and has a lower pH than within the lung itself, making certain organisms (e.g. anaerobes) more pathogenic.

In community-acquired pleural infection,
Streptococcus spp. (largely from the Streptococcus anginosus group (previously
known as the *Streptococcus milleri* group) and *Streptococcus pneumoniae* account for 50% of positive cultures. *Staphylococcus* spp., anaerobic and Gram-negative organisms make up the other half. Anaerobic organisms commonly co-exist with aerobes, particularly with the *S. anginosus* group. Atypical pneumonia organisms such as *Legionella* and *Mycoplasma* spp. are extremely unusual causes of pleural infection.

In nosocomial pleural infection, *Staphylococcus* spp. (including methicillin-resistant *Staphylococcus aureus* (MRSA)) and Gram-negative organisms are responsible for most positive culture results.

**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, and fluid and blood should also be sent for protein and lactate dehydrogenase measurement.

In the correct clinical context, features suggesting that a parapneumonic effusion is complex and, hence, requires chest tube drainage include:

- a pleural fluid pH of <7.2 (or pleural fluid glucose of <2.2 mmol·L⁻¹)
- positive pleural fluid culture or Gram stain
- purulent pleural fluid
- loculation or septation on thoracic ultrasound

A causative organism is not identified in up to 40% of patients with pleural infection, but if one is identified, it can be useful to guide antibiotic treatment. Culturing the fluid in

<table>
<thead>
<tr>
<th>Table 1. Clinical classification of pleural infection</th>
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<tr>
<td><strong>Simple parapneumonic effusion</strong></td>
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<tr>
<td>Pleural fluid appearance</td>
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<tr>
<td>Pleural fluid pH</td>
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<tr>
<td>Pleural fluid Gram stain</td>
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<tr>
<td>Pleural fluid culture</td>
</tr>
<tr>
<td>Thoracic ultrasound appearance</td>
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<tr>
<td>Immediate management</td>
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blood culture bottles as well as a standard container has been shown to improve the microbiological yield and blood cultures may also help to 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).

Thoracic ultrasound is a useful bedside test in suspected pleural infection. It helps to differentiate simple parapneumonic effusions from empyema by the presence of septations and loculations, and should also be used to identify a safe site for fluid drainage. It also has a role in monitoring the degree of residual pleural fluid collection after a chest tube is placed, which may affect the subsequent management plan.

Contrast-enhanced CT demonstrates 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** The following steps should be implemented immediately:

- Broad-spectrum intravenous antibiotics
- Chest tube drainage
- Nutritional supplementation (oral or nasogastric)
- Thromboprophylaxis
- Vigilant monitoring for evidence of worsening sepsis indicating need for early thoracic surgery

Antibiotic choice is usually governed by local prescribing policies and should include antibiotics with broad-spectrum coverage and good penetration to the pleural space. Suitable combinations include penicillin–clavulanic acid in community-acquired infection and carbapenems 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 *S. pneumoniae* is isolated as this is not known to co-exist with anaerobes. Conventionally, ≥5 days’ intravenous antibiotics is followed by 2–4 weeks of oral treatment depending on clinical and radiological response.

In a clinically stable patient with a small empyema, chest tube drainage may be impractical and, hence, treatment with prolonged antibiotics and careful follow-up may suffice. However, in the majority of cases, drainage of the fluid is advocated. Small-bore (12–14 f) chest tubes are 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 some debate). Regular saline flushes (20 mL 6-hourly) may help to maintain tube patency and larger-volume 0.9% saline irrigation of the pleural space has been adopted by some European centres, with reports of improved primary

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*Figure 1. Chest radiograph of left empyema demonstrating a D-shaped, lentiform pleural opacity.*
treatment success rates, although this is not yet supported by published evidence.

The viscosity of the pleural fluid and degree of septation may impair tube drainage. Routine use of intrapleural fibrinolytics alone have not been shown to be of benefit. However, recent data suggests the combination of intrapleural tissue plasminogen activator (tPA) and DNase may result in improved radiological outcomes, and showed trends towards a reduction in need for surgery and duration of hospital stay. However, it has only been evaluated in a small number of patients and, therefore, its place in routine patient management is yet to be fully established.

Approximately 15–20% of patients will ultimately require surgical intervention for empyema, but selecting which patients are best suited to this approach can be challenging. The most compelling indication is failure of sepsis to improve despite appropriate antibiotics and tube drainage, but other reasons may include a significant residual pleural collection despite chest tube drainage. This assessment is usually made after 3–5 days of medical treatment. While surgical and anesthetic complications are more common in the elderly and frail, the vast majority of deaths as a result of pleural infection occur in this group and, hence, early surgical referral for a limited surgical drainage procedure may be beneficial. Some European centres advocate early thoracoscopy for these patients.

Available 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)
- thoracoscopy

Outcome It is not possible to reliably identify, by presenting radiological, pleural fluid or clinical feature,s which patients will go on to require thoracic surgery for empyema. However, a variety of risk factors for poor outcome have been identified, including the elderly and hospital-acquired disease. Overall, mean mortality rates of 15% have been reported in a recent series, but vary depending on certain risk factors. In order to identify at presentation which patients are at the highest risk of a poor outcome, a validated clinical risk score is being developed, which may help guide early clinical management in those at highest risk. This has highlighted five particular risk factors for poor outcome, which include age, urea, albumin, hospital-acquired infection and nonpurulence.

Patients should be followed up for $\geq 3$ months to allow the early detection of recurrent sepsis or persistent breathlessness.

Lung abscess

Lung abscesses are caused when an area of infected lung becomes necrotic, which results in the development of a cavity within the lung itself. In contrast to pleural infection, the incidence and mortality rate of lung abscess have steadily declined since the advent of penicillin.

Risk factors include:

- male sex (2:1)
- immunocompromised states
- aspiration of any cause
- pneumonia (particularly $S.\ aureus$ and $Klebsiella\ pneumoniae$).
- bronchial obstruction (e.g. endobronchial neoplasm is present in 10–20% cases)
- haematogenous spread of infection (e.g. tricuspid valve endocarditis and Lemierre’s syndrome (whereby acute oropharyngeal infection caused by $Fusobacterium\ spp.$, results in jugular vein thrombophlebitis and metastatic septic embolisation to the lung))

Diagnosis Symptoms may be acute or insidious in onset and commonly include cough, fever, chest pain, night sweats, weight loss and purulent or blood-stained sputum. There may be no specific examination findings or chest auscultation may mimic pneumonia. Anaemia is common in patients with a chronic lung
abscess and inflammatory markers are likely to be raised.

**Radiology** Plain chest radiography classically demonstrates a well circumscribed opacity within the lung field, which is often thick walled and contains an air–fluid level. Right-sided abscesses are twice as common as left. Dependent segments are most commonly affected when the abscess is caused by aspiration of gastric contents.

CT is usually required to distinguish a parenchymal abscess from empyema and may assist in the detection of neoplastic lesions. 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).

The radiological appearances of a lung abscess may be mimicked by other pathologies, including:

- neoplastic lesions
- pulmonary vasculitis
- pulmonary infarction
- bullae and cysts
- rheumatoid nodules
- pneumoconiosis
- mycobacterial infection

**Bacteriology and obtaining cultures** The microbiology of lung abscesses has changed over recent decades, which is predominantly due to an increase in immunocompromise and immunosuppression. In >50% of cases, lung abscesses are caused by more than one microorganism.

Anaerobes (e.g. *Fusobacterium*, *Prevotella* and *Peptostreptococcus* spp.), often originating from the oropharynx, are present in 30–50% and may be particularly important in the context of aspiration. However, aerobic bacteria now appear to be cultured more commonly than anaerobes (particularly *K. pneumoniae* and *S. aureus*).

Fungi, *Nocardia*, mycobacteria, *Amoeba*, actinomycosis and *Echinococcus* are more unusual causes of a parenchymal lung abscess, and immunocompromise may contribute to their development.

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 but, frequently, no organism is identified.

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, but may help to investigate other potential causes of lung cavitation, such as malignancy or TB. Endobronchial drainage of large lung abscesses is not usually recommended due to the risk of sudden discharge of pus into the airway, which may result in asphyxiation and respiratory compromise.

Image-guided percutaneous aspiration using CT, ultrasound or fluoroscopy obtains a microbiological diagnosis in 80–90% of cases and changes antibiotic choice in up to 47%. Due to a relatively high risk of pneumothorax (~14%) as a complication of these techniques, it is usually reserved for cases that do not respond to empirical broad-spectrum antibiotics.

**Management** A prolonged course of antibiotics is the foundation of treatment and, often, up to 8 weeks of treatment is required depending on clinical and radiological response. $\beta$-lactam/$\beta$-

![Figure 2. CT image of a) right pleural empyema and b) cavitating pulmonary abscess.](image)
lactamase inhibitor combinations cover the majority of causative bacteria and are a good empirical choice. Local antibiotic policies differ and should be used to guide antibiotic choices.

Patients with very large abscesses should ideally be placed in the lateral decubitus position with the abscess side down. This may help to prevent spread of the infection to the contralateral lung and respiratory compromise should the abscess suddenly discharge the contents into the airway. Chest physiotherapy also plays an important role in management and postural drainage may help to clear secretions from the abscess itself. Preventative measures to avoid further aspiration of gastric contents are also important.

Fever and infective symptoms usually settle within a week of appropriate antibiotics. Failure to improve should raise the suspicion of drug-resistant organisms, such as MRSA (particularly in the case of hospital-acquired infection), or other pathologies, such as TB or malignancy. Sustained resolution of sepsis is the most important marker of successful conservative management as radiological resolution can take up to 3 months.

When appropriate antibiotic therapy fails, invasive intervention to drain the abscess itself may become necessary. This is more common in the elderly or immunocompromised and for very large abscesses (>6 cm) and may be necessary in 11–21% of patients. This can either be performed using a percutaneous technique or surgery.

Image-guided percutaneous drainage is successful in 84% of cases and can be achieved with CT, ultrasound or fluoroscopic guidance. Complications such as bronchopleural fistulae, haemothorax and empyema are infrequent. As it is usually performed under local anaesthesia, this approach is preferred in patients with significant comorbidities.

The precise indications for surgical intervention are not well established, but it may be considered in the context of localised obstructing malignancy or life-threatening complications such as intractable haemoptysis, bronchopleural fistula or empyema. A VATS approach is less invasive than open surgical resection.

Perioperative mortality rates of up to 16% have been reported following surgery for lung abscess and, hence, an attempt at radiological drainage may be considered prior to undertaking a surgical procedure.

Lung abscesses are associated with a 10% mortality rate.

The elderly or immunocompromised and those with large abscesses (>6 cm), underlying malignancy, malnutrition or a delay in diagnosis and treatment have a particularly poor outcome.

Further reading
Influenza, pandemics and SARS

Wei Shen Lim

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–H16) and nine neuraminidase types (N1–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 haemagglutinin 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 complications of influenza.

- Neuraminidase inhibitors, such as oseltamivir and zanamivir, are effective in the prophylaxis and treatment of influenza A infection.
- The influenza A (H1N1) 2009 pandemic was of low severity compared to the other pandemics of the 20th century.
- The SARS outbreak of 2003 resulted in 8096 cases, of which 774 died.
- SARS-CoV is the causative agent of SARS. Bats are 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

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- Pneumonia is the most frequent serious complications of influenza.
- Neuraminidase inhibitors, such as oseltamivir and zanamivir, are effective in the prophylaxis and treatment of influenza A infection.
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The management of SARS is chiefly supportive. Basic infection control measures are the cornerstone of containment of any future outbreak.
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.

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 females, the frail elderly, those who are immunosuppressed, and those with chronic medical conditions such as heart disease, chronic respiratory disease (mostly asthma and COPD), cancer, diabetes, renal disease, rheumatologic disease, dementia and stroke. Rates of hospitalisation and death are increased in all these patient groups. Obesity (BMI > 30 kg·m⁻²) was also identified as being associated with adverse outcomes in patients hospitalised with influenza in the 2009 pandemic.

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 the onset of fever. This may be associated with tachypnoea, cyanosis and bilateral lung crackles on chest examination. 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 (ARDS).

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 commonest pathogens implicated are *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae* and *Streptococcus* spp.

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.

Treatment There are two main classes of drug that are active against influenza. The M2 ion channel inhibitors, amantadine and rimantadine, are effective against influenza A.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence</th>
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<tr>
<td></td>
<td>Adults</td>
</tr>
<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>Common</td>
</tr>
<tr>
<td>Myositis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Rare</td>
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<tr>
<td>Encephalitis/encephalopathy</td>
<td>Rare</td>
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<tr>
<td>Reye's syndrome</td>
<td>Rare</td>
</tr>
<tr>
<td>Febrile convulsions</td>
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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 generally preferred over zanamivir because of ease of administration (oral versus inhaled/intravenous). Newer neuraminidase inhibitors, such as peramivir and laninamivir, are also being clinically evaluated. 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 (RR) 0.39, 95% CI 0.18–0.85) and of inhaled zanamivir at 10 mg daily was 62% (RR 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 of whether neuraminidase inhibitors are effective in reducing the complications of lower respiratory tract infection, antibiotic use or admissions to hospital. Oseltamivir use is associated with nausea (OR 1.79, 95% CI 1.10–2.93). A meta-analysis of observational cohort studies of patients with pandemic influenza A (H1N1) 2009 found that antiviral treatment was associated with reduced mortality, hospitalisation and otitis media. However, the quality of the evidence was graded as low or very low, reflecting the underlying risk of bias in these observational cohorts.

For critically ill patients with severe avian H5N1 influenza infection and for patients with severe H1N1 primary viral pneumonitis, an increased dose of antiviral treatment for an extended duration (e.g. oseltamivir 150 mg b.d. for 10 days in adults) has been used. This practice is not based on evidence from randomised controlled trials.

For selected critically ill patients with severe influenza-associated ARDS and in whom conventional ventilation is proving inadequate, extracorporeal membrane oxygenation (ECMO) should be considered based on experience from the 2009 H1N1 pandemic.

Management of influenza-associated exacerbations of underlying comorbid illnesses, such as COPD or heart failure, should follow the same principles for each specific condition regardless of influenza. Antibiotics are usually advised for patients with influenza-associated pneumonia or patients with severe influenza infection who are at high risk of developing secondary bacterial infections. The use of corticosteroids in severe influenza cannot be routinely advocated based on current data; observational cohort studies conducted during the 2009 H1N1 pandemic have reported mixed results including increased harm.

Chemoprophylaxis and vaccination Both oseltamivir and zanamivir, taken as prophylactic agents, reduce the chance of symptomatic, laboratory-confirmed influenza (RR 0.38, 95% CI 0.17–0.85 for zanamivir 10 mg daily; RR 0.39, 95% CI 0.18–0.85 for oseltamivir 75 mg daily). However, the effect of neuraminidase inhibitors on the prophylaxis of influenzalike illness (ILI), 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% to >90%. Efficacy is lower (~40%) in the elderly.

Oseltamivir resistance In 1977, influenza A (H3N2) 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 those of oseltamivir-susceptible strains.

In the USA, the prevalence of oseltamivir resistance among seasonal influenza A (H1N1) viruses increased from <1% before the 2007–2008 influenza season to 12% during the 2007–2008 season and rose to >99% in the 2008–2009 season. This prompted the USA to issue guidelines at the time recommending the use of zanamivir or a combination of oseltamivir and rimantadine when oseltamivir-resistant seasonal influenza A (H1N1) virus infection was suspected.

H275Y mutations in pandemic influenza A (H1N1) 2009 viruses have also been identified. Fortunately, such oseltamivir-resistant isolates remain infrequent and sporadic, many occurring in immunosuppressed patients who appear to be at risk of resistance developing during oseltamivir therapy.

Pandemic influenza In the 20th century, pandemics occurred in 1918 (H1N1), 1957 (H2N2), 1968 (H3N2) and 2009 (H1N1) (fig. 1). Each of these pandemics had a different impact and tempo. The 1918 pandemic was the deadliest, 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.

The 2009 pandemic has been the best studied pandemic of the 20th century. The first cases were identified in Mexico in April 2009 and by June 2009, the World Health Organization had declared a pandemic. The pandemic influenza A (H1N1) 2009 virus was a triple-reassortant virus containing genes from human, swine and avian influenza viruses. It caused an infection that was clinically similar to seasonal influenza although 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 >60 years old, pre-existing cross-reactive antibodies due to previous exposure to antigenically related influenza viruses provided protection against infection.

Compared to the other 20th century pandemics, overall hospitalisation and mortality rates were low. In the UK, the overall estimated case fatality rate was 26 per 100 000; lowest for children aged 5–14 years (11 per 100 000) and highest for those aged ≥65 years (980 per 100 000). Hospitalisation rates varied across countries. Of those hospitalised, 9–31% required intensive care support, predominantly because of diffuse viral pneumonitis or ARDS. The mortality of intensive care unit-admitted patients was 14–46%.

After 2009, some countries experienced a further wave of influenza A (H1N1) 2009 infections in the 2010–2011 influenza season. However, in the following 2011–2012 influenza season, influenza A (H3N2) predominated in most countries and overall influenza activity was much lower compared with previous years. Based on past events, the threat of a future pandemic remains but its timing and severity are not currently predictable.

Severe acute respiratory syndrome

Epidemiology The global outbreak of severe acute respiratory syndrome (SARS) in
2002–2003 affected 8096 individuals in 29 countries, 774 of whom died. The three most severely affected regions were mainland China, Hong Kong and Taiwan with 5327, 1755 and 674, cases respectively.

The first human case was identified in the city of Foshan in Guangdong Province, China on November 16, 2002 and the last known case of the initial outbreak experienced the onset of symptoms on June 15, 2003 in Taiwan.

A novel coronavirus, the SARS coronavirus (SARS-CoV), was identified as the causative 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. While market animals such as the palm civet cat *Paguma larvata* have been identified as the likely animal sources of the 2003 outbreak, bats are now recognised as 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).

Subsequent infections later in the course of the outbreak were due mainly to human-to-human transmission. Molecular evolutionary changes of 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% to 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 the 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 or 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.

Laboratory test abnormalities include lymphopenia, neutropenia, thrombocytopenia, and raised levels of lactate dehydrogenase (LDH), alanine aminotransferase (ALT), creatinine kinase and activated partial thromboplastin time.

Respiratory failure occurs in 20–25% of patients, mainly adults. Unusually, the incidence of barotrauma (manifesting 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, indicating multisystem infection. Diagnostic yields are better with nasopharyngeal aspirates and faeces compared with 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, niclosamide, ribavirin, protease inhibitors (lopinavir and 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 the 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 of 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 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% to 70%. Alternative pathogens to consider in instances of an ILI include parainfluenza virus, adenovirus, rhinovirus, *Mycoplasma pneumoniae* and
even *Streptococcus 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.

**Further reading**

Pulmonary tuberculosis

Giovanni Sotgiu and Giovanni Battista Migliori

The World Health Organization (WHO) has declared 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
- multidrug resistance to anti-TB drugs (i.e. strains resistant to at least isoniazid (H) and rifampicin (R))
- migration from high-incidence countries
- the social determinants of the disease (in particular, poverty, drug abuse and homelessness)

TB can affect virtually every organ, most importantly the lungs (pulmonary TB).

Aetiology

TB is an infectious disease caused by aerobic, nonmotile, non-spore-forming bacteria belonging to the family Mycobacteriaceae in the order Actinomycetales. Among the species belonging to the Mycobacterium tuberculosis complex (Mycobacterium africanum, Mycobacterium bovis, Mycobacterium canettii, Mycobacterium caprae, Mycobacterium microti and Mycobacterium pinnipedi), the most frequent and important agent of human disease is M. tuberculosis. Mycobacteria are 2–4 μm long and 0.2–5 μm wide, with a bacterial generation time of 18–24 h. They are defined as acid-fast bacilli (AFB) by Ziehl–Neelsen staining, owing to their cell wall structure, which is crucial to their survival and characterised by a significant content of mycolic acid attached to the underlying peptidoglycan-bound polysaccharide arabinogalactan. An outermost structure, characterised by an elevated concentration of carbohydrates that function in cell–cell interactions, completes the mycobacterial envelope. The peptidoglycan network, located just outside the cell membrane, confers cell wall rigidity and protects a genome with ~4000 genes. Two groups of genes are crucial in the physiology of the mycobacteria: one encoding β-oxidation related-enzymes for energetic processes; and the other encoding PE and PEE families of proteins functioning in virulence and molecular mimicry processes. Furthermore, a relevant pathogenic role is attributed to the genes encoding glycolipids of the envelope, interplaying with the host innate and adaptive immune responses as well as with

Key points

- With 8.8 million new cases (0.21 being MDR-TB) and 1.1 million deaths, TB is a first-class health priority.
- Diagnosis of pulmonary TB is simple, being primarily based on bacteriology (sputum smear microscopy and culture). Recently, a new molecular technique (Xpert MTB/RIF) for the rapid diagnosis of TB and rifampicin resistance has been recommended as the standard in Europe.
- Treatment of pan-susceptible cases of pulmonary TB is effective and cheap.
- Management of pulmonary TB in MDR-TB/HIV co-infected cases is particularly complicated.
the metabolism of anti-TB drugs, due to their chemical characteristics.

**Pathogenesis**

Mycobacteria are spread through air droplets expelled by infectious pulmonary TB individuals coughing, sneezing or speaking. Close contacts (those with prolonged, frequent or intense contact with pulmonary TB cases) are at highest risk of becoming infected. Climate and human population density may affect the intensity and duration of human relationships and, consequently, the probability of close contact. The majority of mycobacteria, moved on droplet nuclei sized \( \geq 5 \mu m \), are trapped in the upper parts of the airways by the nasal vibrissae and by the mucus secreted by goblet cells, while the cilia of the epithelial cells constantly beat them upward for removal. Environmental factors like humidity, temperature and ventilation can modify the dimension and density of droplets containing mycobacteria. Bacteria in droplet nuclei sized 1–5 \( \mu m \) can bypass the mucociliary system and reach the alveoli, usually located in subpleural and in mid-lung zones, where they are rapidly engulfed by macrophages, which are part of the innate immune system and the most abundant phagocytic cells located in the alveolar spaces; they are readily active without requiring previous antigenic exposure. Macrophages engulfing mycobacteria transfer to draining lymph nodes in order to prime naïve lymphocytes, after having enrolled other mononuclear and nonmononuclear cells in the alveolar spaces. Mycobacteria significantly growing for the first 3 weeks are controlled by phagocytic cells, activated mainly by T-cells producing interferon (IFN)-\( \gamma \). Infection could be crucially favoured by the slow pulmonary enrolment of T-cells. Numerous bacterial and host mechanisms are involved in the uptake of the mycobacteria, such as:

- Toll-like receptors
- nucleotide-binding oligomerisation domain-like receptors
- C-type lectins
- PE and PEE families of acidic, glycine-rich proteins
- induction of regulatory T-cells (delay of priming following the interaction with antigen-presenting cells and the production of interleukin-10)

Unfortunately, innate and adaptive immunity cannot eradicate mycobacterial strains and a latent TB infection (LTBI) follows in the majority of cases; rarely, infection progresses to active disease, called primary progressive pulmonary TB (common among children aged \( \leq 4 \) years). During the initial phase (2–12 weeks), the bacteria continue to multiply slowly but exponentially (a cell division every 25–35 h) and T-cells are attracted by cytokines released by macrophages. In the immunocompetent, the next defensive stage is formation of granulomata around mycobacteria, which limits bacterial replication and spread to other pulmonary sites, establishing latency of the infection (potential sustained T-cell responses). Granulomata, whose size range from 1 mm to 2 cm, are characterised by different macrophage populations that secrete pro-and anti-inflammatory cytokines, and by a chemical and physical microenvironment, which induces mycobacterial dormancy genes. CD4\(^+\) T-cells, primed in the regional lymph nodes and migrating to the site of infection, produce cytokines that function in CD8\(^+\) lymphocyte enrolment (e.g. interleukin-15), the activation of regulatory T-cells and the inhibition of mycobacterial replication (IFN-\( \gamma \)). Lesions in those with an adequate immune system undergo fibrosis and calcification, while in immunocompromised subjects, they progress to primary progressive pulmonary TB.

The majority of infected individuals developing pulmonary TB experience the disease within the first 2 years following infection. Dormant bacilli, however, may persist for years before being reactivated to produce secondary pulmonary TB. Overall, it is estimated that the lifetime risk of developing TB, given infection, is 5–10% in
those who are immunocompetent and 5–10% per year 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 years (35–50% in children close contacts of contagious patients), with a second peak during adolescence and early adulthood. The risk may increase in the elderly, possibly because of waning immunity and comorbidities (e.g. diabetes mellitus, chronic renal failure, silicosis, gastrectomy, jejunoileal bypass, and solid and liquid neoplasias).

Epidemiology

WHO estimates that 8.8 (range 8.5–9.2) million new cases of TB occurred in 2010. India, China, South Africa, Indonesia and Pakistan recorded the highest incidence. Asia (South-East Asia and the Western Pacific region) accounts for 59% of global cases and Africa for 26%. TB/HIV co-infection was detected in 1.1 (range 1.0–1.2) million individuals, mainly living in the WHO African Region (82%). From 1990 to 1997, TB incidence decreased but the positive trend was reverted by the HIV/AIDS epidemic; however, the implementation and scale-up of several preventive measures, as well as the distribution of successful antiretroviral drugs, has favoured a positive declining trend since 2004 at an annual rate of -1.3%. However, the positive declining trend of TB prevalence since 1990 has not been affected by the HIV/AIDS epidemic. The estimated incidence in the WHO European region was 418 000 (range 335 000–496 000) in 2010, with four countries showing an elevated TB notification rate (i.e. Kazakhstan, Moldova, Georgia and Kyrgyzstan with 123, 115, 107 and 106 cases per 100 000 inhabitants, respectively). The global TB notification rate has declined since 2006, from 47.4 per 100 000 inhabitants to 43.2 per 100 000 inhabitants in 2010 (8.7% decrease).

Globally, 12 (range 11–14) million prevalent cases of TB were estimated to exist in 2010, equivalent to a prevalence of 178 cases per 100 000 population.

It was estimated that 210 000–380 000 (best estimate 290 000 individuals) cases of multidrug-resistant (MDR)-TB emerged worldwide in 2010, with an estimated prevalence of 650 000 cases. WHO identified 27 high MDR-TB burden countries, with almost half of them (13) located in the geographical area of the Former Soviet Union. Belarus and Moldova described the highest prevalence among new (26%) and previously treated (65%) patients. In 2006, a new drug-resistant form of TB was described and defined as extensively drug-resistant (XDR)-TB, characterised as MDR strains resistant to fluoroquinolones and to at least one second-line injectable drug (amikacin, capreomycin or kanamycin). The percentage of XDR-TB among MDR-TB cases was 12.2% in the WHO European Region. Globally, drug susceptibility testing (DST) to diagnose MDR/XDR-TB is performed only in <2% and 6% of new and previously treated TB cases, respectively; moreover, MDR-TB therapy was started in only 16% of the 290 000 MDR-TB cases in 2010. Those programmatic shortcomings in the diagnosis and treatment of drug-resistant cases will favour the emergence and spread of mycobacterial strains.

Approximately 1.1 (range 0.9–1.2) million TB patients died in 2010; an estimated 350 000 were HIV positive.

Clinical features

Before the HIV/AIDS epidemic, almost two-thirds of all TB cases were pulmonary; an increase in extra-pulmonary, and pulmonary and extra-pulmonary forms has been reported over recent decades.

Primary pulmonary TB frequently occurs without clinical signs and symptoms or takes a paucisymptomatic course resembling mild respiratory tract infection.

In the majority of cases, the primary infection is contained, largely resolves and a small calcified nodule (Ghon lesion) persists. Mostly in children and in individuals with impaired immunity, the primary infection can progress to pleural effusion; only in certain circumstances it
may develop further to more acute infection, and induce fever, cough, pain and dyspnoea. In children aged <4 years, a systemic disease and/or meningoencephalitis can be diagnosed after primary regional lymphadenitis.

Secondary pulmonary or post-primary TB results from endogenous reactivation of a LTBI and is frequently located in pulmonary areas where the oxygen concentration is higher and favours mycobacterial replication (upper lobes).

Early clinical signs and symptoms consists of low-grade fever, asthenia, weight loss (inappetence and altered metabolism associated with systemic inflammatory response to mycobacteria) and night sweats. A mucopurulent cough develops in the majority of patients: a duration of at least 2–3 weeks has to be considered the main clinical symptom, whereas haemoptysis (i.e. coughing up of blood) in the late stages of the disease might be due to the rupture of a dilated vessel in a cavity (Rasmussen’s aneurysm) or to an aspergilloma in an old cavity. A pleuritic process can cause chest pain. Rales and dullness can be detected in only a few individuals.

Diagnosis

At >100 years old, sputum smear microscopy (Ziehl–Neelsen staining) is still the most widely used technique for the diagnosis of pulmonary TB. Although highly specific, the lower limit of detection of microscopy is $0.5–1 \times 10^4$ organisms per mL sputum and only about half of all culture-positive cases have sputum smear-positive results. At least two sputum samples should be sent to the laboratory for a microscopic examination; at least one of them should be collected in the early morning. The first specimen is positive in 85.8% of the sputum smear positive individuals; the average incremental yield of the second specimen is 11.1%. However, sensitivity may be lower among HIV-infected subjects and in children. AFB microscopy is simple to perform but suboptimal results are described where adequate quality-assurance programmes are absent. Over recent years, fluorescence microscopy was introduced in numerous laboratories, adding 10% sensitivity to that of conventional light microscopy. An increased sensitivity of 10–20% can be obtained after centrifugation and/or sedimentation. 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 sputum 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 mycobacterial exposure.

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. DST 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 (nucleic acid amplification (NAA)) based on gene amplification have shown an unpredictable sensitivity, particularly in sputum smear-positive cases and extra-pulmonary forms, and a low negative predictive value. The major limitation, mainly for low-income countries, is their current high cost and the risk of contamination (false-positive results). Recently, WHO endorsed a new
molecular technique (Xpert MTB/RIF; Cepheid, Sunnyvale, CA, USA) for the rapid (~1 h 45 min) diagnosis of TB and rifampicin resistance, which is deemed a surrogate marker of MDR-TB. Rapid scale-up of this technique has started globally. In 2012, this technique was recommended in the European Union standards for TB care.

Chest radiology (fig. 1) and 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.).

Among the tools indirectly used to detect mycobacterial infection, the tuberculin skin test (TST) is widely used, even if several limitations, including poor specificity, difficult administration and the risk of anergy, are reported. It identifies adaptive immunity to mycobacterial antigens, injected intradermally as a protein precipitate (purified protein derivative (PPD)) in the volar part of the forearm (Mantoux test). PPD, constituted by different molecules, is derived by filtration of *M. tuberculosis* cultures.

False-negative reactions are common in immunocompromised patients and in those with overwhelming pulmonary TB. Positive results are obtained when patients have been infected with *M. tuberculosis* and when subjects have been sensitised by nontuberculous mycobacteria acquired environmentally or *M. bovis* bacille Calmette–Guérin (BCG) vaccination, because of the antigenic cross-reactivity of PPD.

Finally, IFN-γ release assays (IGRAs) have recently been introduced into clinical practice. They detect adaptive cellular immune reactivity towards *M. tuberculosis*-specific antigens encoded by genes located in the RD-1 genomic region. Their application in specimens collected from the infected organ (e.g. bronchoalveolar lavage) or tissue for the clinical diagnosis of TB is still under evaluation, but seems promising (specificity >80%). These techniques can increase the low specificity of TST based on the immune response (release of IFN-γ) to the 6-kDa early secreted antigenic target protein (ESAT-6), the 10-kDa culture filtrate protein (CFP-10) and TB7.7, which are antigens specific to *M. tuberculosis* and are not produced by *M. bovis* BCG or environmental mycobacteria. Although the diagnostic sensitivity of IGRAs performed using blood seems higher than that of TST, it is not sufficient to rule out TB. Their negative predictive value for progression from LTBI to active TB disease is 97.8–99.8% within 2 years.

**Treatment**

Individuals with active TB and positive sputum smear test results are the main source of TB transmission in the community owing to their high bacillary load. The most relevant priority in TB control programmes is the rapid identification of new cases of sputum smear-positive pulmonary TB and their effective treatment. It has been estimated that case-finding and effective treatment of sputum smear-positive individuals could halve the global number of TB cases within a decade.

Short-course regimens are divided into an initial or bactericidal phase and a continuation or sterilising phase.

WHO recommends treatment of new cases of pulmonary TB with a standardised
regimen of four first-line anti-TB drugs, including isoniazid, rifampicin, pyrazinamide (Z) and ethambutol (E) for 2 months (intensive phase), followed by isoniazid and rifampicin for 4 months (continuation phase) (tables 1–3).

Fixed-dose combinations of two (isoniazid and rifampicin), three (isoniazid, rifampicin and pyrazinamide) and four (isoniazid, rifampicin, pyrazinamide and ethambutol) drugs are highly recommended.

Individuals with a previous TB diagnosis and treatment for >1 month are at higher risk of being infected with drug-resistant strains and, consequently, DST is necessary. In settings where rapid molecular-based DST is available, the results should guide the choice of the treatment regimen.

The standard re-treatment regimen containing first-line drugs (2HRZES/1HRZE/5HRE) is recommended by WHO for treatment of TB patients returning after default or relapsing from their first treatment course if country-specific data show low or medium levels of MDR in such patients.

If the setting-specific prevalence of MDR-TB is high, re-treatment cases should be managed as if they harbour MDR-TB strains. While rapid molecular-based methods allow a first orientation, DST for all second-line drugs should be promptly requested to allow the design of an adequate regimen.

Treatment duration is identical in HIV-positive and -negative patients. Antiretroviral therapy should be started within 2 months of the start of the anti-TB therapy in order to reduce the risk of death, irrespective of CD4+ cell counts. However, drug–drug interactions, a relevant pill burden and the potential occurrence of immune reconstitution inflammatory syndrome (IRIS) can hinder an adequate management.

A regimen with at least four effective drugs is recommended for MDR-TB cases. At least four second-line drugs should be administered, with an injectable for the intensive phase of treatment (8 months).

Total duration should be ≥20 months. Management of MDR/XDR-TB cases is more complicated from a clinical and public health perspective, being more expensive, more toxic and less efficacious (table 4).

Treatment of MDR- and XDR-TB cases should be managed in highly specialised reference centres by high skilled healthcare workers, identified by national authorities. Relevant clinical decisions (e.g. when to start and interrupt treatment, how to design the regimen, how to manage an adverse event, etc.) should ideally be taken within a team of experts with complementary competences (a consilium or similar body). Consilia, which are presently only available to cover internationally funded MDR-TB treatment projects, are considered by WHO to be important in ensuring the best possible management of these difficult-to-treat cases and to prevent development of super-resistance. The European Respiratory Society (ERS) and WHO are presently offering this service cost-free via an electronic platform through which clinicians will receive expert advice within 1 week (www.tbconsilium.org).

Scaling-up of culture and DST capacities, and the expanded use of high-technology assays for rapid determination of resistance (e.g. GeneXpert) 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.

However, to reduce the emergence of new cases of TB, it is strategically crucial to identify and treat the infected subjects at higher risk of developing TB. National and international guidelines agree on the screening of HIV-positive patients, children and adults with close contact with an infectious case, individuals who are going to be treated with anti-tumour necrosis factor-α drugs. Isoniazid, administered for
Table 1. Anti-TB drugs, dosages and common adverse effects

<table>
<thead>
<tr>
<th>Anti-TB drug</th>
<th>Recommended daily dosage</th>
<th>Common adverse effects (not exclusive)</th>
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<tbody>
<tr>
<td><strong>Group 1: first-line oral agents</strong></td>
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<tr>
<td>Isoniazid</td>
<td>5 mg·kg⁻¹ OD</td>
<td>Elevated transaminases, Peripheral neuropathy, GI intolerance, CNS toxicity</td>
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<tr>
<td></td>
<td>Should not exceed 300 mg per day</td>
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<td></td>
<td>Always consider co-administration of vitamin B6</td>
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<tr>
<td>Rifampicin</td>
<td>10 mg·kg⁻¹ OD, &gt;50 kg: 600 mg, &lt;50 kg: 450 mg</td>
<td>Elevation of liver enzymes, Hepatitis, Hypersensitivity, Fever, GI disorders: anorexia, nausea, vomiting, abdominal pain, Discoloration (orange or brown) of urine, tears and other body fluids, Thrombopenia</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15–25 mg·kg⁻¹ OD, Maximum 2.0 g per day</td>
<td>Optic neuritis, Hyperuricaemia, Peripheral neuropathy (rare)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>30 mg·kg⁻¹ OD, Maximum 2.0 g per day</td>
<td>Arthralgia, Hyperuricaemia, Toxic hepatitis, GI discomfort</td>
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<td><strong>Group 2: injectables</strong></td>
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<tr>
<td>Streptomycin</td>
<td>0.75–1 g OD, &lt;50 kg: 0.75 g per day, &gt;50 kg: 1 g per day, Maximum cumulative dose 50 g</td>
<td>Auditory and vestibular nerve damage (irreversible), Renal failure (usually reversible), Allergies, Nausea, Skin rash, Neuromuscular blockade</td>
</tr>
<tr>
<td>Amikacin</td>
<td>0.75–1 g OD, &lt;50 kg: 0.75 g per day, &gt;50 kg: 1 g per day, Maximum cumulative dose 50 g</td>
<td>Auditory and vestibular nerve damage (irreversible), Renal failure (usually reversible), Allergies, Nausea, Skin rash, Neuromuscular blockade</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>0.75–1 g OD, &lt;50 kg: 0.75 g per day, &gt;50 kg: 1 g per day, Maximum cumulative dose 50 g</td>
<td>Auditory and vestibular nerve damage (irreversible), Renal failure (usually reversible), Bartter-like syndrome, Allergies, Neuromuscular blockade</td>
</tr>
<tr>
<td>Anti-TB drug</td>
<td>Recommended daily dosage</td>
<td>Common adverse effects (not exclusive)</td>
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<tr>
<td>Kanamycin</td>
<td>375–500 mg <em>b.i.d.</em></td>
<td>Auditory and vestibular nerve damage (irreversible)</td>
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<td></td>
<td>&lt;50 kg: 0.75 g per day</td>
<td>Renal failure (usually reversible)</td>
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<td>&gt;50 kg: 1 g per day</td>
<td>Allergies</td>
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<td>Maximum cumulative dose</td>
<td>Nausea</td>
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<td></td>
<td>50 g</td>
<td>Skin rash</td>
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<td></td>
<td></td>
<td>Neuromuscular blockade</td>
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<td>Group 3: fluoroquinolones</td>
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<tr>
<td>Levofloxacin</td>
<td>500–1000 mg <em>OD</em></td>
<td>GI discomfort</td>
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<td></td>
<td></td>
<td>CNS disorders</td>
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<td>Tendon rupture (rare)</td>
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<td>Hypersensitivity</td>
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<td></td>
<td></td>
<td><em>Clostridium difficile</em> colitis</td>
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<tr>
<td>Ciprofloxacin</td>
<td>500–750 mg <em>b.i.d.</em></td>
<td>GI discomfort</td>
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<td>CNS disorders</td>
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<td>Tendon rupture (rare)</td>
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<td>Hypersensitivity</td>
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<td></td>
<td></td>
<td><em>Clostridium difficile</em> colitis</td>
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<tr>
<td>Moxifloxacin</td>
<td>400 mg <em>OD</em></td>
<td>GI discomfort</td>
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<td></td>
<td></td>
<td>Headache</td>
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<td>Dizziness</td>
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<td>Hallucinations</td>
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<td>Increased transaminases</td>
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<td></td>
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<td>QT prolongation</td>
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<td></td>
<td></td>
<td><em>Clostridium difficile</em> colitis</td>
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<tr>
<td>Group 4: second-line oral agents</td>
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<tr>
<td>Rifabutin</td>
<td>150–450 mg <em>OD</em></td>
<td>Anaemia</td>
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<td></td>
<td>Consider monitoring drug levels</td>
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<td></td>
<td></td>
<td>GI discomfort</td>
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<td></td>
<td></td>
<td>Discoloration (orange or brown) of urine and other body fluids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uveitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Elevated liver enzymes</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>0.75–1 g <em>OD</em></td>
<td>Severe GI intolerance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CNS disorders</td>
</tr>
<tr>
<td>Prothionamide</td>
<td>0.75–1 g <em>OD</em></td>
<td>Severe GI intolerance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CNS disorders</td>
</tr>
</tbody>
</table>
6–12 months at a dosage of 5 mg·kg⁻¹ per day, decreases the probability of developing active disease by 60% for a 2-year period. Longer duration is correlated with a higher probability of hepatic dysfunction, irrespective of efficacy. Other alternative regimens prescribed are: isoniazid and rifampicin for 3 months, or a weekly

<table>
<thead>
<tr>
<th>Anti-TB drug</th>
<th>Recommended daily dosage</th>
<th>Common adverse effects (not exclusive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycloserine</td>
<td>250 mg t.i.d. Maximum 1000 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 1000 mg per day</td>
<td>CNS disorders Anxiety Confusion Dizziness Psychosis Seizures Headache</td>
</tr>
<tr>
<td>PAS</td>
<td>4 g t.i.d.</td>
<td>GI intolerance Nausea Diarrhoea Vomiting Hypersensitivity</td>
</tr>
<tr>
<td>Thioacetazone</td>
<td>50 mg t.i.d.</td>
<td>Hypersensitivity GI intolerance Vertigo Hepatitis</td>
</tr>
</tbody>
</table>

**Group 5: oral reserve drugs with uncertain anti-TB activity**

<table>
<thead>
<tr>
<th>Anti-TB drug</th>
<th>Recommended daily dosage</th>
<th>Common adverse effects (not exclusive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linezolid</td>
<td>600 mg OD (600 mg b.i.d. recommended for MRSA and VRE infections)</td>
<td>Thrombopenia Anaemia Neuropathy</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>100 mg OD</td>
<td>Ichthiosis GI discomfort Nausea Vomiting Discoloration of the skin</td>
</tr>
<tr>
<td>Amoxicillin–clavulanate</td>
<td>875–125 mg b.i.d. or 500–250 mg t.i.d.</td>
<td>GI discomfort Diarrhoea Rash</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500 mg b.i.d.</td>
<td>GI discomfort</td>
</tr>
</tbody>
</table>

PAS: para-aminosalicylic acid; OD: once daily; MRSA: methicillin-resistant *Staphylococcus aureus*; VRE: vancomycin-resistant *Enterococcus*; GI: gastrointestinal; CNS: central nervous system. #: intravenous/intramuscular administration only; #: intravenous administration only; #: also available from intravenous administration.
administration of isoniazid and rifapentine for 3 months.

Prevention

In 1993, the United Nations stated that the global fight against TB must be a priority alongside with the fight against HIV/AIDS and malaria. On this basis, in 1996, WHO issued a public health strategy called DOTS (directly observed treatment, short course), aimed at diagnosing 70% of sputum smear-positive patients and successfully treating 85% of them by 2005. It was composed of five elements:

1. political commitment to TB control
2. bacteriological diagnosis through smear microscopy
3. supervised and standardised short-course therapy
4. supply of quality drugs without interruption
5. standardised recording and reporting system for treatment outcomes

In 1996, a new WHO strategy called STOP-TB was issued in order to address the new global epidemiological issues, such as MDR-TB and TB/HIV co-infection. It was aimed to meet the 2015 Millennium Development Goals (i.e. to halve TB prevalence and mortality compared to the data recorded in 1990) and showed a more comprehensive approach (for instance, involvement of the private sector, and engagement of the community and of all healthcare providers). WHO and partners are presently discussing the new post-2015 strategy, which will be centred around three main pillars:

1. intensified and innovative TB care
2. development and enforcement of bold health-system and social development policies
3. promotion and intensification of research and innovation

A relevant tool for the clinical and public health management of TB called the International Standards of Tuberculosis Care (ISTC) was developed by several stakeholders, coordinated by WHO, to give evidence-based standards. Recently, the ERS

### Table 2. Recommended treatment regimens for new TB cases

<table>
<thead>
<tr>
<th>TB treatment regimen</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intensive phase</strong></td>
<td><strong>Continuation phase</strong></td>
</tr>
<tr>
<td>2HRZE</td>
<td>4HR</td>
</tr>
<tr>
<td>2HRZE</td>
<td>4HRE</td>
</tr>
</tbody>
</table>

Ethambutol (E) must be prescribed during the intensive phase in individuals with noncavitary, smear-negative pulmonary TB, or in HIV-negative patients with extrapulmonary TB. In TB meningitis, it should be replaced by streptomycin (S). Number preceding regimen indicates the length of treatment in months. H: isoniazid; R: rifampicin; Z: pyrazinamide.

### Table 3. Recommended treatment regimens for previously treated patients

<table>
<thead>
<tr>
<th>Probability of MDR-TB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High (failure)</strong></td>
</tr>
<tr>
<td>Pending DST results: empirical MDR-TB regimen, modified once DST results are available</td>
</tr>
</tbody>
</table>

Number preceding regimen indicates the length of treatment in months. H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; S: streptomycin.
### Table 4. General principles for designing an empiric regimen to treat MDR-TB

<table>
<thead>
<tr>
<th>Basic principles</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **1. Use at least four drugs of known effectiveness or highly likely to be effective** | Effectiveness is supported by a number of factors (the more of them that are present, the more likely it is that the drug will be effective).  
Susceptibility at DST  
No previous history of treatment failure with the drug  
No known close contacts with resistance to the drug  
DRS indicates resistance is rare in similar patients  
No common use of the drug in the area  
If at least four drugs are not certain to be effective, use five to seven drugs, depending on the specific drugs and level of uncertainty |
| **2. Do not use drugs for which resistance crosses over** | Rifamycins (rifampicin, rifabutin, rifapentine and rifalazil) have high level of cross-resistance  
Fluoroquinolones: variable cross-resistance; in vitro data show some later generation agents remain susceptible when earlier generation are resistant (clinical significance of the phenomenon still unknown)  
Aminoglycosides and polypeptides: not all are cross-resistant; in general, only kanamycin and amikacin are fully cross-resistant |
| **3. Eliminate drugs likely to be unsafe for the patient** | Known severe allergy or difficult-to-manage intolerance  
High risk of severe adverse effects including: renal failure, deafness, hepatitis, depression and/or psychosis  
Unknown or questionable drug quality |
| **4. Include drugs from groups 1–5 in a hierarchical order, based on potency** | Use any group 1 drugs that are likely to be effective (see principle 1 above)  
Use an effective injectable aminoglycoside or polypeptide (group 2 drugs)  
Use a later-generation fluoroquinolone (group 3)  
Use the remaining group 4 drugs starting from ethionamide (or prothionamide) to make a regimen consisting of at least four effective drugs plus pyrazinamide in the intensive phase of treatment  
Regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent (kanamycin, amikacin or capreomycin), ethionamide (or prothionamide), and either cycloserine or PAS if cycloserine cannot be used  
An intensive phase of 8 months’ duration is recommended; a total treatment duration of 20 months is recommended in patients without any previous MDR-TB treatment  
For regimens with up to four effective drugs, add second-line drugs most likely to be effective, to give five to seven drugs in total, with at least four of them highly likely to be effective  
The number of drugs will depend on the degree of uncertainty  
Use group 5 drugs as needed so that at least four drugs are likely to be effective |
| **5. Be prepared to prevent, monitor and manage adverse effects for each of the drugs selected** | Ensure laboratory services for haematology, biochemistry, serology and audiometry are available  
Establish a clinical and laboratory baseline before starting the regimen  
Initiate treatment gradually for a difficult-to-tolerate drug, splitting daily doses of ethionamide/prothionamide, cyclosporin and PAS  
Ensure ancillary drugs are available to manage adverse effects  
Organise intake supervision for all doses |

DRS: drug resistance surveillance; PAS: para-aminosalicylic acid.
and the European Centre for Disease Prevention and Control adapted the ISTC to the European Union/European Economic Area scenario, focusing on the goal of TB elimination.

Only one vaccine is currently available for the primary prevention of TB: it consists of a live attenuated strain of \( M. \text{bovis} \) BCG, the efficacy of which has been proven in children for TB meningitis and miliary TB but not for pulmonary TB in endemic geographical areas. Safety concerns have been reported, particularly in HIV-positive patients.

The goal of the global elimination of TB, i.e. an incidence of new sputum smear-positive cases \(<1\) per 1 million inhabitants, seems difficult to meet, but the epidemiological scenario could improve with a multi-sector approach oriented by the evidence-based WHO strategies.

Further reading

Extrapulmonary tuberculosis

Aik Bossink

Definition

The World Health Organization (WHO) defines of extrapulmonary TB (EPTB) as ‘A patient with tuberculosis of organs other than the lungs (e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, 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 antituberculosis chemotherapy’.

A patient diagnosed with both pulmonary TB (PTB) and EPTB should be classified as a case of PTB.

The definition does not mention eyes or the ear–nose–throat region. However, these tissues are also, rarely, possible localisations.

General aspects of EPTB

Only a minority of TB 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), EPT localisations comprise nearly 50% of all cases. With the arrival of new, more sensitive detection methods, EPTB could well be even more common. EPTB has always been considered less important than PTB because of the low infectious potential and the difficulties involved in the diagnosis EPT.

In low-income countries, males appear to be affected by TB more often than females. However, in high-income countries, this difference is not so clear. This mechanism is not clearly understood. No evidence is available that EPTB affects one sex more often than the other.

Immunosuppression appears to be an important cause of EPTB and this 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, biologicals 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’ (Wilkinson, 1940). 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 EPT are the cervical lymph nodes and pulmonary pleura. Other sites are, in declining order, bones and joints, the meninges and central
nervous system (CNS), abdominal lymph nodes, the peritoneum and gastrointestinal tract, the genitourinary tract, and the pericardium.

It should be noted that gastric aspirate from children with EPTB often contains mycobacteria. This is, however, not an indication of EPT but should be considered as local spread of mycobacteria by swallowing sputum.

In immunocompromised hosts, the presentation of EPTB is often different compared to immunocompetent hosts. Dissemination of the disease is more common and clinicians should be aware of other localisations. Dissemination is more likely because ill-formed granulomata are more common in immunocompromised hosts.

The term miliary TB is a radiological finding of 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 samples. Furthermore, some of the EPTB localisations contain 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 cases.

In low-income countries, specific staining is often the only available diagnostic tool and, because of its relative simplicity, should always be undertaken. A relatively novel method, the Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA), could well be promising in low-income countries with few laboratory facilities. This real-time automated nucleic acid amplification technique runs in a closed system and is suitable for use outside conventional laboratory settings. Most experience of the performance on this technique is based on sputum samples but a review (Lawn et al., 2012) mentions good performance in EPTB samples. However, culture and drug susceptibility testing remain the cornerstone of adequate treatment.

Some promising reports of the use of interferon-γ release assays on materials other than blood in the diagnosis of EPTB (pleural, peritoneal, pericardial 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 DST.

An increasing number of case and brief reports has been published on the use of 18-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT for the detection of both PTB and EPTB sites. Unfortunately, most prospective studies have been designed to differentiate between malignancies and TB. Nuclear medicine is, in general, not an appropriate tool to differentiate between these. However, FDG-PET/CT appears to have a high sensitivity in the detection of lymph-node TB and organ localisations. The performance on visceral TB localisations remains unclear. A recent review (Sathekge et al., 2012) concludes that ‘Available data, reviewed above, suggest that SPECT [single-photon emission CT] and PET may prove to be valuable adjuncts for the differentiation of TB from malignant lung lesions, active from nonactive disease, and for treatment follow-up, and may thus play a major role in the work-up of TB patients’. It can be expected that with the use of more sensitive methods of detection, the proportion of EPTB localisations will increase.

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 then another 4–7 months of isoniazid
and rifampicin in culture-confirmed cases with normal drug susceptibility. 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 cases and, therefore, generalised symptoms are unusual. During medical treatment, the lymph nodes can rapidly increase in size (paradox reaction) and fine-needle aspiration of its content may prove beneficial in preventing fistula. 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, TB 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. Often, large amounts of pleural fluid are observed with relatively low numbers of mycobacteria. An accompanying hypersensitivity reaction is 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 abducens nerve. 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 stage II and III. Survival is positively influenced by this regimen but neurological outcome is no better in the groups treated with steroids. Others recommend steroids independent of the stage. Antibiotic treatment should be for ≥9 months. However, according to the British Infection Society guidelines, treatment should be continued for 1 year. WHO recommends replacing ethambutol with 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. To reduce the effusion and to prevent thickening of the pericardium, adjuvant steroids are recommended. No data are available on the amount and duration of steroid treatment. It seems reasonable to prescribe 0.5 mg·kg⁻¹ for the first 2 months and then 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 monoarthritis. 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.
Further reading

- KNCV. Epidemiologie en surveillance [Epidemiology and surveillance]. www.kncvtbc.nl/nl/epidemiologie-en-surveillance
Tuberculosis in the immunocompromised host

Martina Sester

The incidence of active TB and attendant mortality 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. The relative risk for TB varies with the type of immunodeficiency (table 1) and mortality rates may be as high as 75% (Sester et al., 2012). This emphasises the particular importance of the cellular arm of the adaptive immune response for efficient control of Mycobacterium tuberculosis (Sester et al., 2010, 2012; Bumbacea et al., 2012; Solovic et al., 2010). Moreover, the presence of M. tuberculosis-specific CD4+ T-cell immunity is used as a surrogate marker for a previous contact (Mack et al., 2009). 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 in immunocompromised patients

The general incidence of TB in immunocompromised patients may vary depending on the geographic location and may range from <1% to 15% in low- and high-prevalence countries, respectively. The relative risk of developing 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 (Sester et al., 2010).

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 (Sester et al., 2009). This not only facilitates reactivation but also contributes to a decreased sensitivity of immune-based testing (Bumbacea et al., 2012; Sester et al., 2009; Singh et al., 1998). 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 (Girndt et al., 2001). Finally, an increased incidence of active TB in patients receiving TNF-α antagonists is attributed to impaired T-cell function and failure to maintain the integrity of granulomata.

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 LTBI prior to immunosuppressive treatments can be a useful preventive measure.
Clinical presentation of active TB in immunocompromised patients

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 (Sester et al., 2012). In addition, treatment is frequently complicated due to complex drug interactions and altered pharmacokinetics (Bumbacea et al., 2012). The treatment of TB is also more difficult to manage in HIV-infected patients, as immune restoration induced by antiretroviral therapy may be responsible for a paradoxical worsening of TB manifestations, a phenomenon defined as immune reconstitution inflammatory syndrome (IRIS) (Sester et al., 2012).

Diagnostic and treatment of active TB

In active TB suspects, diagnosis should follow a clinical algorithm that includes acid-fast bacilli (AFB) staining from two sputum samples, and nucleic acid amplification (NAA) testing. In the case of negative results, bronchoalveolar lavage (BAL) should be obtained for microscopy, NAA and culture (Sester et al., 2012; Lange et al., 2010).

The first-choice treatment of immunocompromised patients with active TB does not differ from immunocompetent individuals, and should consist of a regimen including isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months (2HRZE), followed by a continuation phase with isoniazid and rifampicin for 4 months (4HR). Treatment of active TB may be complicated by interactions between antibacterial and immunosuppressive or antiretroviral drugs. Evidence in favour of extending the continuation phase is limited. Longer duration is recommended in patients with cavitation on their initial chest radiograph and/or positive cultures after 2 months of treatment, or in patients with involvement of the central nervous system (Sester et al., 2012).

Preventative approaches in immunocompromised patients

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 (Sester et al. 2012). Although risk assessment in immunocompromised patients is often hampered by a low sensitivity of commonly used immune-based tests, current guidelines recommend 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 (Sester et al., 2012; Bumbacea et al., 2012; Solovic et al., 2010; Singh et al., 1998). Until recently, LTBI

<table>
<thead>
<tr>
<th>Relative risk</th>
<th>Pathomechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>100–170</td>
<td>Low CD4+ T-cell counts</td>
</tr>
<tr>
<td>50–100</td>
<td>Low CD4+ T-cell counts</td>
</tr>
<tr>
<td>20–74</td>
<td>Decreased T-cell function and numbers</td>
</tr>
<tr>
<td>10–25</td>
<td>Co-stimulation deficiency, chronic inflammation</td>
</tr>
</tbody>
</table>

Table 1. Pathomechanisms and relative risk for TB in immunocompromised patients relative to persons without known risk factors (risk=1)
screening was exclusively carried out by the use of tuberculin skin testing (TST), where the cut-off of positivity is defined by the extent of immunodeficiency. At present, however, novel interferon-γ release assays (IGRAs) are more widely applied that are of higher specificity than TST. In addition, accumulating evidence suggests that IGRAs may be of higher sensitivity in immunocompromised patients (Sester et al., 2012).

Preventive chemotherapy should be given to patients with a positive immune-based test (TST ≥5 or 10 mm depending on the type of immunodeficiency, or IGRA), signs of TB on chest radiograph in patients with no or insufficient previous TB treatment, or recent close contact with a patient with active TB in severely immunocompromised patients.

Among immune-based assays, IGRA testing is preferred over TST because of operational advantages, including internal positive controls. When using IGRAs as a predictive measure for development of active disease, a recent meta-analysis suggests that in vitro tests are superior for predicting development of TB (Diel et al., 2011). Nevertheless, the actual risk of progression to active disease is still overestimated and may differ according to the local prevalence of TB (Rangaka et al., 2012). The considerably low predictive value is due to the fact that a positive immune response towards M. tuberculosis does not necessarily reflect a true infection with viable bacilli that bears a higher risk of disease progression (Barry et al., 2009). As decisions for chemoprophylaxis depend, to a great extent, on the results of immunodiagnostic testing, large studies are needed to determine more precisely the negative and positive predictive values of IGRAs in each specific population of immunocompromised patients and in regions of different TB prevalence.

Conclusions

TB in immunocompromised patients is more frequent than in the general population, and morbidity and mortality are high. This high mortality is primarily due to delayed diagnosis and increased incidence of disseminated disease. Risk assessment needs integrative approaches that should consider clinical findings, the extent of immunodeficiency and the overall prevalence of TB.

Further reading

Latent tuberculosis

Jean-Pierre Zellweger

Individuals who are in close contact with a patient with a transmissible form of 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 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 TB infection’ (LTBI).

LTBI and risk of TB

Individuals with latent TB have no signs or symptoms of active disease, and only immunological markers of a prior contact with mycobacteria. It is therefore impossible to know whether individuals with LTBI 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 years after infection, and 90% will never develop the disease. Some infected individuals have a higher risk of later reactivation than others (e.g. 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 infection, even in the absence of living mycobacteria.

Treatment of LTBI

As the persons in contact with a case of TB have a much higher risk of developing the disease in the future than the general population, particularly if they have a positive tuberculin reaction or a positive interferon-γ release assay (IGRA) test, the detection of LTBI 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

Key points

- The risk of 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 cost-effective 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 IGRA. The latter has the advantage of a greater specificity.
and the 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 a combination of isoniazid and rifampicin. Recently, the use of rifapentine and isoniazid once a week for 3 months has also been demonstrated to be very effective.

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 years), a first test 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 to the market, measuring in vitro 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–Guérin (BCG) 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 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 that is higher than the general population if they are infected. 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 current 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. Contacts of patients with multidrug-resistant TB have to be managed with special care.

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. The search for infection in HIV-positive contacts and prescription of preventive treatment is also recommended.

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 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 reaction). Prospective studies on the risk of reactivation among contacts with a positive immunological reaction will help to clarify these issues.

Further reading

Nontuberculous mycobacterial diseases

Claudio Piersimoni

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 anti-TB drugs is an important distinctive issue. The majority of the >140 NTM species recognised 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 by environmental exposure and pulmonary infection is likely to be via the aerosol route.

The epidemiology of NTM disease has been difficult to determine because reporting is not mandatory in most countries and differentiation between infection/colonisation and disease may be problematic. However, recent studies from North America and Europe have documented a steady increase of pulmonary disease over the past decade, reporting prevalence rates (range 1.08–8.6 cases per 100 000 persons) that may exceed those of TB.

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 50 cells·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-term, heavy smoking) and bronchiectasis. Thin-walled cavities with scarce parenchymal infiltrate and a marked pleural thickening are characteristic. Signs 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 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.

Hypersensitivity pneumonitis A syndrome indistinguishable from hypersensitivity pneumonitis 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 Mycobacterium kansasii.
- Immune reconstitution disease: this clinical syndrome has been described in HIV-infected patients with poor immune function soon after the initiation of antiretroviral therapy (ART). ART-induced restoration of the immune response may cause subclinical mycobacterial disease to manifest suddenly or be 'unmasked'.
- Transplantation including both solid-organ and haematopoietic stem cell transplants: these infections generally occur late in the post-transplantation period, presenting as cutaneous lesions of the extremities, tenosynovitis, arthritis or pulmonary disease. Pleuropulmonary disease is the predominant manifestation among lung transplant recipients and also represents a significant proportion of NTM infections after heart transplant. The most common species reported to cause pulmonary disease include M. kansasii, M. avium, Mycobacterium abscessus and Mycobacterium xenopi.

Table 1. American Thoracic Society criteria for diagnosis of pulmonary disease caused by NTM

<table>
<thead>
<tr>
<th>Clinical criteria (both required)</th>
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<tbody>
<tr>
<td>Pulmonary symptoms, cavitary or noncavitary lung disease</td>
</tr>
<tr>
<td>Appropriate exclusion of other causes for the disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Microbiological criteria (only one required)</th>
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</thead>
<tbody>
<tr>
<td>Positive culture results from at least two separate expectorated sputum samples</td>
</tr>
<tr>
<td>Positive culture results from at least one bronchial wash or lavage</td>
</tr>
<tr>
<td>A transbronchial or lung biopsy showing granulomata and/or AFB and positive culture for NTM</td>
</tr>
<tr>
<td>Biopsy showing granulomata and/or AFB and one or more sputa or bronchial washing that are culture-positive for NTM</td>
</tr>
</tbody>
</table>

AFB: acid-fast bacilli.
Treatment with tumour necrosis factor-α antagonists

CF

Laboratory diagnosis

Mycobacterial culture remains the cornerstone of 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 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 impaired 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 anti-TB...
drug, correlation between DST results and clinical outcome is poor.

Further reading

Laboratory diagnosis of mycobacterial infections

Claudio Piersimoni

Although the prevalence of TB in industrialised countries is low, one thing remains certain, TB, including multidrug-resistant (MDR) and extensively drug-resistant (XDR)-TB, is no longer restricted to developing regions of the globe. In addition, many species of nontuberculous mycobacteria (NTM) are now recognised as a cause of pulmonary disease in man with increasing frequency.

The rapid and accurate diagnosis of TB is of the utmost importance; it involves the isolation and identification of the aetiiological agent, *Mycobacterium tuberculosis* complex (MTC), while design of an appropriate therapeutic regimen relies on the results of anti-TB drug susceptibility testing (DST).

Laboratory services are an essential component of effective TB control and elimination. Unfortunately, they are at the end of decision tree for the patient’s health improvement; thus, they are unable to prevent delays in diagnosis related to both the patient and the physician.

Seven tests performed in clinical microbiological laboratories are recommended for TB control and elimination:

- microscopy for acid-fast bacilli (AFB)
- nucleic acid amplification (NAA)
- AFB detection by culture
- identification of cultured mycobacteria
- molecular detection of drug resistance
- DST for first-line drugs
- DST for second-line drugs

These tests should not only be available to every clinician involved in TB diagnosis and management but also be available in a timely manner according to well-defined turnaround times.

Specimen procurement, transport and processing

Success in detecting and isolating mycobacteria strongly depends on the following principles.

1. Select patients soundly suspected of having an active disease.
2. Submit appropriate specimens, collected from the body sites most likely to yield mycobacteria. Inappropriate or redundant specimens must be discouraged.
3. Ensure that adequate volumes of samples are properly collected, stored and delivered to the laboratory.

Most clinical specimens contain an abundance of nonmycobacterial organisms.

### Key points

- Think of TB; if you do not, the laboratory cannot help you.
- Do not use microbiological tests as screening tests.
- Remember that the best way to improve testing sensitivity is to submit high-quality specimens.
- Molecular tests cannot replace conventional culture.
- If your laboratory does not meet current quality standards (testing and turnaround times), refer your specimens to a larger laboratory.
Unless an attempt is made to get rid of such contaminants, they will easily suppress the slow growth of mycobacteria. In addition, it is also necessary to liquefy respiratory samples so that mycobacteria can be easily harvested after centrifugation. This key procedure is referred to as 'decontamination', and is usually performed using a mixture of 1% N-acetyl-L-cysteine and 2% sodium hydroxide. As a rule of thumb, ideal decontamination should be mild enough to kill contaminants without damaging mycobacteria.

**Microscopy**

The first step in the laboratory diagnosis of TB is microscopic examination of sputum smears stained by an acid-fast procedure. Microscopy is rapid, easy and inexpensive, providing the physician with a presumptive diagnosis of TB and a simultaneous assessment of the patient's infectiousness.

Since the sensitivity of microscopy is relatively low, requiring $10^3$–$10^4$ bacilli per mL of specimen to allow detection, smears should always be prepared from concentrated specimens. Centrifugation is a key step, and must be performed with sufficient g-force in appropriately refrigerated and enclosed biosafe centrifuges.

The acid-fast staining procedure depends on the ability of mycobacteria to retain dye when treated with acid or acid–alcohol solution. Two types of acid-fast stains are commonly used:

- the carbol fuchsin stain, which includes the Ziehl–Neelsen and Kinyoun methods
- a fluorochrome procedure using auramine O or auramine–rhodamine dyes

The latter provides a 10% more sensitive performance and also permits a faster screening of smears.

AFB seen on smear may represent either MTC or NTM. However, because of the infectious potential of MTC, sputum smear microscopy should be performed within one working day of specimen receipt and positive results should be reported immediately by telephone, fax or other electronic means, as soon as they are available.

**Molecular detection of MTC**

With the purpose of obtaining faster results and a more accurate diagnosis of TB than those achievable with microscopy and liquid culture, several molecular methods were introduced and have been evaluated worldwide.

These technologies allow for the amplification of specific target sequences that can be detected through the use of a complementary nucleic acid probe. Both RNA and DNA amplification systems have been developed.

Although many in-house amplification methods have been described in published studies, most amplification tests currently used in clinical laboratories are supplied commercially. While these assays have demonstrated an excellent specificity, their sensitivity cannot equal that of culture-based methods, especially for smear-negative samples. In a recent meta-analysis, pooled sensitivities and specificities of 85% and 97%, respectively, were reported.

NAA methods can be applied to decontaminated respiratory specimens within hours, producing a positive result with as few as $10^2$ bacilli per mL of specimen. They should be performed within 48 h of specimen receipt. NAA tests are applied to smear-positive respiratory samples to provide rapid confirmation that the infecting mycobacteria belong to the MTC. In addition, it is recommended that NAA tests are used on the first sputum or other respiratory sample of all smear-negative TB suspects.

Since the clinical utility of NAA tests is for ruling in active TB, it is of utmost importance that they are employed on the basis of a sound clinical suspicion. Routine implementation of NAA testing without consideration of clinical data lacks cost-effectiveness and may be misleading.
Culture

All clinical specimens suspected of containing mycobacteria should be inoculated onto culture media for the following reasons.

- Culture is the most sensitive method, being able to detect as few as 10 mycobacteria per mL of specimen
- Growth of the organisms is necessary for proper species identification
- DST requires culture of the organism
- Genotyping of the cultured strain may be useful to study clusters of TB cases

Three different types of culture media are currently available: egg-based (Löwstein–Jensen), agar-based (Middlebrook 7H10 or 7H11 medium) and liquid (Middlebrook 7H9 and other 7H9-based commercial broths) whose selectivity may be greatly improved by adding antibiotics. A combination of liquid and solid culture gives the most rapid and optimal rates of mycobacterial recovery from clinical specimens.

Among liquid media, automated culture systems have been developed that are continuously monitored and also able to perform DST. Since none of the above liquid systems can distinguish between a pure and mixed mycobacterial culture, parallel culture on solid media will provide confirmation of a single colonial morphology. For these reasons, liquid culture systems should be available in all laboratories willing to perform mycobacteriology.

Identification

The genus *Mycobacterium* consists of >140 different species, all of which appear similar on acid-fast staining. More than two-thirds of them, both saprophytes and (potential) pathogens, may be recovered from human sources.

Causative agents of TB in humans (*M. tuberculosis*, *Mycobacterium bovis*, *M. bovis* bacille Calmette–Guérin (BCG), *Mycobacterium africanum*, *Mycobacterium caprae*, *Mycobacterium microti*, *Mycobacterium pinnipedii* and *Mycobacterium canettii*) are referred to as MTC and most clinical laboratories identify these organisms only to the level of the complex. This practice is supported by two rapid identification procedures that, based on distinctive molecular and antigenic characteristics of the MTC, have gained widespread use:

- nucleic acid hybridisation
- immunochromatographic assay

It is recommended that laboratories culture and identify MTC within 21 days of receiving the patient’s specimen (table 1). This goal can be obtained only by combining liquid culture with the above rapid identification methods.

Drug susceptibility testing

DST should be performed on the initial isolate from all new TB cases. In addition, it should be repeated if the patient continues to be culture-positive after 2–3 months of treatment or exhibits positive culture after a period of negative cultures.

The source for DST may be either a smear-positive specimen (direct method) or, most often, growth is first isolated in pure culture from clinical specimens and then inoculated into a drug-containing medium (indirect method). Growth of mycobacteria in the presence of the drug(s) is then compared with a drug-free control.

Among different DST methods, the proportion method is the most widely used. It allows determining the proportion of MTC organisms that are resistant to a given drug at a single (critical) concentration. The susceptibility proportion was set at 1%, because higher proportions of drug-resistant bacilli were shown to be associated with treatment failure. The critical concentration of a drug is the level of drug that inhibits the growth of most organisms within the population of a wild-type strain without affecting the growth of strains recovered from clinically resistant patients (table 2).

Several studies have established that drug resistance in MTC isolates does not rely upon a ‘on/off’ mechanism, but, on the contrary, different mutations may lead to different levels of resistance. This means that
mutation(s) causing low-level resistance do not necessarily imply clinical resistance. Unfortunately, these data on different levels of resistance are not available when single critical concentrations are used. Moreover, the resistance level determined in vitro bears little relationship to the drug concentrations achievable in vivo.

Results of first-line drugs assay (isoniazid, rifampicin, ethambutol and pyrazinamide) should be reported within 4 weeks from specimen receipt. Although agar proportion is currently the reference method, two commercially available automated systems (BACTEC MGIT 960 (BD, Franklin Lakes, NJ, USA) and ESP culture system (Thermo Scientific, East Grinstead, UK)) have been cleared for susceptibility testing of first-line drugs. The use of these liquid systems has not yet been approved for susceptibility testing of second-line drugs (amikacin, capreomycin, ethionamide, kanamycin, moxifloxacin, paraaminosalicylic acid, rifabutin, streptomycin and linezolid), which still relies on the agar proportion method.

Compared to other laboratory tests, accuracy is much more important than speed in the case of drug susceptibility. Thus, results should come from a small number of well-equipped, experienced laboratories enrolled in a national and/or supranational DST quality control scheme.

During the past 10 years, triggered by the increasing prevalence of MDR- and XDR-TB, renewed efforts were spent to develop new drugs for the chemotherapy of TB. Several classes of drugs including diarylquinoline (bedaquiline), nitroimidazole (PA-824 and delamanid), and oxazolidine compounds have shown promise for the treatment of both fully susceptible as well as drug-resistant TB. These drugs have unique, new action mechanisms, and no cross-resistance between them and the existing TB drugs has been reported. To date, no information is available on DST for these new drugs.

**Molecular detection of resistance**

Although detection of drug resistance in MTC has traditionally been accomplished by culture-based assays, the emergence of MDR- and XDR-TB demands improved and faster detection methods. In this context, several molecular approaches have been developed aimed at detecting gene mutations known to be associated with phenotypic resistance to a particular drug.

As DNA sequencing (the reference method to look for specific mutations) would be almost impossible for most diagnostic laboratories, simpler procedures such as the line probe assay (LiPA) have recently been introduced. It relies on the reverse hybridisation of oligonucleotides on plastic strips to which specific probes have been immobilised. Amplified target sequences from the strain under evaluation are bound to probes and hybridisation is revealed by the development of a coloured line on the strip.
There are currently three commercially available LiPAs for the rapid detection of drug resistance in MTC: the INNO-LiPA Rif TB (Innogenetics, Ghent, Belgium) for detecting resistance to rifampicin; the GenoType MTBDRplus (Hain Lifesciences, Nehren, Germany) for the simultaneous detection of resistance to rifampin and isoniazid; and the newly released GenoType MTBDRsl (Hain Lifesciences), which detects the most frequent mutations associated with resistance to fluoroquinolones, aminoglycosides and ethambutol. These tests are validated for use in cultured strains as well as in smear-positive respiratory samples.

Real-time PCR technology has also been proposed for the rapid detection of drug resistance in MTC. Different assays have been developed, which include the XpertMTB/RIF (GeneXpert system; Cepheid, Maurens-Scopont, France), an automated molecular test for simultaneous detection of MTC and rifampicin resistance. This cartridge-based NAA assay employs a hemi-nested real-time PCR and requires just a single manual step with minimal sample manipulation. The remaining analysis is performed by the GeneXpert instrument, relatively rapidly (~2 h). Clinical validation trials performed in many different settings showed a high diagnostic accuracy for rapid diagnosis of both smear-positive and -negative pulmonary TB. For diagnosis of rifampicin resistance, false-positive results were observed in settings characterised by a low prevalence of resistance. XpertMTB/RIF may have the potential to complement the current reference standard of TB diagnostics, and increase its overall sensitivity and speed. Further studies are required to determine the optimal level of the healthcare system where this system can be used cost-effectively.

**Genotyping of MTC isolates**

Genotyping or DNA fingerprinting of MTC refers to procedures developed to identify isolates that are identical in specific parts of the genome. The most extensively used method in the last two decades has been restriction fragment length polymorphism (RFLP) analysis of the distribution of the insertion sequence IS6110. The more recently developed spoligotyping and 24-locus variable number of tandem repeats (VNTR) techniques are similarly based on genetic polymorphism of additional mycobacterial repetitive sequences. The various DNA fingerprinting methods serve different purposes and have variable characteristics that enable their use in specific applications. They currently support
routine contact tracing as well as investigations on person-to-person transmission, early disease outbreak identification and laboratory cross-contamination, and permit determination of whether new cases of TB are due to re-infection or re-activation. In addition, the recognition of different genotype families has facilitated studies on the population structure of MTC and its dynamic. Due to the fact that VNTR typing combines a more user-friendly technique with a significantly shorter turnaround time than RFLP typing, it is now considered the gold standard.

Organisation of laboratory services

Any TB laboratory-based diagnostic procedure should be performed by appropriately trained staff working to standardised operating procedures in appropriately equipped and safe laboratories, to well-defined national and international proficiency and quality standards. In this context, mycobacteriology laboratory consolidation at the regional level is strongly recommended.

Further reading

Chronic rhinitis

Arnaud Bourdin and Pascal Chanez

Rhinitis is one of the most common 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 suffers from rhinitis, which is often linked to IgE 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 from school or 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 lacks 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 COPD, 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.

Key points

- The prevalence of rhinitis is increasing in most countries.
- Asthma is present in 20–50% of allergic rhinitis patients, while up to 80% of asthma patients have rhinitis.
- Treatment is anti-inflammatory and directed according to whether rhinitis is allergic or nonallergic.
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 (regulated on activation, normal T-cell expressed and secreted), IL-4, IL-13 and granulocyte–macrophage colony-stimulating factor. Most of these molecules trigger a local eosinophilic inflammatory 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 pro-inflammatory mediators such as histamine and sulfidoleukotrienes. 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 persistent 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 Allergic Rhinitis and Its Impact on Asthma (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 airway diseases need to be clarified. New treatments and management strategies are required, especially in the most chronic severe forms.

Further reading

- Allergic Rhinitis and its Impact on Asthma. www.whiar.org
Asthma is a chronic inflammatory disease of the airways characterised clinically by recurrent respiratory symptoms of dyspnoea, wheezing, chest tightness and/or cough, associated with reversible airflow limitation. Other characteristics of asthma are an exaggerated responsiveness of the airways to various stimuli, and, in most cases, a specific type of chronic inflammation of the airways characterised by an increased number of CD4+ T-helper (Th) type 2 lymphocytes, eosinophils and metachromatic cells in the airway mucosa, increased thickness of the reticular layer of the epithelial basement membrane, and increased volume of airway smooth muscle (fig. 1).

Familial predisposition, atopy, and exposure to allergens and occupational 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 different 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 an appropriate clinical history, together with the demonstration of variable and/or reversible airflow limitation, using lung function tests, particularly peak expiratory flow (PEF) or spirometry. Allergy tests are also often performed during the initial 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 IgE-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

Patients with asthma seek medical attention because of respiratory symptoms. A typical feature of asthma symptoms is their variability. One or more of the symptoms

- wheezing
- chest tightness
- episodic shortness of breath
- cough

Key points

- Asthma is diagnosed based on clinical history and lung function testing. Allergy testing may also have a role.
- The differential diagnosis is extensive. In particular, COPD may be difficult to distinguish from asthma.
- The goal of pharmacological asthma treatment is to achieve and maintain control of symptoms and prevention of exacerbations.
- Asthma is a chronic, lifelong disease and must therefore be managed in partnership with the patient.
are reported by >90% of patients with asthma. However, the presence of these symptoms is not diagnostic because similar symptoms can be present with other respiratory or even cardiac diseases, or 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 cause of symptoms for most asthma patients, particularly in children, and for some it is the only cause. Exercise-induced bronchoconstriction usually develops not during exercise but 5–10 min afterward and resolves spontaneously within 30–45 min. Prompt relief of symptoms after the use of an inhaled β₂-agonist or their 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, such as dusty environments, forced air heating systems or exposure to allergens (e.g. pets, house dust mites or cockroaches) to which the patient is sensitised, workplace conditions, environmental tobacco smoke or even the general environment (e.g. diesel fumes in traffic).

Since respiratory symptoms of asthma are nonspecific, the differential diagnosis is quite extensive, and 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 has been negative.

When respiratory symptoms suggest asthma, the sine qua non condition for the objective diagnosis of asthma is the presence of reversible airflow obstruction. In patients who have persistent airway obstruction, reversibility may be demonstrated as response to treatment (e.g. 200–400 μg albuterol or after a period of regular treatment). In subject presenting without persistent airway obstruction, reversibility may be demonstrated either by measuring airway responsiveness or PEF variability.

Physical examination

In mild asthma, physical examination is usually normal under stable conditions, but becomes characteristically abnormal during
asthma attacks. 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 on percussion or the use of accessory muscles of respiration). Some patients, particularly children, may present with a predominant nonproductive cough. 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 obstruction. 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 patients with asthma. Spirometric measurements – FEV1 and slow vital capacity (VC) or 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 asthma. It should be repeated to monitor the disease and when there is a need for reassessment, such as during exacerbations.

Poorly or nonreversible airflow limitation is usually defined by the absolute reduction of the post-bronchodilator FEV1/FVC ratio to <0.7. However, because this parameter varies with ageing, it should be confirmed by post-bronchodilator FEV1/VC values below the lower limit of normal, particularly in younger subjects. Measurements of residual volume and TLC may be useful in assessing 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 or for assessment of the 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 later).

**Peak expiratory flow** An important tool for the diagnosis and subsequent treatment of asthma is the PEF meter. If spirometry does not reveal airflow limitation, then home monitoring of PEF for 2–4 weeks may help to detect an increased variability of airway calibre, and assist in making the diagnosis of asthma. 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

$$\text{Diurnal variability} = \frac{\text{PEF}_{\text{max}} - \text{PEF}_{\text{min}} \times 100}{\text{PEF}_{\text{max}} + \text{PEF}_{\text{min}}/2}$$

where PEF_{max} and PEF_{min} are maximal and minimal PEF, respectively. A diurnal variability of PEF >20% is diagnostic of asthma and the magnitude of the variability

<table>
<thead>
<tr>
<th>Localised pathology</th>
<th>Inhaled foreign body</th>
<th>Endobronchial tumour</th>
<th>Vocal cord dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse airway pathology</td>
<td>COPD</td>
<td>Eosinophilic bronchitis</td>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>Other pathologies</td>
<td>Gastro-oesophageal reflux</td>
<td>Left ventricular failure</td>
<td>Pulmonary embolism</td>
</tr>
</tbody>
</table>
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 of 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** Clinical and/or functional reversibility on repeated testing is required for the diagnosis of asthma. Thus, even a single reversibility test (defined as \[>12\% \text{ reversibility and/or } >200 \text{ mL in FEV}_1 \text{ after bronchodilator}\]) can establish the diagnosis. However, reversibility is often not present at the time of examination, particularly in patients on treatment, and thus the absence of reversibility does not exclude the diagnosis. 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 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 current 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 the presence of irreversible 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 respiratory failure. This test should be performed in all patients with clinical signs of acute or chronic respiratory and/or heart failure, patients with an acute asthma exacerbation and PEF \[50\% \text{ predicted}\], patients who do not respond to treatment, and those with a \[S_aO_2 \leq 92\%\].

**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

---

**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><strong>Onset</strong></td>
<td>Mainly in childhood</td>
<td>In mid- to late adult life</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>Often nonsmokers</td>
<td>Almost invariably smokers</td>
</tr>
<tr>
<td><strong>Chronic cough and sputum</strong></td>
<td>Often absent</td>
<td>Frequent (chronic bronchitis)</td>
</tr>
<tr>
<td><strong>Dyspnoea on effort</strong></td>
<td>Variable and reversible to treatment</td>
<td>Constant, poorly reversible and progressive</td>
</tr>
<tr>
<td><strong>Nocturnal symptoms</strong></td>
<td>Relatively common</td>
<td>Relatively uncommon</td>
</tr>
<tr>
<td><strong>Airflow limitation</strong></td>
<td>Increased diurnal variability</td>
<td>Normal diurnal variability</td>
</tr>
<tr>
<td><strong>Response to bronchodilator</strong></td>
<td>Good</td>
<td>Poor</td>
</tr>
<tr>
<td><strong>Airway hyperresponsiveness</strong></td>
<td>In most patients, with or without airflow limitation</td>
<td>In most patients, with airflow limitation</td>
</tr>
</tbody>
</table>
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 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 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 these 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 can be fully established on the basis of clinical history and lung function tests, additional tests are sometimes 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. In contrast, noninvasive markers of airway inflammation have been increasingly used in research protocols, particularly to differentiate asthma from COPD and measure response to treatment. These noninvasive measurements include induced sputum and exhaled nitric oxide fraction (FeNO) measurement. Induced sputum is not helpful in the diagnosis of asthma but can be very useful in the management of severe asthma. In particular, induced sputum helps identify the persistence of airway eosinophilia or airway neutrophilia in patients with difficult-to-treat asthma, which can be useful in deciding appropriate doses of inhaled corticosteroids and in reducing the risks of severe asthma exacerbations. FeNO is increased in atopic asthma but less so in nonatopic asthma. Again, it is not useful in diagnosis but can be helpful in

<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, residual volume, TLC</td>
<td>Usually normal or, if increased, reversible</td>
<td>Usually irreversibly increased</td>
</tr>
<tr>
<td>Diffusion capacity</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Airway hyperresponsiveness</td>
<td>Increased</td>
<td>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</td>
</tr>
<tr>
<td>Sputum</td>
<td>Eosinophilia</td>
<td>Neutrophilia</td>
</tr>
<tr>
<td>FeNO</td>
<td>Increased</td>
<td>Usually normal</td>
</tr>
</tbody>
</table>
monitoring adherence to inhaled corticosteroids, as it is effectively reduced by inhaled corticosteroids but not by bronchodilators.

Differentiating between asthma and COPD

Both asthma and COPD are characterised by chronic airway inflammation but with very different characteristics (fig. 1). In most patients, the clinical presentation and the history provide the strongest diagnostic criteria to distinguish asthma from COPD (table 2). Results of pulmonary function tests, particularly spirometric measurements that show a nearly complete reversibility of airflow limitation, will confirm a diagnosis of asthma, and measurements 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 when the patient has airflow limitation that is poorly reversible after treatment. In these cases, symptoms, lung function, airway responsiveness, imaging and even pathological findings may overlap, and thus may not provide solid information to establish a diagnosis. Because an accurate diagnosis is needed 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 diffusion capacity, analysis of sputum and FeNO, and imaging of the chest may help to demonstrate whether asthma or COPD is the predominant cause of airflow limitation in these patients (table 3).

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><strong>Daytime symptoms</strong></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*+5</td>
</tr>
<tr>
<td>Limitation 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)*8,9</td>
<td>Normal</td>
<td>&lt;80% predicted or personal best (if known)</td>
<td></td>
</tr>
</tbody>
</table>

Assessment of future risk (risk of exacerbations, instability, rapid decline in lung function, side-effects)

Features that are associated with increased risk of adverse effects in the future include: poor clinical control, frequent exacerbations in the past year*, admission to critical care for asthma, low FEV1, exposure to cigarette smoke and high-dose medications

*§: not reliable for children aged <5 years; §*: without administration of a bronchodilator; *+: any exacerbation should prompt a review of maintenance treatment to ensure it is adequate; §*: by definition, an exacerbation in any week makes that an uncontrolled week. Reproduced and modified from Global Initiative for Asthma (2012) with permission from the publisher.
Comorbidities of asthma

The coexistence of chronic rhinitis, nasal polyposis and sinusitis may contribute to the severity of asthma. There is evidence to show that adequate treatment of these upper airway diseases is beneficial to asthma by mechanisms that are not clearly understood. The ‘one airway’ concept 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 likely due to smoking, which is as common in asthmatics as in the general population. Smoking modifies the airway pathology of asthmatics to a COPD-like pattern and reduces the response to treatment. Comorbidities may become important in severe asthmatics, whereas they play a much less important role overall in the clinical manifestations of mild-to-moderate asthma.

Management

Considering its chronic nature and life-long duration, asthma can be effectively managed only by developing a partnership between the patient and their doctor or health professional, who may provide the tools for guided self-management, and possibly a

![Diagram of asthma management approach](image)

**Figure 2.** Asthma management approach based on control for children aged >5 years, adolescents and adults. Alternative reliever treatments include inhaled anticholinergics, short-acting oral β2-agonists, some long-acting β2-agonists and theophylline. Regular dosing with short- and long-acting β2-agonists is not advised unless accompanied by an inhaled glucocorticosteroid. ICS: inhaled corticosteroids. #: recommended treatment (shaded boxes) based on group mean data; individual patient needs, preferences and circumstances (including costs) should be considered. +: inhaled glucocorticosteroids. -: receptor antagonist or synthesis inhibitors. Reproduced and modified from Global Initiative for Asthma (2012) with permission from the publisher.
written plan including self-monitoring, and periodically review of treatment and level of asthma control. Education plays a major role in this partnership.

**Long-term pharmacological treatment** The aim of pharmacological treatment of asthma is to achieve and maintain control of day-to-day symptoms, as well as preventing future severe asthma exacerbations (table 4), while using the safest treatment algorithm. While the initial treatment should be started according to the degree of asthma control at the first visit, subsequently treatment should be adjusted according to the level of asthma control achieved (fig. 2). Usually, regular treatment is lowered only after a significant period of acceptable asthma control (e.g. ≥ 3 months). This means that monitoring of asthma is essential to maintain asthma control and establish the minimal treatment requirements. Step-up and -down of treatment are 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 this approach is the most effective way to treat asthma and has the fewest side-effects. Controller medications (inhaled corticosteroids alone or in combination with long-acting β₂-agonists) are taken daily on a long-term basis 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.

Only in patients not controlled by optimal doses of inhaled corticosteroids combined with long-acting β₂-agonists should other secondary agents may be considered. These include anti-leukotrienes, theophylline, systemic corticosteroids or anti-IgE monoclonal antibodies in very specific cases.

Reliever medications (predominantly short-acting β₂-agonists) are medications used on an as-needed basis that act quickly to reverse bronchoconstriction and relieve asthma symptoms. Ideally, if patients are adequately controlled, they should rarely need rescue medications. The use of a combination of an inhaled short-acting β₂-agonist and a corticosteroid both as controller and reliever is effective in maintaining high levels of asthma control.

Smoking asthmatics are resistant to anti-asthma medications and should be primarily treated for smoking addiction. Asthmatic smokers may develop features of COPD.

Specific immunotherapy in asthma is limited as:

1) it requires the identification of a single clinically relevant allergen
2) it can be used safely only in mild asthmatics who are usually well controlled by environmental interventions or pharmacotherapy
3) it may be associated with adverse events

**Treatment of exacerbations**

Shortness of breath, cough, wheezing and/or chest tightness may develop or worsen in a subject with asthma even when they are under regular treatment. Milder exacerbations are usually managed by the patients with an increased as-needed use of short-acting β₂-agonists alone or in combination 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, corticosteroids, with oxygen supplementation in very severe cases (fig. 3). Severe exacerbations require medical attention and, in some instances, hospital admission.

**Special considerations**

Special considerations are required for patients with specific comorbidities, such as rhino/sinusitis and/or nasal polyps, aspirin-induced asthma (particularly if associated
Criteria for severe episode:
• History of risk factors for near fatal asthma
• PEF <60% pred/personal best
• Physical exam: severe symptoms at rest, chest retraction
• No improvement after initial treatment
• Sedation is contraindicated in the treatment of an exacerbation

Treatment:
• Oxygen
• Inhaled \( \beta_2 \)-agonist and inhaled anticholinergic
• Systemic glucocorticosteroids
• Intravenous magnesium

Reassess after 1–2 h
• Physical examination, PEF, \( \text{SaO}_2 \) and other tests as needed

Good response within 1–2 h:
• Response sustained 60 min after last treatment
• Physical exam normal: No distress
• PEF >70%
• \( \text{SaO}_2 >90\% \) (95% in children)

Incomplete response within 1–2 h:
• Risk factors for near fatal asthma
• Physical exam: mild to moderate signs
• PEF <60%
• \( \text{SaO}_2 \) not improving

Admit to acute care setting
• Oxygen
• Inhaled \( \beta_2 \)-agonist ± anticholinergic
• Systemic glucocorticosteroid
• Intravenous magnesium
• Monitor PEF, \( \text{SaO}_2 \), pulse

Poor response within 1–2 h:
• Risk factors for near fatal asthma
• Physical exam: symptoms severe, drowsiness, confusion
• PEF <30%
• \( PaCO_2 >45 \text{ mmHg} \)
• \( PaO_2 <60 \text{ mmHg} \)

Admit to intensive care
• Oxygen
• Inhaled \( \beta_2 \)-agonist + anticholinergic
• Intravenous glucocorticosteroids
• Consider intravenous \( \beta_2 \)-agonist
• Consider intravenous theophylline
• Possible intubation and mechanical ventilation

Improved: criteria for discharge home
• PEF >60% pred/personal best
• Sustained on oral/inhaled medication

Home treatment:
• Continue inhaled \( \beta_2 \)-agonist
• Consider, in most cases, oral glucocorticosteroids
• Consider adding a combination inhaler
• Patient education: Take medicine correctly
• Review action plan
• Close medical follow-up

Poor response (see above):
• Admit to intensive care

Incomplete response in 6–12 h (see above)
• Consider admission to intensive care if no improvement within 6–12 h

Improved (see opposite)

Figure 3. Management of asthma exacerbations in the acute care setting. Reproduced and modified from Global Initiative for Asthma (2012) with permission from the publisher.
with episodes of anaphylaxis), occupational asthma and obesity.

In addition, patients with asthma may require specific competent medical attention in case of smoking addiction, pregnancy, surgery, infections (e.g. influenza epidemics) and, more importantly, if asthma is severe.

Further reading

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 with them, 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 hysteric croup, Munchausen’s stridor, pseudo-asthma, factitious asthma, upper airway dysfunction, functional upper airway obstruction, irritable larynx syndrome, emotional laryngeal wheeze, laryngeal hyperresponsiveness and paradoxical vocal cord movement (PVCM). Indeed, there is disagreement over 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 an all-encompassing VCD definition of all cases demonstrating PVCM.

Epidemiology

While the true prevalence of VCD in the general population is unknown, it is more common in females, athletes, army recruits, asthmatics and patients with chronic cough (table 1). Using dynamic CT imaging, 50% of 46 difficult asthmatics demonstrated PVCM, which was severe in nine patients (Low et al., 2011).

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 a 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 (Cukier-Blaj et al., 2008). 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

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.
central brain activity have been postulated to underlie development of VCD (Ayers et al., 2002).

Clinical presentation

VCD presentation varies from cases with predominant throat symptoms usually referred to ENT specialists, to asthma presenting to the 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, the 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 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 extrathoracic airflow obstruction. The maximum inspiratory/expiratory flow ratio at 50% FVC (MIF50%/MEF50%) can be reduced due to predominant inspiratory flow limitation. An abnormally high forced inspiratory flow at 25%/75% FVC ratio (FIF25%/FIF75%) would indicate an initially normal flow followed by rapid flow decline, reflecting PVCM during inspiration. However, various studies reported the insensitivity of spirometry for diagnosing VCD (Ruppel, 2009). Sensitivity of spirometry may be enhanced by histamine or other forms of airway challenge.

Impulse oscillometry (IOS) can discriminate between central and peripheral airway obstruction, and may be more sensitive than spirometry. Airway fluoroscopy and colour Doppler ultrasound imaging of vocal cord movement are other noninvasive tools that have not been standardised against laryngoscopy.

Integrated CT software programs have been used to obtain continuous dynamic axial, sagittal and coronal multiplanar images of the larynx, measuring airway diameters at the level of the vocal cords and the first tracheal ring. The ratio of vocal cord

<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>

The reported mean age at VCD diagnosis is 14.5 years in children and 33 years in adults. *: presenting to emergency department.
diameter to tracheal diameter was used as a marker of PVCM (Low et al., 2011).

Laryngoscopy

VCD diagnosis is established by laryngoscopic demonstration of PVCM while the patient experiences spontaneous or induced symptoms. Bicycle ergometry combined with fiberoptic videolaryngoscopy has been developed as a diagnostic test for VCD in patients with exercise-induced dyspnoea. One study reported that if the symptom of dyspnoea appeared, the most frequent diagnosis was exercise-induced VCD (Tervonen et al., 2009).

Agreed laryngoscopy standards have not been developed, with some advocating pre-procedure sedation and analgesia, while others recommend avoiding these measures. Following a short period of quiet breathing, specific manoeuvres such as repeating low- and high-pitched sounds, forceful inspiration and expiration are conducted to induce an attack (Wood et al., 1996). 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 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 laryngopharyngeal reflux (Belafsky et al., 2002). VCD should be distinguished from vocal cord immobility due to paralysis, amyotrophic lateral sclerosis, cricoarytenoid joint dysfunction and Reinke’s oedema. Laryngeal electromyography (EMG) 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 and thorax, and bronchoscopy.

Investigations directed at 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 diseases symptoms or laryngeal refluxive changes on laryngoscopy should prompt further testing (e.g. oesophageal manometry and pH studies). Underlying psychological issues should be assessed.

Differential diagnosis

- Laryngeal oedema (angio-oedema)
- Allergic laryngitis
- Subglottic stenosis
- Laryngomalacia or tracheomalacia
- Vocal cord paralysis
- Systemic disease affecting the larynx/ upper airways (e.g. relapsing chondritis or granulomatosis with polyangiitis (Wegener’s))

Treatment

Diagnosis and treatment are best conducted in a multidisciplinary team setting comprised of a respiratory physician, speech therapist, ENT specialist and psychologist. The diagnosis is explained to the patient, preferably with the support of imaging or illustration. The patient’s good understanding of VCD is prerequisite to effective treatment. A management plan should be formulated that bears in mind

Figure 1. Laryngoscopy demonstrating inspiratory vocal cord adduction and posterior glottic chink.
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 the 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 have 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 the vocal cords is recommended.

Long-term treatment

Speech therapy forms the mainstay of VCD treatment, with the primary aim of teaching patients to relax the upper airways and control the 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 (Wood et al., 1996). 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 the speech therapist extends to making the diagnosis, identification and treatment of triggers, and relaxation therapy.

Psychotherapy should form an integral part of VCD management, given VCD’s link to adverse psychology. Psychotherapy can include relaxation therapy, management of stress and anxiety, and development of coping strategies.

Other, unproven therapies for VCD include inhaled anticholinergic drugs to abort exercise-induced VCD attacks (O’Connell et al., 2006), enhancing inspiratory resistance by a face mask device, CPAP and vocal cord injection of 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-year time frame, with symptoms disappearing within 6 months in many who had a good response to speech therapy. However, intractable forms of disease did not seem to improve over a 10-year observation period (Doshi et al., 2006).

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.

Further reading

Bronchitis

Gernot Rohde

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% of cases 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 between two to six times per year, and adults two to three times per year. The prevalence in the UK is 44 cases per 1000 adults per year. 82% of episodes occur during the cold months.

Aetiology/risk factors

Respiratory infections are the main trigger of acute bronchitis. However, pathogens can only be detected in 55% of cases. Respiratory viruses are the most frequent pathogens. Rhinovirus, adenovirus, echovirus, influenza virus, parainfluenza virus, enterovirus, coronavirus, Coxsackie virus, human metapneumovirus and respiratory syncytial virus (RSV) represent the usual spectrum. Parainfluenza viruses, enteroviruses and rhinoviruses mainly infect in the autumn, while the influenza viruses, RSV and coronaviruses mainly infect in the winter and early spring. Typical bacteria are *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. Atypical bacteria, e.g. *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*, and *Bordetella pertussis* also play a role.

Specific risk factors have not been 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 the 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 adults 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 patients developed asthma or chronic bronchitis symptoms.

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 two successive years.
Diagnosis

Diagnosis is purely clinical. Cough, sputum production and 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, e.g., 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 a chronic cough. Laboratory investigations are not necessary. In more severe cases, sputum culture can be considered to guide antibiotic therapy.

Therapy

Therapeutic goals are the reduction of symptoms and the 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.

Further reading

Gastro-oesophageal reflux

Lieven Dupont

Gastro-oesophageal reflux (GOR), defined as the retrograde flow of gastric contents into the oesophagus, is a normal physiological phenomenon that occurs to some extent in most people. Brief exposure of the oesophagus to gastric contents does not necessarily result in injury or disease. When reflux is prolonged and/or when there is a breakdown of the defence mechanisms that act to protect mucosal integrity, symptoms and/or lesions in the oesophagus occur. This is then referred to as gastro-oesophageal reflux disease (GORD). GORD is an increasingly prevalent condition that affects >20% of the Western population. Although GORD often causes typical symptoms such as heartburn or regurgitation, 32% of the patients with reflux disease have extraoesophageal symptoms, including respiratory and ENT symptoms and disorders. 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 extraoesophageal GORD symptoms has not been equally well established.

Mechanisms of increased reflux

The oesophagogastric junction (OGJ) is the first line of defence against reflux. It comprises two important components: the lower oesophageal sphincter (LOS) and the crural diaphragm that regulate the exchange of contents between the oesophagus and the stomach. Transient lower oesophageal sphincter relaxations (TLOSRs), defined as relaxations of the LOS not triggered by swallowing, account for the majority of reflux episodes, both in healthy subjects and in GORD patients. Not all TLOSRs are associated with reflux. In healthy subjects, almost half of the TLOSRs are followed by a reflux episode, which is significantly higher in GORD patients, where ~70% of the TLOSRs lead to reflux. A hiatal hernia, which is the separation of the LOS from the crural diaphragm, further diminishes the capacity of the OGJ to prevent reflux. GORD patients have a higher gastro-oesophageal pressure

Key points

- GORD is a common disorder caused by the reflux of gastric contents into the oesophagus because of impaired function of the LOS and may result in oesophageal and extraoesophageal 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 PPIs has been shown to improve cough in patients with acid GOR-induced cough but the effect of PPIs remains disappointing when treating GOR in other respiratory diseases.
- Antireflux surgery is associated with improved allograft function after lung transplantation.
gradient during a TLOSR than healthy subjects. The higher pressure gradient is due to a higher intra-abdominal pressure and correlates with BMI. Although a delay in gastric emptying has been shown in ~30% of GORD patients, a clear causal relationship between rate of gastric emptying and reflux parameters remains controversial.

**Pathophysiology**

There are a number of potential mechanisms of interaction between the oesophagus and the lung that explain the complex interplay between GOR(D) and respiratory symptoms and disease:

- aspiration of gastric contents into the airways
- stimulation of a vagally mediated reflex pathway
- hypersensitivity

Direct microaspiration of (duodeno)gastric refluxate into the airway occurs as a consequence of failure of the normal protective mechanisms against foreign material, *i.e.* reflex contraction of the upper oesophageal sphincter and closure of the glottis and vocal cords. Aspiration can be demonstrated by the presence of pepsin and bile acids in saliva, sputum or bronchoalveolar lavage (BAL) fluid. While pepsin and bile acids are clearly increased in patients with CF and idiopathic pulmonary fibrosis (IPF), and after lung transplantation, there was no difference between chronic cough, patients with asthma and healthy controls.

Aspiration of (duodeno)gastric contents into the lungs can lead to chemical injury, which may be followed by an inflammatory response, characterised by the recruitment of neutrophils to the airways. It has been widely accepted that acid causes damage to bronchial epithelial cells, but recent data demonstrated that nonacidic gastric contents are also important in the pathogenesis of reflux-induced airway inflammation. Pepsin and bile acids may even cause cell damage at normal pH, which may explain why some patients have refractory symptoms on maximal proton pump inhibitor (PPI) therapy.

The oesophagus is innervated by sensory-type nociceptors that express the TRPV1 channel. These afferents of the vagus nerve converge centrally with capsaicin-sensitive C-fibres and capsaicin-insensitive, acid-sensitive mechanoreceptors from the respiratory tract. The convergence of these vagal afferent neurons in the brainstem may allow sensitisation of vagally mediated reflexes from the (distal) oesophagus to be triggered by chemical or mechanical stimuli. A vagally mediated oesophageal–bronchial 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, resulting in 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 cause cough symptoms even in the absence of increased oesophageal acid exposure or esophagitis.

**GOR in asthma and COPD**

GORD is a common condition among patients with obstructive pulmonary diseases. At least one-third of asthmatics present with GORD (prevalence 34–89%) and 50–60% of COPD patients have abnormally high oesophageal acid exposure times. Often, COPD or asthmatic patients with GORD do not have typical symptoms of GORD. The relationship between GOR and the clinical course of asthma and COPD needs to be better understood but it has been shown that that abnormal GOR may worsen asthma symptoms and has been associated with increased risk of asthma and COPD exacerbations. Oxygen desaturation coincides with episodes of increased oesophageal acidity in 40% of patients with severe COPD and GORD.

Several mechanisms may be involved (vagus nerve mediated mechanisms, chronic microaspiration and bronchial hyperreactivity): β₂-agonists and theophylline decrease LOS tone and may consequently promote oesophageal reflux. Airway
obstruction resulting in increased thoracic pressure changes, hyperinflation and exaggerated diaphragmatic flattening may also contribute to the occurrence of GOR.

Multiple trials have examined the treatment of GORD with histamine antagonists or PPIs in asthma. A Cochrane systematic review concluded that acid-suppressive therapy did not result in a consistent benefit in patients with asthma. Similarly, there was no effect on lung function, airway responsiveness or asthma symptom control. Even though nine out of 12 trials included in the meta-analysis reported at least one significant outcome, there was no consistency in these effects. The Study of Acid Reflux in Asthma (SARA), a large randomised control trial evaluated high-dose PPI (esomeprazole 40 mg b.i.d.) in patients with uncontrolled asthma that did not have typical GOR symptoms. PPI therapy did not improve asthma control, quality of life or lung function and, although 40% of these patients had abnormal asymptomatic acid GOR upon oesophageal pH monitoring, there was also no improvement with PPIs in this subgroup. A recent study in children yielded similar results. However, these studies did not test for nonacid reflux and did not evaluate the effect of treating nonacid reflux on asthma control. A retrospective study showed improvement of FEV1 with antireflux surgery in patients with adult-onset asthma, typical reflux symptoms and proximal extent of the reflux.

No large-scale studies have evaluated therapeutic options for GOR in patients with COPD. Uncontrolled data suggest that PPI treatment may decrease the number of COPD exacerbations. Future randomised controlled trials are needed.

For patients with asthma or COPD and who have typical reflux symptoms, empirical prescription of acid suppression therapy is appropriate but the effect on respiratory end-points may be limited. Current evidence does not support the initiation of empirical acid suppression therapy in asthma patients who lack symptoms that suggest the presence of GORD. Additional testing by means of endoscopy and ambulatory pH/impedance is indicated in asthma or COPD patients with a suspected GORD syndrome who do not respond to an empirical trial of PPI therapy, in elderly patients with asthma or COPD, or in patients with severe refractory asthma.

GOR-induced cough

Studies have determined GOR to be a cause of chronic cough in >40% of patients referred for specialist evaluation. GOR-induced cough is currently thought to occur predominantly via an oesophageal–bronchial reflex. Studies using combined pH/impedance and cough monitoring have shown that both acid and nonacid reflux events can be associated with cough. The acidity of the refluxate may thus be unimportant if the oesophageal–bronchial reflex is already sensitised. Findings of an equal number of cough events preceding as well as following reflux also suggest the possibility that cough may precipitate TLOSRs. Reflux should not be considered as a single independent cause but rather as a contributing factor as well as a consequence of chronic cough.

Only a minority of patients with chronic cough and GORD have typical digestive symptoms and/or clear evidence of oesophagitis. As a result and in accordance with published guidelines, objective evaluation of GOR is indicated in patients with chronic cough. Detection of both acid and nonacid reflux events with simultaneous cough detection allows for an objective assessment of the relationship between the two.

Treating GOR with the therapeutic strategies currently available may result in only a partial symptomatic improvement, as chronic cough is often a multifactorial process. The treatment of cough-associated reflux with acid-suppressive therapy has been evaluated in many uncontrolled and a few controlled trials. A Cochrane review concluded that PPI administration was not efficacious for cough associated with GORD symptoms in children. There was insufficient evidence to conclude that treating GOR with PPI in adults with cough was beneficial, although a slight improvement in cough scores was found in
those receiving PPIs. Further randomised, parallel-design, placebo-controlled, double-blind trials are needed. Based on these data, an empirical course of PPIs for 8 weeks could be advocated in all patients with possible reflux-induced cough, especially in patients who also have typical reflux symptoms. Prokinetic drugs have no efficacy in GORD-related cough and gastric emptying has not been shown to be delayed in patients with GOR-related cough. In patients who failed to respond to empirical therapy with PPIs, reflux-induced cough is not necessarily excluded, as nonacid reflux may also be implicated. Fundoplication provides an alternative method to treat GORD, which similarly controls acid and nonacid reflux. Uncontrolled studies with surgical treatment in patients with possible reflux-induced cough showed a positive response in 56–100% of surgically treated patients. A positive symptom association between acid or nonacid reflux was a good predictor of successful surgical outcome. In selected patients with refractory acidic or nonacidic reflux and a documented correlation between reflux episodes and cough, antireflux surgery may be indicated for long-term control.

GOR in advanced lung disease

GOR is an important comorbidity in patients with bronchiectasis. The prevalence of abnormal GOR in CF is estimated to be between 35% and 81%, and a somewhat smaller increase in GORD prevalence has also been reported in patients with non-CF bronchiectasis. Acid GOR is most predominant in CF, but weakly acidic GOR may also occur. CF patients with increased GOR often have a high proximal extent of the reflux into the oesophagus. Many CF patients have oesophageal hypomotility and low basal LOS pressure. The number of TLOSRs is similar to controls but TLOSRs in CF patients are more often associated with reflux, due to an more pronounced reduction in thoracic pressure during inspiration. Patients with CF have a high risk of gastric aspiration, as demonstrated by increased bile acids in saliva, sputum or in BAL 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 the material aspirated depend on the genotype, with bile acid aspiration being more important in CFTR<sup>ΔF508</sup> homozygotes.

The available evidence suggest a possible relationship between GOR, aspiration and the severity of CF lung disease, generation of cough symptoms, airway inflammation, and the progression of the lung disease. CF 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 correlate with elastase levels in sputum and FEV<sub>1</sub>; raised pepsin levels in BAL fluid are associated with higher levels of interleukin (IL)-8 in the BAL fluid. GOR might also be involved in earlier onset of first acquisition of <i>Pseudomonas aeruginosa</i> and the pathogenesis of CF exacerbations.

Retrospective data suggested that CF patients on acid suppression therapy had a smaller yearly decline of FEV<sub>1</sub>. However, a Cochrane review failed to show any relationship between reflux treatment and improvement of pulmonary damage in CF. Antireflux surgery may be considered as a more efficacious treatment of GOR in CF patients and uncontrolled studies showed an improvement in FEV<sub>1</sub> decline and cough symptoms and a reduction in CF exacerbation rate.

GOR may play a role in the pathogenesis and/or progression of IPF as a recurrent inflammatory stimulus. Studies have found a high prevalence of reflux (36–87%) among patients with interstitial lung diseases (ILDs), especially those with IPF or connective tissue disease (CTD)-associated ILD. Hypopharyngeal multichannel intraluminal impedance measurement in patients with IPF demonstrated frequent occurrence of abnormal proximal reflux events despite the absence of typical GOR symptoms and a frequently negative DeMeester score. Aspiration, assessed by means of increased BAL fluid pepsin levels,
was associated with an increased odds ratio for an acute exacerbation in IPF patients. Pre-transplant patients with IPF undergoing antireflux surgery had reduced supplementary oxygen dependence compared with other pre-transplant patients with IPF. There are anecdotal cases of IPF disease stability and less radiological fibrosis on HRCT following treatment for reflux. In addition, a recent cohort analysis found that the use of medications to suppress reflux was an independent predictor of longer survival time.

GOR and microaspiration 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 the 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, especially during the night, and was associated with a reduced concentration of pulmonary surfactant collectin proteins, reduced freedom from BOS and reduced survival. Aspiration, even in the absence of an increased number of GOR events, might therefore be a risk factor for the development of BOS after lung transplantation. Retrospective studies have linked prophylactic antireflux surgery to improved allograft function and decreased incidence and/or severity of BOS.

While it cannot be absolutely proven that disease stability is related to the control of reflux, the aforementioned study data suggest that a subset of patients with advanced lung disease may benefit from antireflux therapy. Proximal gastrointestinal tract motility studies, pH/impedance testing and markers of microaspiration appear to be important in management decisions. Future studies should seek to identify the most effective tool to determine the timing and efficacy of antireflux treatment.

Sleep and GOR

Sleep-related reflux is common, affecting between 47% and 79% of GORD patients. Between 54% and 57% of GORD patients and 25% of the general adult population report heartburn during the night. Sleep-related reflux is more commonly associated with oesophageal mucosal injury, malignant transformation and extraoesophageal manifestations of GORD. Poor quality of sleep and sleep disturbances have also been recently documented in a significant number of GORD patients with night-time reflux.

Sleep-related GOR occurs primarily during arousals or conscious awakenings in the first few hours of the sleep period and is primarily caused by TLOSR. Most conscious awakenings during sleep that also demonstrated reflux were not associated with typical GORD-related symptoms. Testing for reflux may thus be helpful in patients without typical GOR symptoms who have disrupted sleep without an identifiable cause found despite having undergone polysomnography sleep testing.

Up to 62% of OSA patients have sleep-related GOR symptoms and CPAP improves GOR symptoms and reduces oesophageal contact times. Treatment of sleep-related GOR includes behavioural treatment (weight loss, not eating prior to bedtime and avoiding foods known to worsen GOR) and PPI therapy given an hour before the last meal. Fundoplication can be helpful in selected patients with GOR and OSA.

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 the 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 reflux events and allows testing while the patient is taking a PPI. The detection of biomarkers of aspiration (e.g. pepsin and bile acid concentrations in saliva, sputum or BAL fluid) has increasingly been recognised as a tool to identify patients at risk of disease worsening due to GORD but, currently, there is no consensus on how best to detect aspiration.

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 extraoesophageal symptoms. Symptoms that persist during standard acid suppressive therapy regimens have also been related to nonacid reflux. There is little evidence that further intensification of acid suppression beyond high-dose PPIs twice daily is of any benefit for these patients. Dopaminergic antagonists with prokinetic activity (metoclopramide and domperidone) enhance gastric emptying and gastroduodenal coordination, but they do not appear to improve LOS pressure or reduce reflux events. Serotonin receptor prokinetic agents (cisapride and tegaserod) might be useful in the treatment of GOR but these drugs are no longer available due to concerns over possible adverse cardiovascular side-effects. A number of selective 5-HT₄ agonists/antagonists (prucalopride and mosapride) show some promise and are undergoing investigation for reflux treatment. Baclofen is a γ-aminobutyric acid (GABA) receptor blocking agent that diminishes acid and nonacid reflux through GABA receptor inhibition of TLOSRs and is now being used off label in the treatment of GOR. Baclofen may also reduce the exposure to duodenogastric reflux but its use has been limited by side-effects. Other GABA agonists (arbaclofen and lesogaberan) are currently under evaluation for their ability to reduce TLOSRs and improve 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, metabotropic glutamate receptor-5 antagonists and endoscopic antireflux procedures.

At present, the only alternative is a surgical fundoplication. Laparoscopic antireflux surgery creates a mechanically competent cardia, and is more effective in preventing microaspiration and in eliminating proximal reflux. However, 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. The key is thus the identification of patients who, with certainty, have GOR as an important cause of their pulmonary symptoms.

Further reading

Chronic obstructive pulmonary 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 as much as 50%; COPD is projected to rank as the fifth largest worldwide burden of disease by 2020. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2013 report, 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 enhanced inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Exacerbations and comorbidities contribute to the overall severity in individual patients. 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 individuals with the disease. Airflow limitation in COPD is caused by the presence of an 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. These result 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 of the disease are recognized: chronic bronchitis and emphysema. Chronic bronchitis is characterised by cough and sputum production for ≥3 months in each of two consecutive years. The symptoms may precede the development of 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

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.
increasing cardiac output (ventilation/perfusion ($V'Q'$) mismatch), leading to hypoxaemia, polycythaemia and increased carbon dioxide retention, and eventually these patients develop signs of right heart failure.

**Emphysema** The second major COPD phenotype is the emphysematous patient. Emphysema is defined by destruction of airways distal to the terminal bronchiole, and gradual destruction of alveolar septa and the pulmonary capillary bed, leading to a 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.

**Diagnosis and assessment**

A clinical diagnosis of COPD should be considered in any patient who has dyspnoea, chronic cough and/or sputum production, a history of exposure to risk factors for the disease (tobacco smoke, occupational dusts and chemicals) and a family history of COPD (table 1). Overall COPD assessment should include the evaluation of current symptoms, the degree of airflow limitation, the risk of exacerbations and comorbidity. Combined COPD assessment including symptoms, spirometric classification and risk of exacerbation is presented in table 2, categorising COPD patients in four groups (A, B, C and D).

First, assess symptoms using either the modified Medical Research Council (mMRC) questionnaire or the COPD Assessment Test (CAT). Although the mMRC questionnaire is a validated tool to assess disability due to dyspnoea and CAT has a broader coverage of patients' health status, the proposed classification cut-offs are relatively arbitrary. Thus, further real-life studies are needed to better assess COPD patients.

**Table 1. Risk factors for COPD**

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<tr>
<th>Genes</th>
<th>Exposure to particles</th>
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<td></td>
<td>Tobacco smoke</td>
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<td></td>
<td>Occupational dusts, organic and inorganic</td>
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<td></td>
<td>Indoor air pollution (heating and cooking with biomass fuel)</td>
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<td></td>
<td>Outdoor air pollution</td>
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<td>Lung growth</td>
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<td>Oxidative stress</td>
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<td>Sex</td>
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<td>Age</td>
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<tr>
<td>Respiratory infections</td>
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<td>Socioeconomic status</td>
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<td>Nutrition</td>
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Secondly, assess disease severity by spirometry and by the frequency of exacerbations. Spirometry is required to assess the degree of airflow limitation as it is the most widely available and reproducible lung function test. The presence of a post-bronchodilator FEV1/FVC ratio $<0.70$ confirms the presence of airflow obstruction, and thus of COPD. The classification of severity of airflow obstruction in COPD into four stages is presented in table 3. Where possible, values should be compared to age-related normal values (a cut-off based on the lower limit of normal (LLN) values for FEV1/FVC) to avoid overdiagnosis of COPD in the elderly and less frequent diagnosis in adults younger than 45 years.

COPD exacerbations deteriorate health status, and enhance lung function decline and mortality. Thus, the assessment of exacerbation risk can reflect the risk of poor outcome and prognosis. The best predictor of having frequent exacerbations (two or more exacerbations per year) is a history of previous episodes, especially hospital admissions, as the exacerbation rate varies greatly between patients.

Comorbidities such as cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis,
depression and lung cancer can occur frequently in patients with COPD. Comorbidities influence mortality and hospitalisations independently, and should thus be recognised and treated properly in all COPD patients.

Risk factors

Although smoking is the best-studied COPD risk factor, it is not the only one and there is consistent evidence from epidemiological studies that nonsmokers may develop chronic airflow obstruction (table 1). 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 females. Nevertheless, not all subjects exposed to noxious agents develop COPD. Thus, a strong genetic component in relation with an environmental insult (gene–environment interaction) most probably accounts for the development of the disease (table 1). Familial clustering of COPD has been observed and twin studies have supported the concept of a genetic predisposition to COPD. 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.

Although rare, hereditary α1-antitrypsin (AAT) deficiency is the best documented genetic risk factor for emphysema. The AAT gene is located on chromosome 14q23.1–3 and is a serum protein made in the liver that is capable of inhibiting the activity of serine proteases. Neutrophil elastase is the main target of AAT; if not inactivated by AAT, 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 COPD 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 and modified from GOLD (2013) with permission from the publisher.
neutrophil elastase destroys lung connective tissue, particularly elastin, and this leads to the development of emphysema. Over 90 different phenotypes of AAT have been described. The common gene variants are M, S and Z. Emphysema associated with AAT 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 AAT deficiency, and current smokers have an accelerated decline in FEV1 compared with ex-smokers and never-smokers with AAT deficiency. Homozygous Z patients have a very low AAT levels and generally show a rapid decline in FEV1 even without smoking. However, this homozygous state is rare in the general population (one in 5000 live births) and, thus, as genetic risk factor, it 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. Under normal conditions, cells are equipped with a number of repair pathways that remove 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. Patients who still smoke 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

<table>
<thead>
<tr>
<th>Table 4. The recommended therapeutic management per severity group</th>
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<tr>
<td><strong>Group A: low risk, fewer symptoms</strong></td>
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<tr>
<td><strong>First-choice treatment</strong></td>
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<tr>
<td><strong>Second-choice treatment</strong></td>
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<tr>
<td><strong>Alternative choice</strong></td>
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Treatments are presented in alphabetical order not in order of preference. SABA: short-acting β2-agonist; SAMA: short-acting muscarinic antagonist; LABA: long-acting β2-agonist; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroid; PDE4i: phosphodiesterase-4 inhibitor. Reproduced and modified from GOLD (2013) with permission from the publisher.
exercise tolerance, thus improving overall the quality of life. A summary of the proposed pharmacological management across COPD groups is presented in table 4. Bronchodilator medications are central to the symptomatic management of COPD. These drugs improve emptying of the lungs, tend to reduce static and dynamic hyperinflation, and improve exercise performance. Inhaled therapy is preferred and bronchodilators are prescribed either on an as-needed basis or on 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 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 COPD patients in groups C and D and repeated exacerbations according to the guidelines (table 4). 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% predicted, 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 as 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 and pneumococcal polysaccharide vaccine are strongly recommended for all COPD patients, as they decrease serious illness and death rates by ~50%.

**Pulmonary rehabilitation** aims to improve exercise capacity, reduce symptoms and improve overall 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 the hospital, reduces anxiety and depression related to COPD and improves survival. A comprehensive rehabilitation programme includes exercise training, education and nutrition counselling.

**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 BMI, seen in ~25% of stage III and IV COPD patients, is an independent risk factor for mortality. The present evidence suggests a combination of nutritional support and exercise regimes should be used to induce anabolic action.

**Further reading**

Definition

COPD is a chronic inflammatory airway condition associated with episodes of acute deterioration termed exacerbations. An exacerbation of COPD is defined in the 2011 revision of the Global Strategy for the Diagnosis, Management and Prevention of COPD as an acute event characterised by a worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication. However, around half of all COPD exacerbations identified by symptom worsening are not reported, hence may not be treated, and thus could remain unidentified if a strict healthcare utilisation definition for exacerbations is used. For this reason, considerable interest exists in the potential of patient reported outcomes, such as the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) to detect and quantify the severity of exacerbations.

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. Unreported exacerbations are also important events, significantly impairing quality of life. 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. Every new, severe exacerbation that requires hospitalisation increases the risk of a subsequent exacerbation, and every new severe exacerbation increases the risk of death, up to five times after the tenth hospitalisation when compared with after the first COPD hospitalisation. Mortality peaks in the first week after admission, stabilising after 3 months and long-term prognosis is poor, with all-cause mortality approaching 50% at 3 years 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 NIV. 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 with 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, decline in FEV₁, and inflammation all being more severe in the presence of bacteria and viruses. These subjects are discussed further in the section on Infective exacerbations of COPD.

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 (sulfur 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 when there are colder temperatures; small but significant falls in lung function occur with a reduction in outdoor temperature during the winter in COPD patients. The mechanisms behind these observations are not clearly understood but may relate to increasing prevalence of respiratory viruses in the low temperature winter months and/or increased susceptibility to upper respiratory tract viral infections in cold weather.

Cardiovascular disease, comorbidities and exacerbations
Comorbid ischaemic heart disease is associated with longer exacerbations characterised by increased dyspnoea and wheeze. The presence of cardiac complications is increasingly being recognised as a predictor for COPD outcome. Data from The Health Improvement Network (THIN) database demonstrated a 2.27-fold increased risk of myocardial infarction 1–5 days after outpatient exacerbations (defined by the prescription of both steroids and antibiotics). And in hospitalised exacerbations, raised troponin, chest pain and serial ECG changes are common, with one in 12 patients meeting the criteria for myocardial infarction. Furthermore, elevated troponin levels predict 30-day mortality in hospitalised COPD exacerbations, and so these studies challenge the way that exacerbations are conventionally treated. Patients receiving β-blockers appear to have a reduced risk of COPD exacerbations and a lower mortality from exacerbations. Therefore, COPD patients in the future, especially those with elevated cardiac biomarkers, may be considered for increased cardiac treatment at exacerbation.

Diabetes is also an important influence on COPD exacerbations. Comorbid diabetes mellitus prolongs the length of stay in hospital and increases the risk of death in patients hospitalised with acute exacerbations of COPD.

Frequent exacerbator phenotype
Patients with a history of frequent exacerbations have a worse quality of life, increased risk of hospitalisation and greater mortality (fig. 2). Frequent exacerbators also exhibit a 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 appear to be susceptible to exacerbations, irrespective of disease severity. This phenotype of susceptibility to exacerbations is stable over time and the major determinant of frequent exacerbations is a

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**Figure 1.** Triggers of COPD exacerbations and associated pathophysiological changes leading to increased exacerbation symptoms. Reproduced from Wedzicha et al. (2007) with permission from the publisher.
history of prior exacerbations. This phenomenon is seen across all GOLD stages (Global Initiative for Chronic Obstructive Lung Disease), including patients with stage II disease, of whom 22% had frequent exacerbations in the first year of the ECLIPSE study (the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints). Therefore, suggesting patients with frequent exacerbator phenotypes 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 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-7 chemokines, which are increased in the sputum and airways of patients with COPD exacerbations. *H. influenzae* also increases the 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. A pneumococcal polysaccharide vaccine has been shown to reduce the incidence of community-acquired pneumonia in COPD patients under the age of 65 years 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 study (Inhaled
Steroid in Obstructive Lung Disease in Europe) showed a 25% reduction in exacerbation frequency with inhaled corticosteroids (ICS). Long-acting β-agonists (LABA) also reduce exacerbation frequency, and in the TORCH study (Towards a Revolution in COPD Health), in which 6112 patients were followed for over 3 years, 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 also been found with other LABA/ICS combinations, such as formoterol and budesonide.

Long-acting antimuscarinics (LAMA) also reduce exacerbation frequency. In the UPLIFT trial (Understanding Potential Long-Term Impacts on Function with Tiotropium), 5993 patients were randomised to tiotropium or placebo for a 4-year duration, with concomitant therapy being allowed. Although the primary end-point of the trial (reduction in the rate of decline in FEV1) was negative, tiotropium was associated with a reduction in exacerbation risk, related hospitalisations and respiratory failure. The POET-COPD trial (Prevention of Exacerbations with Tiotropium in COPD) showed that in patients with moderate-to-very-severe COPD, tiotropium is more effective than salmeterol in preventing exacerbations.

Newer bronchodilators, such as indacaterol, may also play a role in future maintenance regimens to reduce COPD exacerbations. To date, indacaterol has shown comparable exacerbation reduction rates in comparison with tiotropium in short clinical trials; however, whilst indacaterol in combination with tiotropium has recently been shown to provide enhanced bronchodilatation compared to tiotropium alone, further research is required to assess if this combination provides synergistic benefits to reduce exacerbation frequency.

**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 III and IV), 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 year, 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 a prophylaxis in patients with CF and, when added to usual treatment, azithromycin has also been shown to decrease exacerbation frequency and improve quality of life in COPD patients. However, the benefits were most significant in the treatment-naive patients with mild disease (GOLD stage II), and significant rates of hearing decrement (as measured by audiometry) and antibiotic resistance were found. In addition, a recent large epidemiological study has suggested a small increase in cardiovascular deaths in patients receiving azithromycin, particularly in those with a high baseline risk of cardiovascular disease.

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.

Hence, before prescription of long-term antibiotics in COPD, patients should be:

- Treated with an optimum combination of inhaled therapy
- Show evidence of ongoing frequent exacerbations
- Be carefully assessed for risk of potential cardiovascular and auditory side effects.

**Pulmonary rehabilitation with 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 ventilator support may reduce hospital admission, but controlled trials have not yet addressed these issues. These subjects are discussed in detail in the sections on Pulmonary rehabilitation, Acute oxygen therapy and Long-term ventilation.

A summary of the different therapies used to prevent COPD exacerbations is given in table 1.

**Further reading**

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, with the majority of patients dying from cardiovascular diseases or cancer and not primarily from a respiratory disease. 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, musculoskeletal 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 heterogeneous and inflammatory cells 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: interleukin (IL)-6, IL-8 and tumour necrosis factor-α (TNF-α); acute-phase proteins, i.e. C-reactive protein (CRP) and fibrinogen; and circulating inflammatory cells, such as monocytes, neutrophils and lymphocytes. It is debatable whether this systemic inflammation is the result of: 1) a ‘spill-over’ of local inflammation in the lungs; 2) a systemic inflammatory effect that affects multiple organ systems; or 3) is attributable to some comorbid conditions that affect the lungs (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

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Table 1. Systemic manifestations and comorbidities of COPD

<table>
<thead>
<tr>
<th>Cardiovascular diseases</th>
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<tbody>
<tr>
<td>Ischaemic heart disease</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Pulmonary hypertension</td>
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<td>Congestive heart failure</td>
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<table>
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<tr>
<th>‘Metabolic’ disorders</th>
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<tbody>
<tr>
<td>Osteoporosis</td>
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<tr>
<td>Skeletal muscle weakness</td>
</tr>
<tr>
<td>Cachexia: weight loss and muscle wasting</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Metabolic syndrome</td>
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<table>
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<tr>
<th>Other comorbid diseases</th>
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<tbody>
<tr>
<td>Lung cancer</td>
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<tr>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>OSA(S)</td>
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<td>Normocytic anaemia</td>
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Figure 1. Systemic effects and comorbidities of COPD. Peripheral lung inflammation may cause a ‘spill-over’ of cytokines, such as IL-6, IL-1β and TNF-α, into the systemic circulation, which may increase the acute-phase proteins, such as CRP. Systemic inflammation may then lead to skeletal muscle atrophy and cachexia, and may initiate and worsen comorbid conditions. Systemic inflammation may also accelerate lung cancer. An alternative model is that systemic inflammation causes several inflammatory diseases, including COPD. Reproduced from Barnes et al. (2009).
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 using spirometry, but the severity of the disease is clearly dependent on the presence of comorbidities. Therefore, it has been proposed that any patient aged >40 years with a positive smoking history (>10 pack-years), 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 solely 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 FEV1. 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 so far suggest that statins, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers might all have dual cardiopulmonary properties and, thereby, 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 more specifically pulmonary rehabilitation 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.

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**Table 2. Components of the chronic systemic inflammatory syndrome**

<table>
<thead>
<tr>
<th>Component</th>
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<tr>
<td>Aged &gt;40 years</td>
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<tr>
<td>Smoking &gt;10 pack-years</td>
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<tr>
<td>Symptoms and lung function compatible with COPD</td>
</tr>
<tr>
<td>Chronic heart failure</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
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<tr>
<td>Increased CRP</td>
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</table>

At least three components are required for diagnosis. Reproduced from Fabbri et al. (2007) with permission from the publisher.
Further reading

The pharmacology of asthma and COPD involves understanding the mechanisms and clinical use of bronchodilators and anti-inflammatory or controller therapies.

- **Relievers** (bronchodilators) give immediate reversal of airway obstruction, largely by relaxing airway smooth muscle.
- **Controllers** (preventers) suppress the underlying disease process (anti-inflammatory treatments) and provide long-term control of symptoms.
- The most effective therapies are given by inhalation to reduce side-effects.

### $\beta_2$-adrenergic agonists

Inhaled $\beta_2$-agonists are the bronchodilator treatment of choice in asthma because they reverse all known bronchoconstrictor mechanisms and have minimal side-effects when used correctly.

#### Mode of action

- $\beta_2$-agonists produce bronchodilatation by directly stimulating $\beta_2$-receptors in airway smooth muscle, leading to relaxation of central and peripheral airways. $\beta_2$-agonists are functional antagonists as they reverse bronchoconstriction irrespective of the contractile agent. This is important in asthma as many bronchoconstrictor mechanisms (neural and mediators) contribute, whereas in COPD, their major effect is to reverse cholinergic tone. Activation of $\beta_2$-receptors results in the activation of adenylyl cyclase via the stimulatory G-protein ($G_s$), which increases intracellular cyclic AMP, leading to relaxation of myosin fibrils. $\beta_2$-receptors are localised to several types of airway cell and $\beta_2$-agonists may have additional effects.
- $\beta_2$-agonists may also have other beneficial effects, by inhibiting the release of mediators from mast cells and of neurotransmitters from airway nerves, as well as reducing plasma exudation from airway blood vessels.
- However, $\beta_2$-agonists have no significant long-term effects on chronic inflammation of the airways so in asthma patients they need to be used with a controller therapy.

### Key points

- Long-acting $\beta_2$-agonists are effective as add-on therapy to inhaled corticosteroids in asthma and for reducing symptoms in COPD, and act as functional antagonists.
- Inhaled corticosteroids are the mainstay of asthma control and suppress activated inflammatory genes, but are largely ineffective in COPD (corticosteroid resistance).
- Long-acting muscarinic antagonists are effective bronchodilators in COPD where cholinergic tone is the only reversible component.
- Low-dose theophylline may be useful as an add-on therapy in severe asthma and COPD and may reduce corticosteroid resistance.
Short-acting inhaled β₂-agonists (SABAs) (e.g. salbutamol and terbutaline) bronchodilate for 3–4 h (less in severe asthma) and used mainly by inhalation as reliever therapy in asthma and COPD. They have a rapid onset and are without significant side-effects. They also protect against bronchoconstrictor stimuli such as exercise, cold air and allergens. SABAs are the bronchodilators of choice in acute severe asthma and COPD, in which the nebulised route of administration is as effective as i.v. use. Inhaled delivery is preferable to oral because side-effects are less common and it may be more effective (better access to surface cells such as mast cells). They should not be used on a regular basis; increased use indicates a need for more anti-inflammatory therapy.

Long-acting inhaled β₂-agonists (LABAs) (e.g. salmeterol and formoterol twice daily, and indacaterol once daily) have a prolonged bronchodilator and bronchoprotective action. Formoterol has a more rapid onset of action but is a fuller agonist than salmeterol, so tolerance is more likely. Formoterol, but not salmeterol, is more effective as a reliever than SABAs. Inhaled LABAs are added to low or moderate doses of inhaled corticosteroids (ICS) and this is more effective than increasing the dose of ICS but should never be used without an ICS in asthma. Combination inhalers with an ICS and a LABA (fluticasone propionate and salmeterol, budesonide and formoterol, or beclomethasone dipropionate and formoterol) are an effective and convenient way to control asthma and are also useful in COPD. Budesonide/formoterol is very effective as a reliever when added to maintenance treatment with the same drug. LABAs are effective bronchodilators in COPD and reduce exacerbations. Indacaterol has a duration of action >24 h and is approved as a once daily treatment for COPD patients.

Side-effects Unwanted effects result from stimulation of extrapulmonary β-receptors and include muscle tremor, palpitations, restlessness and hypokalaemia. Side-effects are uncommon with inhaled therapy, but more common with oral or i.v. administration

Safety A large trial in the USA showed that salmeterol increased mortality and near-death asthma attacks in asthmatic patients, but this was mainly in poor patients who were not using concomitant ICS. This provides a strong argument for prescribing LABAs only in a combination inhaler. There are no safety concerns about LABA use in COPD.

Tolerance Loss of bronchodilator action is minimal, but there is some loss of the bronchoprotective effect against exercise, for example. This is incomplete and not progressive, and does not appear to be a clinical problem.

Anticholinergics

Atropine is a naturally occurring compound that was introduced for the treatment of asthma but, because of side-effects (particularly drying of secretions), less soluble quaternary compounds (e.g. ipratropium bromide) were developed.

Mode of action Anticholinergics are specific antagonists of muscarinic receptors and block cholinergic nerve-induced bronchoconstriction. A small degree of resting bronchomotor tone is present because of tonic cholinergic nerve impulses, which release acetylcholine in the vicinity of airway smooth muscle, and cholinergic reflex bronchoconstriction may be initiated by irritants, cold air and stress. Although anticholinergics protect against acute challenge by sulfur dioxide and emotional factors, they are less effective against allergens, exercise and fog. They inhibit reflex cholinergic bronchoconstriction only and have no significant blocking effect on the direct effects of inflammatory mediators, such as histamine and leukotrienes. In COPD, cholinergic tone is the only reversible element of airway narrowing.

Clinical use Ipratropium bromide and oxitropium bromide are inhaled three or four times daily, whereas tiotropium bromide is inhaled once daily. In asthmatics, anticholinergic drugs are less effective bronchodilators than β₂-agonists and offer less protection against bronchial challenges.
Nebulised anticholinergics are effective in acute severe asthma, but less effective than β₂-agonists, so may be added if responses to nebulised β₂-agonists are insufficient. Recent studies have demonstrated that tiotropium may be an effective add-on bronchodilator in some patients with severe asthma. Inhaled anticholinergic drugs are the bronchodilators of choice in COPD and once-daily tiotropium bromide is an effective bronchodilator for COPD, which also reduces exacerbations, mortality and possibly disease progression in early disease.

**Side-effects** Inhaled anticholinergic drugs are well tolerated, and systemic side-effects are uncommon because very little systemic absorption occurs. Ipratropium bromide, even in high doses, has no detectable effect on airway secretions. Nebulised ipratropium bromide may precipitate glaucoma in elderly patients as a result of a direct effect of the nebulised drug on the eye; this is avoided by use of a mouthpiece rather than a facemask. Dry mouth occurs in about 10% of patients on tiotropium bromide but rarely requires discontinuation of treatment. Urinary retention and glaucoma are rare adverse effects.

**Theophylline**

Theophylline remains the most widely used asthma therapy worldwide because it is inexpensive, but the greater incidence of side-effects with theophylline and the greater efficacy of β-agonists and ICS have reduced its use. It remains a useful drug in patients with severe asthma and COPD.

**Mode of action** Theophylline is a weak, nonselective phosphodiesterase (PDE) inhibitor, which causes bronchodilatation by inhibiting PDE3 in airway smooth muscle at concentrations >10 mg·L⁻¹. At these concentrations, it is also an antagonist of adenosine receptors and inhibition of A1-receptors on mast cells could contribute to its beneficial effect in asthma, but blockage of A₂ receptors may lead to serious side-effects, such as cardiac arrhythmias and seizures. At lower concentrations (5–10 mg·L⁻¹) theophylline may have anti-inflammatory effects in asthma and COPD, either through PDE4 inhibition or, more likely, through inhibition of phosphoinositide-3-kinase-δ. This may also explain how theophylline can reverse corticosteroid resistance in asthma and COPD by increasing histone deacetylase (HDAC)2 activity to allow corticosteroids to switch off activated inflammatory genes.

**Clinical use** Intravenous aminophylline (a stable mixture or combination of theophylline and ethylenediamine that confers greater solubility in water) is less effective than nebulised β₂-agonists in the treatment of acute severe asthma, and should therefore be reserved for the few patients who fail to respond to β₂-agonists. Theophylline is less effective as a bronchodilator than inhaled β₂-agonists and is more likely to have side-effects. There is increasing evidence that low doses (giving plasma concentrations of 5–10 mg·L⁻¹) may be useful when added to inhaled corticosteroids, particularly in more severe asthma and in COPD, reducing hyperinflation and improving dyspnoea.

**Pharmacokinetics** Theophylline is reliably absorbed from the gastrointestinal tract, but there are many factors affecting plasma clearance and, thus, plasma concentration. Clearance may be increased by drugs that induce hepatic cytochrome P450 (e.g. rifampicin and ethanol), by smoking and in children, so higher doses may be needed in these cases, whereas clearance is reduced by drugs that inhibit hepatic metabolism (e.g. cimetidine, erythromycin and ciprofloxacin), congestive cardiac failure, liver disease, viral infections, and in the elderly.

**Side-effects** These are related to plasma concentration and tend to occur when plasma levels exceed 20 mg·L⁻¹, although some patients develop them at lower plasma concentrations. The severity of side-effects may be reduced by gradually increasing the dose until therapeutic concentrations are achieved. The most common side-effects are headache, nausea and vomiting, abdominal discomfort.
(probably due to PDE4 inhibition), and the dangerous side-effects are cardiac arrhythmias and seizures (due to A1-receptor antagonism).

Corticosteroids

Corticosteroids are the most effective controller therapy available for asthma, but are poorly effective in COPD.

Mode of action Corticosteroids enter target cells and bind to glucocorticoid receptors in the cytoplasm. The corticosteroid–receptor complex is transported to the nucleus, where it binds to specific sequences on the upstream regulatory element of responsive target genes, resulting in increased or decreased transcription and, subsequently, increased or decreased protein synthesis. Glucocorticoid receptors may also inhibit transcription factors, such as nuclear factor-κB, which activate inflammatory gene expression by a nongenomic mechanism. Corticosteroids inhibit histone acetylation and, thereby, inflammatory gene expression by recruiting HDAC2 to the transcriptional complex. The mechanism of action of corticosteroids in asthma is most related to their anti-inflammatory effects and, particularly, suppression of transcription of activated inflammatory (e.g. cytokine) genes. They also have inhibitory effects on many inflammatory and structural cells that are activated in asthma, resulting in reduced airway hyperresponsiveness. By contrast, corticosteroids have no anti-inflammatory effects in COPD and reduced benefit in severe asthma, which may be explained by a reduction in HDAC2 activity as a consequence of oxidative stress.

Clinical use Systemic corticosteroids are used in acute exacerbations of asthma and accelerate their resolution. There is no advantage with high doses of i.v. corticosteroids (e.g. methylprednisolone, 1 g). Prednisolone (40–60 mg orally) has an effect similar to i.v. hydrocortisone and is easier to administer. Maintenance oral corticosteroids are reserved for patients whose asthma cannot be controlled by other therapy (Global Initiative for Asthma (GINA) step 5); the dose is titrated to the lowest that provides acceptable symptom control. Short courses of oral corticosteroids (prednisolone, 30–40 mg daily for 1–2 weeks) are indicated for exacerbations of asthma; the dose may be tapered over 1 week once the exacerbation is resolved.

ICS are currently recommended as first-line therapy in all patients with persistent asthma and may be started in any patient who needs to use a SABA inhaler for symptom control more than twice a week. In most patients, ICS are used twice daily, but once daily use may be possible in patients with mild asthma. If a dose of >800 μg daily via a metered-dose inhaler is administered, a spacer should be used to reduce the risk of oropharyngeal side-effects and of absorption from the gastrointestinal tract. ICS in doses of ≤400 μg daily may be used safely in children. Patients with COPD show a poor response to ICS with no effect on disease progression or mortality, but reduce exacerbations in patients who have severe disease and frequent exacerbations.

Side-effects Corticosteroids inhibit cortisol secretion by a negative feedback effect on the pituitary gland. Hypothalamic–pituitary–adrenal axis suppression is dependent on dose and usually occurs when an oral dose of prednisolone of more than 7.5–10 mg daily is used. Significant suppression after short courses of corticosteroid therapy is not usually a problem but prolonged suppression may occur after several months or years; corticosteroid doses after prolonged oral therapy must therefore be reduced slowly. Symptoms of ‘corticosteroid withdrawal syndrome’ include lassitude, musculoskeletal pains and occasionally fever.

Side-effects of long-term oral corticosteroid therapy include fluid retention, increased appetite, weight gain, osteoporosis, capillary fragility, hypertension, peptic ulceration, diabetes, cataracts and psychosis. The incidence tends to increase with age.

Systemic side-effects of ICS have been investigated extensively. Effects such as cataract formation and osteoporosis are reported, but often in patients who are also receiving oral corticosteroids. There has
been particular concern about growth suppression in children using ICS but, in most studies, doses of \( \leq 400 \text{mg} \) have not been associated with impaired growth and there may even be a growth spurt because asthma is better controlled. In COPD patients, high doses of ICS have been associated with cataracts, diabetes and pneumonia.

The fraction of corticosteroid inhaled into the lungs acts locally on the airway mucosa and may be absorbed from the airway and alveolar surface, thereby reaching the systemic circulation. The fraction of ICS deposited in the oropharynx is swallowed and absorbed from the gut, and then is metabolised in the liver before it reaches the systemic circulation. Budesonide and fluticasone propionate have a greater first-pass metabolism than beclomethasone dipropionate and are therefore less likely to produce systemic effects at high inhaled doses. The use of a spacer reduces oropharyngeal deposition, thereby reducing systemic absorption of corticosteroid.

**Antileukotrienes**

Antileukotrienes (leukotriene receptor antagonists) are much less effective than ICS in the control of asthma.

**Mode of action** Elevated concentrations of leukotrienes are detectable in bronchoalveolar lavage fluid and sputum of asthmatic patients. Cysteinyl-leukotrienes (Cys-LTs) are generated from arachidonic acid by the rate-limiting enzyme 5-lipoxygenase. Cys-LTs are potent constrictors of human airways *in vitro* and *in vivo*, cause airway microvascular leakage in animals, and stimulate airway mucus secretion. These effects are all mediated in human airways *via* Cys-LT receptors. Montelukast and zafirlukast are potent Cys-LT, receptor antagonists that markedly inhibit the bronchoconstrictor response to inhaled leukotrienes, reduce allergen-, exercise- and cold air-induced asthma by about 50–70%, and inhibit aspirin-induced responses in aspirin-sensitive asthmatics almost completely. They may also have weak anti-inflammatory effects and may reduce eosinophilic inflammation.

**Clinical use** Antileukotrienes may have a small and variable bronchodilator effect, indicating that leukotrienes may contribute to baseline bronchoconstriction in asthma. Long-term administration reduces asthma symptoms and the need for rescue \( \beta_2 \)-agonists, and improves lung function. However, their effects are significantly less than with ICS in terms of symptom control, improvement in lung function and reduction in exacerbations. They may be useful in some patients whose asthma is not controlled on ICS as an add-on therapy, but are less effective in this respect than a long-acting \( \beta_2 \)-agonists or low dose theophylline. They are effective in some but not all patients with aspirin-sensitive asthma. Patients appear to differ in their response to antileukotrienes, and it is impossible to predict which patients will respond best. A major advantage is that they are orally active and may improve compliance with long-term therapy. However, they are expensive, and a trial of therapy is indicated to determine which patients will benefit most.

**Side-effects** Antileukotrienes are well tolerated and there are no class-specific side-effects. Zafirlukast may produce mild liver dysfunction, so liver function tests are important. Several cases of Churg–Strauss syndrome (systemic vasculitis with eosinophilia and asthma) have been observed in patients on antileukotrienes, but these may be because a concomitant reduction in oral corticosteroids (made possible by the antileukotriene) allows the vasculitis to flare up.

**Cromones**

Cromones include sodium cromoglycate and the structurally related nedocromil sodium.

Although they protect against indirect bronchoconstrictor stimuli such as exercise, allergens and fog, they are poorly effective compared with low doses of ICS, as they have a short duration of action. Systematic reviews have concluded that they provide little benefit in chronic asthma so they are
now rarely used. There is no role for cromones in the management of COPD.

**Anti-IgE**

**Mode of action** Omalizumab is a humanised recombinant monoclonal antibody that binds to circulating IgE and, thus, blocks it from activating high-affinity IgE receptors on mast cells and low-affinity IgE receptors on other inflammatory cells, resulting in reduced responses to allergens. Over time, the blocking of IgE reduces its synthesis by B-cells and results in a sustained reduction in IgE.

**Clinical use** Omalizumab reduces airway inflammation in patients with mild-to-moderate asthma and reduces the incidence of asthma exacerbations, with improved control of asthma in patients maintained on reduced doses of ICS or oral steroids. Omalizumab is most useful in patients with severe asthma who are not controlled on maximal doses of inhaled therapy as it reduces exacerbations and improves asthma control. Only ~30% of patients show a good response and this is not predictable by any clinical features; therefore, a trial of therapy over 4 months is indicated. Omalizumab should be given only to patients with serum IgE levels of 20–700 IU·mL⁻¹; above these levels, it is not possible to give enough antibody to neutralise the IgE. The dose of omalizumab is determined by serum IgE levels and body weight, and is given either once or twice a month. Because of its high cost, only patients at GINA steps 4 and 5 with frequent exacerbations are suitable for this therapy.

**Side-effects** Occasionally, local reactions occur at the injection sites and, very rarely, anaphylactic reactions have been reported.

**Immunosuppressive/corticosteroid-sparing therapy**

Immunosuppressive therapy has been considered in asthma when other treatments have been unsuccessful or when a reduction in the dosage of oral corticosteroids is required; it is therefore indicated in very few (<1%) asthmatic patients at present.

**Methotrexate** Low-dose methotrexate (15 mg weekly) has a corticosteroid-sparing effect in some patients with asthma, but side-effects are relatively common and include nausea (reduced if methotrexate is given as a weekly injection), blood dyscrasia and hepatic damage. Careful monitoring (monthly blood counts and liver enzymes) is essential.

**Gold** has long been used in the treatment of chronic arthritis. A controlled trial of an oral gold preparation (auranofin) demonstrated some corticosteroid-sparing effect in chronic asthmatic patients maintained on oral corticosteroids, but side-effects (skin rashes and nephropathy) are a limiting factor.

**Cyclosporin A** Low-dose oral cyclosporin A in patients with corticosteroid-dependent asthma is reported to improve control of symptoms but, in clinical practice, it is unimpressive and its use is limited by severe side-effects (nephrotoxicity and hypertension).

**Roflumilast**

Roflumilast is a once daily oral PDE4 inhibitor that has anti-inflammatory effects in COPD patients. The dose is limited by side-effects (nausea, vomiting, diarrhoea and headaches) so its clinical efficacy is relatively small. Weight loss may also occur but this is nonprogressive and reversible. COPD patients with severe disease (FEV₁ <50% predicted), chronic bronchitis and frequent exacerbations, there is a small improvement in lung function and a reduction in severe exacerbations. It is therefore used as an add-on therapy in this subgroup of patients with COPD. It should never be co-administered with theophylline, which also has PDE4 inhibitory effects.

**Further reading**

Bronchiectasis is a disorder characterised by abnormal bronchial wall thickening and luminal dilation 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 an increase in symptoms, i.e. increase in cough and change in purulence and volume of sputum associated with an increase in malaise. These exacerbations are almost always associated with infections of bronchiectasis. Aetiological agents of bronchiectasis include bacteria (Haemophilus influenzae, Pseudomonas aeruginosa, Moraxella catarrhalis, Streptococcus pneumoniae and Staphylococcus aureus), mycobacteria (Mycobacterium avium-intracellulare complex, Mycobacterium kanssai and Mycobacterium fortuitum) and fungi (Aspergillus fumigatus). The pattern of microbiology is quite stable; however, resistance to antibiotics may increase in time. Pseudomonas is associated with more severe disease. Nontuberculous mycobacteria are frequently associated with Aspergillus.

Underlying causes of bronchiectasis may be acquired or inherited, and include post-infective causes, mechanical obstruction, an excessive or 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,

Key points

- Diagnosis of bronchiectasis is based on the presence of daily production of mucopurulent phlegm and chest imaging that demonstrates dilated and thickened airways. HRCT is the gold standard.
- The diagnosis of bronchiectasis should lead to the investigation and treatment of possible causes and associated conditions.
- Antibiotics form the mainstay of treatment of bronchiectasis. Acute exacerbations should be treated promptly with short courses of antibiotics.
- The efficacy of continuous administration of antibiotics, mucolytics, anti-inflammatory agents and bronchodilators is not clear, but may be considered on an individual basis.
- Bronchopulmonary hygiene physical therapy techniques are widely used, yet there is not enough evidence to support or refute them.
- Surgery may be considered if the area of the bronchiectatic lung is localised and if the patient’s symptoms are debilitating or life threatening (e.g. massive haemoptysis).
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). Particularly in patients younger than 40 years of age, CF, primary ciliary dyskinesia (PCD) and common variable immunodeficiency should be considered, and in the presence of suggestive symptoms, further work-up is indicated.

Work-up

The work-up of bronchiectasis comprises the following.

- Blood tests: C-reactive protein, white blood count and differentiation, IgG, IgM, IgA, total IgE, Aspergillus serology, and α-antitrypsin
- Consider specific antibodies at baseline, and re-assay 21 days after immunisation where screening baseline levels are low
- Specific tests to identify underlying causes or contributing conditions depending on the clinical setting
- Spirometry
- Sputum smear and cultures for bacteria, mycobacteria and fungi
- Radiography of chest and sinus; if necessary, a HRCT scan of the lung

The chest radiograph is abnormal in most patients; however, a normal chest radiograph does not exclude bronchiectasis. HRCT is 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 to allergic bronchopulmonary aspergillosis (central/perihilar), CF (upper lobes), PCD (middle lobe) and idiopathic bronchiectasis (lower lobes). Severity of bronchiectasis on HRCT images is poorly correlated with clinical indices.

Figure 1. HRCT image demonstrating the signet ring sign (arrow). Reproduced and modified from Perera et al. (2011).

Management

Management of bronchiectasis should aim for:

- 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. 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. A recent extensive guideline of the British Thoracic Society (BTS) has assessed the level of evidence for each referred paper and the grade of each recommendation (Pasteur et al., 2010).

Acute exacerbations Antibiotic treatment is the mainstay of acute exacerbations and is targeted to probable organisms (table 1) or the results of sputum culture(s). A fluoroquinolone is recommended for 7–10 days in outpatients without a history of
recurrent exacerbations or sputum cultures. Hospitalised patients may be treated with two intravenous antibiotics with efficacy for *Pseudomonas* (www.uptodate.com). Supportive management may consist of inhaled bronchodilators, systemic corticosteroids and measures to improve bronchial clearance (physical therapy, hydration and mucolytic agents).

**Prevention of exacerbations** Prolonged use of antibiotics (>4 weeks) may be considered in patients who quickly relapse (three or more times per year according to the BTS guideline) or demonstrate progressive lung function decline. Several treatment strategies have been described:

- oral antibiotic two or three times daily
- oral macrolide three times weekly
- aerosoled tobramycin, gentamycin, colistin, ceftazidime or aztreonam twice daily (aerosoled antibiotics in non-CF bronchiectasis are frequently not licensed or stopped because of side-effects)
- i.v. antibiotics, 2–3-week courses with 1–2-month intervals (www.uptodate.com)

A Cochrane review concluded that there is a small benefit in overall clinical response scores but not exacerbation rates. A recent randomised controlled trial (RCT) demonstrated that 500 mg azithromycin three times a week for 6 months significantly improved exacerbation frequency in adult non-CF bronchiectasis patients with a history of at least one exacerbation in the past year (Wong et al., 2012).

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 recombinant human DNAse (rhDNase) administered to stable non-CF bronchiectasis patients has been associated with increased exacerbation frequency and greater FEV1 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; 7% saline was superior to 0.9%. Two systematic reviews found insufficient evidence to 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 an absence of an ongoing underlying cause. Although surgery is widely used, there have been no RCTs of this. Recent studies reported that selected cases were treated successfully with lobectomy using video-assisted thoracoscopy. Inhaled fluticasone improved dyspnoea, sputum production, days without cough, β₂-agonist use and health-related quality of life. Inhaled medium-dose budesonide combined with formoterol in a single inhaler was more effective than high-dose budesonide (Martinez-Garcia et al., 2012).

**Lung function** RCTs on short- and long-acting β₂-agonists, anticholinergic therapy, oral methylxanthines, leukotriene antagonists, and oral corticosteroids were not included 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, 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.
Further reading

Cystic fibrosis

Andrew Bush and Jane C. Davies

The autosomal recessive condition CF is the most common inherited disease of white races; its 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. The nomenclature of the individual CF genes has recently been revised (table 1). 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 Phe508del (previously termed ΔF508), 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

Key points

- Adult pulmonologists need to know about CF; it is common across Europe, patients are surviving into middle age and beyond, and new diagnoses of CF are being made even in old age; as diagnosis by newborn screening becomes more widespread across Europe, it is likely that fitter CF patients will be transferred to the adult clinics, and survival will improve further.
- CF is now a true multisystem disease; to the well-known complications of chronic respiratory infection and malabsorption have been added conditions such as cirrhosis, insulin deficiency and diabetes, osteopenia, stress incontinence, and infertility.
- Furthermore, with longevity are coming new complications, including the selection of resistant microorganisms and antibiotic allergy; other organ systems will probably be affected in the aging CF population.
- Treatment of CF thus requires a dedicated multidisciplinary team, comprising physicians, specialist nurses, physiotherapists, dieticians, clinical psychologists and pharmacists.
- The increasing knowledge of the molecular pathophysiology of CF is leading the way in the development of genotype-specific therapies, which will be a paradigm for other diseases.
ENaC, possibly triggered by viral infection. Median survival for current newborns is predicted to be ~50 yrs, longer for males. In parts of Europe there are now more adult than paediatric CF patients.

Adult physicians will encounter CF patients by two routes:

1. **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.

2. **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. Around 10–15% of CF patients present in adult life (table 2). Conversely, always consider the possibility that the diagnosis of CF made in childhood is incorrect and whether a repeat diagnostic work-up should be done. The diagnosis should be considered even in people born in areas where CF newborn screening is offered. Mild cases may be missed by screening; the screening test may not have been performed or the result lost; there may have been a technical issue in the laboratory; and finally, the patient may have moved from an area where screening is not offered.

**Table 1. Old and new nomenclature of the 32 common CFTR mutations (ARMS-32 kA)**

<table>
<thead>
<tr>
<th>Old Nomenclature</th>
<th>New nomenclature</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔF508</td>
<td>p.Phe508del</td>
</tr>
<tr>
<td>ΔI507</td>
<td>p.Ile507del</td>
</tr>
<tr>
<td>V320F</td>
<td>p.Val320Phe</td>
</tr>
<tr>
<td>R117H</td>
<td>p.Arg117His</td>
</tr>
<tr>
<td>G542X</td>
<td>p.Gly542X</td>
</tr>
<tr>
<td>G551D</td>
<td>p.Gly551Asp</td>
</tr>
<tr>
<td>R553X</td>
<td>p.Arg553X</td>
</tr>
<tr>
<td>R360T</td>
<td>p.Arg360Thr</td>
</tr>
<tr>
<td>S549R</td>
<td>p.Ser549Arg</td>
</tr>
<tr>
<td>S549N</td>
<td>p.Ser549Asn</td>
</tr>
<tr>
<td>369delC</td>
<td>p.Thr1176fs</td>
</tr>
<tr>
<td>W1282X</td>
<td>p.Trp1282X</td>
</tr>
<tr>
<td>390insT</td>
<td>p.Leu1283fs</td>
</tr>
<tr>
<td>N1303K</td>
<td>p.Asn1303Lys</td>
</tr>
<tr>
<td>G85E</td>
<td>p.Gly85Glu</td>
</tr>
<tr>
<td>A455E</td>
<td>p.Ala455Glu</td>
</tr>
<tr>
<td>R347W</td>
<td>p.Arg347Trp</td>
</tr>
<tr>
<td>1078delT</td>
<td>p.Phe316fs</td>
</tr>
<tr>
<td>R347H</td>
<td>p.Arg347His</td>
</tr>
<tr>
<td>R347P</td>
<td>p.Arg347Pro</td>
</tr>
<tr>
<td>2183AA&gt;G</td>
<td>p.Lys684fs</td>
</tr>
<tr>
<td>1717-1G&gt;A</td>
<td></td>
</tr>
<tr>
<td>621+1G&gt;T</td>
<td></td>
</tr>
<tr>
<td>3849+10kbC&gt;T</td>
<td></td>
</tr>
<tr>
<td>711+1G&gt;T</td>
<td></td>
</tr>
<tr>
<td>1898+1G&gt;A</td>
<td></td>
</tr>
<tr>
<td>2789+5G&gt;A</td>
<td></td>
</tr>
<tr>
<td>R1162X</td>
<td>p.Arg1162X</td>
</tr>
<tr>
<td>3876delA</td>
<td>p.Ser1248fs</td>
</tr>
<tr>
<td>3120+1G&gt;A</td>
<td></td>
</tr>
<tr>
<td>394delTT</td>
<td>p.Leu888fs</td>
</tr>
<tr>
<td>2184delA</td>
<td>p.Lys684fs</td>
</tr>
</tbody>
</table>

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:** >1,800 variants are described and many rare ones are usually undetected in the routine clinical laboratory, so a negative genotype cannot exclude disease. Furthermore, <50 mutations are definitely accepted as disease-causing, so the presence of rare mutations should always be interpreted with caution. There is an ongoing US CF Foundation project which aims to try to clarify the significance of these rarer mutations (www.cftr2.org).
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 (CBAVD).

Management of CF
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 knowledge of CF (ENT surgeon, obstetrician, and endocrinologist) (table 3). 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 segregation of patients and the aggressive use of antibiotics; although the conventional teaching is that airway infection occurs with a relatively narrow spectrum of microorganisms, recent work based on the use of molecular techniques suggests much greater numbers of infecting organisms including anaerobes. Molecular techniques are still in the research arena and cannot be used to guide clinical decisions. 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.

Recently, the importance of CF exacerbations has been appreciated. They have more than mere nuisance value, and are termed ‘CF lung attacks’ by some. There is no uniformly accepted definition, even though time to first exacerbation is a common end-point in clinical trials. Around 25% of patients never return to their pre-exacerbation spirometry values, and frequent exacerbations are a marker of accelerated decline in lung function.

Gastrointestinal disease (table 4) 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

<table>
<thead>
<tr>
<th>Table 2. Late presentation of CF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recurrent respiratory infections</strong></td>
</tr>
<tr>
<td><strong>Atypical ‘asthma’</strong></td>
</tr>
<tr>
<td><strong>Bronchiectasis</strong></td>
</tr>
<tr>
<td><strong>Nasal polyps, severe sinusitis</strong></td>
</tr>
<tr>
<td><strong>Male infertility</strong></td>
</tr>
<tr>
<td><strong>Electrolyte disturbance</strong></td>
</tr>
<tr>
<td><strong>Atypical mycobacterial infection</strong></td>
</tr>
<tr>
<td><strong>Acute pancreatitis</strong></td>
</tr>
<tr>
<td><strong>CF liver disease</strong></td>
</tr>
<tr>
<td><strong>Cascade screening</strong></td>
</tr>
</tbody>
</table>

Such patients are usually but not invariably pancreatic sufficient. New diagnoses of CF have been made even in old age; CF diagnosis should always be considered.
### Table 3: Management of 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 milder forms of CF)</td>
<td>Pre-infection</td>
<td>Mucus clearance</td>
<td>Airway clearance techniques (physiotherapy and adjuncts)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>These include exercise and mucolytics (e.g. rhDNase, hypertonic saline, inhaled mannitol)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prevent infection</td>
<td>Segregation and cohorting to prevent cross-infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prophylactic antibiotics controversial: used against S. aureus in UK but not in USA and other parts of Europe; avoid cephalosporins</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prophylaxis against P. aeruginosa with nebulised colomycin has been trialled and is without benefit</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Influenza vaccination</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Intermittent isolation of <em>Pseudomonas aeruginosa</em></td>
<td>Eradication of infection; energetic treatment is essential</td>
<td>High doses of appropriate antibiotics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>P. aeruginosa</em> eradication protocols include both topical (nebulised) and systemic (usually oral ciprofloxacin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Eradication achieved in 80–90%; however, a recent trial has shown no additional benefit from prolonged eradication regimes</td>
</tr>
<tr>
<td></td>
<td>Chronic infection with usual organisms (<em>Pseudomonas aeruginosa</em>, eventually present in 80% of patients; <em>Staphylococcus 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 twice daily) or colomycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nebulised aztreonam lysine more expensive, but now available, and other nebulised antibiotics are in development</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Use the new, faster nebuliser devices, e.g. eFlow (PARI GmbH, Starnberg, Germany) and I-neb (Philips Respironics, Murrysville, PA, USA), or the newly available dry powder devices</td>
</tr>
<tr>
<td>Disease Stage</td>
<td>Pulmonary status</td>
<td>Aim</td>
<td>Management</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------</td>
<td>-----</td>
<td>------------</td>
</tr>
<tr>
<td>Treat infective exacerbations</td>
<td>Oral or intravenous antibiotics (some centres use regular elective courses, but no evidence to prefer this over symptomatic use)</td>
<td>Culture results usually guide choice, but no evidence that this improves outcome</td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td>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)</td>
<td>Ibuprofen not much used in most of Europe; beware synergistic nephrotoxicity with intravenous aminoglycosides</td>
<td></td>
</tr>
<tr>
<td>Azithromycin is useful, but mode of action unknown</td>
<td>Confirm diagnosis in a reference laboratory</td>
<td>Treat on an individual basis with specialist microbiological advice</td>
<td></td>
</tr>
<tr>
<td>Infection with less common organisms (Burkholderia cepacia complex, Stenotrophomonas maltophilia, Achromobacter xylosoxidans)</td>
<td>Eradication if early; suppression of bacterial load most commonly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABPA</td>
<td>Reduce allergic response Prevent bronchiectasis</td>
<td>Oral corticosteroids (long course often required), consider pulsed methyl prednisolone</td>
<td>Addition of an antifungal agent common but evidence limited</td>
</tr>
<tr>
<td>Nontuberculous mycobacterial infection</td>
<td>Eradication or suppression (Mycobacterium abscessus may be very difficult to eradicate)</td>
<td>Infection with these organisms appears to be becoming more common</td>
<td>Diagnosis and management difficult; seek specialist advice, especially for Mycobacterium abscessus infection Prolonged courses of multiple chemotherapies will be needed: ethambutol, rifampicin, azithromycin, amikacin, ciprofloxacin, moxifloxacin are among the agents used</td>
</tr>
</tbody>
</table>

Table 3. Continued
<table>
<thead>
<tr>
<th>Disease Stage</th>
<th>Pulmonary status</th>
<th>Aim</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobar or segmental</td>
<td>Re-inflation of the lung</td>
<td>Intensive physiotherapy, with rhDNase</td>
<td>Fibroptic bronchoscopy; consider endobronchial instillation of rhDNase if conventional</td>
</tr>
<tr>
<td>atelectasis</td>
<td>(may be seen at any stage of CF)</td>
<td>and hyper tonic saline as appropriate</td>
<td>management fails</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
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<td></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>
<td>Admit for intravenous antibiotics and clotting studies; bronchoscopy not useful; can consider the</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>use of tranexamic acid; Bronchial artery embolisation for ongoing bleeding; Lobectomy is a last resort</td>
</tr>
<tr>
<td>Pneumothorax (carries</td>
<td>Control air leak</td>
<td>Conservative management for trivial</td>
<td></td>
</tr>
<tr>
<td>a very bad prognosis</td>
<td>Prevent recurrence</td>
<td>pneumothoraces, otherwise tube</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>drainage</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-stage respiratory failure</td>
<td>Optimise conventional treatment</td>
<td>Oxygen therapy (no survival</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>benefit demonstrated, unlike for COPD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iatrogenic (usually</td>
<td>Novel particularly Gram-negative organisms</td>
<td>Prevention by segregation, careful</td>
<td>Seek specialist microbiological advice if treatment is contemplated</td>
</tr>
<tr>
<td>late unless acquired by cross-infection</td>
<td></td>
<td>hygiene and targeted use of antibiotics when treating conventional organisms</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

ABPA: allergic bronchopulmonary aspergillosis; rhDNase: recombinant human deoxyribonuclease.
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 BMI calculated at least 3-monthly.

Other organ system disease (table 5) 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, the effects

Table 4. Management of gastrointestinal manifestations of 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 Supplementation with enteric coated microsphere pancreatic enzymes and fat-soluble vitamins Fat absorption may be aided by alkaline environment (H₂-blockers or proton pump inhibitors) 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 Surgery if refractory symptoms</td>
</tr>
<tr>
<td>Small bowel</td>
<td>DIOS</td>
<td>Oral Gastrografin (Bracco, Princeton, NJ, USA) or Klean-Prep (Norgine, Amsterdam, the Netherlands) Review dose of, and adherence to, pancreatic enzyme replacement therapy; perform 3-day faecal fat collection Consider pro-kinetic agents Severe acute cases, relieve with colonoscopy; laparotomy a last resort</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 DIOS</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 years Ursodeoxycholic acid, taurine (seek specialist advice) Severe cases may need transplantation</td>
</tr>
<tr>
<td></td>
<td>Macronodular cirrhosis (variceal bleeding, splenomegaly, hypersplenism)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatocellular failure a late manifestation</td>
<td></td>
</tr>
</tbody>
</table>
Table 5. Treatment of other manifestations of CF in the adult

<table>
<thead>
<tr>
<th>Organ</th>
<th>Manifestation</th>
<th>Management</th>
</tr>
</thead>
</table>
| Upper airway           | Nasal polyps (can cause OSA)         | Topical steroids; long courses of antibiotics  
Surgery if medical management fails; re-operation often needed |
| Sinusitis              | Most patients have asymptomatic changes on radiography or CT scan and require no treatment  
Topical steroids and antibiotics are given initially in prolonged courses if mandated by symptoms  
Surgery if medical management fails, but results often disappointing  
Some use sinus drainage tubes and repeatedly instil antibiotics into the sinuses |
| Endocrine pancreas    | Insulin deficiency, which causes reduced lung function and nutrition before overt hyperglycaemia  
Frank diabetes; although there may be an element of peripheral insulin resistance, the main root cause is diminished insulin secretion |
|                        | Screen regularly with annual glucose tolerance test  
Increasingly, continuous glucose monitoring is used to diagnose this condition  
Have a low threshold for starting insulin, especially in females, who have a worse prognosis if they develop diabetes  
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 |
| Sweat gland            | Electrolyte depletion, often leading to acute collapse |
| Bones and joints       | Osteopenia (CFTR is expressed in bones)  
Pathological fracture  
CF arthropathy (large or small joint) |
|                        | Measure bone mineral density at least every 2 years  
Prevention: weight-bearing exercise, high dairy intake, vitamin D and K therapy  
Treat with bisphosphonates if severe  
Nonsteroidal anti-inflammatory agents, prednisolone  
Seek specialist rheumatological advice if more than mild |
| Male reproductive tract| CBAVD leading to male infertility |
| Female reproductive tract| Vaginal candidiasis |
|                        | Sperm aspiration and in vitro fertilisation  
Genetic counselling prior to procedure  
Topical antifungal agents |
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 (www.cfgenetherapy.org.uk). The age of genotype-specific therapy dawned with the use of agents such oral ataluren (PTC124) to override premature stop codons (class I mutations); the results of a large phase III trial have been reported at the US CFF meeting; significance was not reached with the primary end-point but in a planned subgroup analysis, those not receiving nebulised tobramycin, a compound which also overrides premature stop codons, did show significant improvements. More work is needed to determine the role of PTC124 in CF. Other approaches include the use of ‘correctors’ to allow misfolded protein (class II mutations) to travel to the apical cell membrane (VX-809 and VX-661, currently in early-phase trials) and ‘potentiators’ to improve activity when they reach this site. The most successful of these has been ivacaftor (Kalydeco, VX-770; Vertex, Cambridge, MA, USA), which has been shown to improve lung function significantly in patients with the commonest class III mutation, p.Gly551Asp (G551D). This agent works by increasing the probability that CFTR will be open and, therefore, may also be useful for other classes of mutations where CFTR reaches the apical membrane including other rare Class III mutations, or in conjunction with correctors for class II mutations. Alternative strategies under investigation include inhibition of ENaC and stimulation of alternative chloride channels; unfortunately, trials with the P2Y2 receptor agonist denufosol, despite showing some early promise, have recently been reported as negative. There is no doubt that we are on

Table 5. Continued

<table>
<thead>
<tr>
<th>Organ</th>
<th>Manifestation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late iatrogenic</td>
<td>Antibiotic allergy</td>
<td>Consider desensitisation in hospital</td>
</tr>
<tr>
<td></td>
<td>Chronic renal failure</td>
<td>Cause controversial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Variously related to multiple courses of intravenous aminoglycosides, so use these agents appropriately sparingly, and diabetes, so work to ensure good glycaemic control</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Vasculitis</td>
<td>Rare, usually responds to steroids, but seek specialist rheumatological advice</td>
</tr>
<tr>
<td></td>
<td>Epithelial cancer</td>
<td>Small but definite increase in risk; careful clinical surveillance mandatory</td>
</tr>
</tbody>
</table>

Table 5. Continued
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.

Further reading

- Breathing Room. Caregiver Stories. www.thebreathingroom.org
- CFTR2. www.cftr2.org
- Cystic Fibrosis Mutation Database www.genet.sickkids.on.ca/cftr.


• UK Cystic Fibrosis Gene Therapy Consortium. www.cfgenetherapy.org.uk

• United Kingdom National External Quality Assessment Service. www.ukneqas.org.uk


Work-related and occupational asthma

Eleftherios Zervas and Mina Gaga

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 as:

- occupational asthma (OA), which refers to asthma caused specifically by exposure to an agent present at the workplace; or
- work-aggravated or work-exacerbated asthma (WEA), in which pre-existing asthma is exacerbated by conditions in the work environment.

Thus, the American College of Chest Physicians consensus document and British Occupational Health Research Foundation guidelines define WRA as including OA (i.e. asthma induced by sensitiser 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. sensitiser-induced OA, characterised by a latency period between first exposure to a respiratory sensitiser at work and the development of symptoms
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 airway dysfunction syndrome.

Key points

- The burden of WRA is still very high, accounting for one in 10 cases of adult asthma, and causing morbidity, disability and high costs.
- Prevention is very important. Health officials, workplace managers and doctors must be aware of the problem, and strict measures for exposures to known sensitisers 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 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.

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 in the
workplace, similar to OA. A recent consensus definition is that ‘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 et al., 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 kDa. 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 IgE 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 the 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 nonoccupational asthma. 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 sensitiser-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
Table 1. LMW and 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 cedar)</td>
<td>Leather</td>
</tr>
<tr>
<td>Wood dust</td>
<td>Enzymes</td>
</tr>
<tr>
<td>Hairdressing products</td>
<td>Talc</td>
</tr>
<tr>
<td>Epoxy resins</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>
</tbody>
</table>


Table 2. Examples of occupations/industries with sentinel health events for sensitiser-induced OA

<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, adhesive 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 sulfate 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>Persulfates and acrylates (artificial nails)</td>
</tr>
</tbody>
</table>

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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 PC20 (the provocative concentration of histamine or methacholine causing a 20% fall in FEV1). 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 leave 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 European Union (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, biological agents and 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 prevention of deterioration is greater in workers who have no further exposure to the causative agent, have relatively normal lung function at diagnosis, and have a 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 nonoccupational asthma.

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 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.

Further reading

Acute inhalation injury may occur in the workplace, at home or in the community (e.g. as a result of fires and explosions, volcanic eruptions, industrial disasters, and accidents involving trains or vehicles transporting chemicals). Inhalation accidents may be of catastrophic proportions, as occurred with the release of methylisocyanate (MIC) 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.

### Inhalation fever

Inhalation fever is the name given to a group of nonallergic, noninfectious, influenza-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 biological 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 similar to those at the beginning of influenza. The actual exposure may or may not have been experienced as irritant to the eyes and respiratory tract. 4–8 h after 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 radiography are normal, but in more severe cases, crackles may be heard and there may be transient infiltrates on the 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 leucocytosis, with a rise in neutrophils, is a consistent finding in the first 24 h after the exposure; other blood tests should be normal, except for indicators of an inflammatory response. Broncho-alveolar lavage studies have shown pronounced and dose-dependent increases in polymorphonuclear leucocytes 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.

Water-soluble irritants, such as ammonia, sulfur dioxide, hydrochloric acid, formaldehyde and acetic acid, have good warning properties and mainly affect the upper respiratory tract, unless massive quantities have been inhaled.

Gases of intermediate water solubility, such as chlorine and hydrogen sulfide, 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 (sodium hypochlorite) with acids; mixing bleach with ammonia leads to the release of volatile and irritant chloramines (including trichloramine). Hydrogen sulfide, which is formed by the putrefaction of organic material in sewage drains, manure pits or the holds of ships, and is also a frequent contaminant in the petrochemical industry, not only causes mucosal irritation but also leads to chemical asphyxia by mechanisms that are somewhat similar to those of cyanide.

Poorly water-soluble agents, such as nitrogen dioxide, phosgene, ozone, mercury vapours and cadmium oxide fumes, are particularly hazardous because they cause little sensory irritation and are, therefore, hardly noticed; 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 (carbon monoxide and hydrogen cyanide) and irritants, and 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, and 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 then 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 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 peribronchial 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 exposure, asymptomatic persons must remain under observation for 24 h; they should not exercise, nor should they be overfilled with intravenous fluids. Oxygen treatment should be given according to $\text{S}_\text{aO}_2$.

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 an incident must accurately document the clinical condition of and all relevant data in these patients. Documentation of the damage by bronchoscopy and HRCT 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 lipoid 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 silicoproteinosis) and by other agents, such as indium tin oxide.

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 foods.

Occupational or environmental aetiologies should always be envisaged even in patients presenting with common forms of pulmonary disease, such as asthma, bronchitis, COPD, sarcoidosis or interstitial lung disease (ILD). To discover such aetiologies, a thorough environmental history must be taken in all patients. A high degree of suspicion should exist when the occurrence or presentation of the disease is unusual. This includes severe pneumonia in young, previously healthy subjects, COPD in nonsmokers, or ILD in subjects <40 years of age. Clustering of a rare disease in time or space should also lead to scrutiny. Concomitant skin disease (especially airborne dermatitis) may also point to occupational exposures. Referral to a specialist with expertise in occupational medicine may also be warranted for: patients who report previous or ongoing high exposure to mineral or organic dust, vapours or gases; patients whose work involves burning or heating metals, plastics or solvents, or recycling materials; patients using high-speed mechanical tools for drilling, polishing or crushing; and patients involved in air spraying or aerosolising paints or other agents. Attention should also be given to patients reporting recent changes in procedures, ingredients or
suppliers, and those claiming that fellow workers have similar trouble.

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.

Further reading

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 in over 30 different occupations and environments. Regardless of the causative agents or its environmental setting, the pathogenesis and clinical manifestations of the disease are similar. The hallmark of the disease is a massive lymphocytic inflammation with accumulation of activated T-lymphocytes in the lung interstitium.

Epidemiology

In a large, general population-based cohort of HP patients from the UK, the overall incidence rate was approximately 1 per 100 000 population and in Japan the summer-type HP occurs every year in approximately 1 per million population. Most other studies have focused on the risk of developing clinical disease amongst 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-years. 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 causes were 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 countries; however, it has since been described in 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.

Key points

- Hypersensitivity pneumonitis (HP) is an immunologically mediated inflammatory lung disease of the parenchyma.
- HP is induced by the inhalation of a variety of organic or inorganic antigens, and is characterised by hypersensitivity to the antigens.
- The main characteristic of HP is massive lymphocytic inflammation with accumulation of activated T-lymphocytes in the lung interstitium.
- The only treatment is to avoid exposure to the offending allergen; if the exposure ceases the symptoms usually subside rapidly, but lung function impairment may persist.
Host factors

Smoking seems to protect towards HP, although the disease has been described in a small number of smokers. The reason behind this protection might be the downregulation of the immune system by tobacco smoke and nicotine.

In animal models, 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 still is only partly understood. When Pepys (1978) found precipitating antibodies to mould antigen in many of the cases, it was believed that, for many years, the immune complexes were the basis of the lung changes. It is now believed that the disease is driven by the cellular immune response. Following inhalation of antigen, a complex formed by soluble antigens and IgG antibodies triggers the complement cascade and alveolar macrophage activations is induced resulting in an increase of macrophages. These cells secrete cytokines and chemokines that attract neutrophils in the 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 observations made 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. Radiograph 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 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 with the offending agent. In many cases it is obvious what the reason might be, for example with 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 micro-organisms 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 the six significant predictors of HP.

Diagnostic criteria of extrinsic allergic alveolitis are as follows:

- 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 pose 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.
The only treatment for allergic diseases is to avoid the exposure to the offending allergen. This can be done in many circumstances, such as when the occurrence is sporadic and not part of the daily work of the patient. However, in some cases, for example in farmers, it might be difficult to completely avoid the exposure for a range of different reasons. Under such circumstances, respiratory protection can be used to minimise the exposure as much as possible.

The effect of medical treatment on the outcome of HP has been discussed. Cortisone has been found to reduce IL-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 is derived from long-term treatment. Cortisone treatment should be given for about 2 months.

**Prognosis**

If the exposure ceases, the symptoms usually subside rapidly, but lung function

<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>Saccharopolyspora rectivirgula</td>
</tr>
<tr>
<td>Bagassosis</td>
<td>Mouldy bagasse</td>
<td>Thermoactinomyces sacchari</td>
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<tr>
<td>Mushroom worker's lung</td>
<td>Mushroom spores, mushroom compost</td>
<td>Thermophilic actinomycetes</td>
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<tr>
<td>Malt worker's lung</td>
<td>Mouldy barley</td>
<td>Aspergillus clavatus, Faenia rectivirgula</td>
</tr>
<tr>
<td>Humidifier/air-conditioner lung</td>
<td>Contaminated water reservoirs</td>
<td>Thermophilic actinomycetes</td>
</tr>
<tr>
<td>Grain handler's lung</td>
<td>Mouldy grain</td>
<td>Saccharopolyspora rectivirgula, Thermoactinomyces vulgaris</td>
</tr>
<tr>
<td>Cheese worker's lung</td>
<td>Cheese mould</td>
<td>Penicillium casei</td>
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<tr>
<td>Paprika splitter's lung</td>
<td>Paprika dust</td>
<td>Mucor stolonifer</td>
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<tr>
<td>Compost lung</td>
<td>Compost</td>
<td>Aspergillus spp.</td>
</tr>
<tr>
<td>Peat moss worker's lung</td>
<td>Peat moss</td>
<td>Monocillium spp., Penicillium citreonigrum</td>
</tr>
<tr>
<td>Suberosis</td>
<td>Mouldy cork dust</td>
<td>Penicillium frequentans</td>
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<tr>
<td>Maple bark stripper's lung</td>
<td>Mouldy wood bark</td>
<td>Cryptostroma corticale</td>
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<tr>
<td>Wood pulp worker's lung</td>
<td>Mouldy wood pulp</td>
<td>Alternaria spp.</td>
</tr>
<tr>
<td>Wood trimmer's disease</td>
<td>Mouldy wood trimmings</td>
<td>Rhizopus spp.</td>
</tr>
<tr>
<td>Japanese summer-type HP</td>
<td>Indoor air</td>
<td>Trichosporon cutaneum</td>
</tr>
<tr>
<td>Metal-grinding</td>
<td>Metalworking fluids</td>
<td>Mycobacteria</td>
</tr>
<tr>
<td>Hot tub lung</td>
<td>Mist from hot tubs</td>
<td>Mycobacteria</td>
</tr>
<tr>
<td>Bird breeder's lung</td>
<td>Pigeons, parakeets, fowl and rodents</td>
<td>Avian or animal proteins</td>
</tr>
<tr>
<td>Mollusk-shell hypersensitivity</td>
<td>Sea snail shells</td>
<td>Shell dust</td>
</tr>
<tr>
<td>Chemical worker's lung</td>
<td>Manufacture of plastics, polyurethane foam and rubber</td>
<td>Trimellitic anhydride, diisocyanate, methylene diisocyanate</td>
</tr>
</tbody>
</table>
impairment may persist for a longer period and become permanent with a restrictive pattern and decreased diffusing capacity. Repeated attacks increase the risk of a poor prognosis. It is therefore important to treat the patient as soon as possible in order to avoid more damage to the lung parenchyma in addition to that already present 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’: acute, febrile, noninfectious, flu-like, short-term reactions that can be produced by inhalation of bio-aerosols and organic dusts. 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.

**Further reading**

Pneumoconiosis

Allan F. Henderson

Pneumoconiosis is the non-neoplastic reaction of the lung to inhaled dust. Conventionally, asthma, bronchitis and emphysema are excluded from the definition, but these will be included here, where relevant.

Exposure to dusts varies greatly throughout the world, including Europe. The prevalence of pneumoconiosis differs as well, even within countries. Another confounding factor is that dust-related diseases may occur many years after exposure. For example, asbestosis may be seen years after the closure of shipyards. The practicing pneumologist is recommended to become familiar with the industrial history of their locale. Most cases of pneumoconiosis are due to occupational exposure. There are frequently issues of compensation, and the pneumologist working in industrial and post-industrial situations should become familiar with the local arrangements as well as the purely medical issues.

Asbestos

Asbestos is a collective term for a number of silicaceous minerals. The amphiboles crocidolite and amosite are no longer mined or used industrially, but the serpentine chrysotile is still produced and used extensively in Africa, South America and Asia. It is less harmful, but there is frequently contamination with amphiboles. Asbestos was used extensively in construction before its use was curtailed and it is exceedingly persistent. This leads to workers involved with renovation, demolition, etc. being at risk of exposure. This may be particularly relevant in the causation of mesothelioma in cohorts not exposed to asbestos at the time of its active importation and use.

Pleural plaques

Hyaline pleural plaques are discrete areas of thickening on the parietal pleura. They are a common manifestation of asbestos exposure. Their development is correlated with cumulative dose exposure to asbestos, but only loosely. They may be absent or profuse in similarly exposed individuals. Their diagnosis is usually an incidental radiographic finding and they are not usually seen on conventional radiology <15 years from the subject’s first exposure. However, earlier detection, particularly of small, uncalcified lesions, is possible with CT. Plaques become increasingly calcified over time.

Key Points

- Pleural plaques indicate exposure to asbestos, but rarely cause problems.
- Asbestos-related diseases (except mesothelioma) are becoming increasingly rare.
- Pleural thickening may result from unrecognised benign asbestos pleurisy.
- CWP and silicosis are much rarer now in Europe but remain significant problems worldwide.
- CWP and silicosis can both be associated with airways obstruction.
- Silicosis and asbestosis increase the risk of lung cancer.
They are generally regarded as asymptomatic but, rarely, grating pleuritic discomfort is reported. Breathlessness is usually due to other causes, but very extensive plaques may exert a cuirass effect. Some series report impaired lung function with plaques, which has been attributed to a number of explanations including subradiographic interstitial fibrosis and peripheral small airway disease.

Plaques are not pre-malignant but they are a marker of asbestos exposure, which implies an increased risk of other asbestos-related diseases. This may cause anxiety. In the UK, this is compensable in Scotland, but not in the rest of the UK.

Benign asbestos pleurisy and diffuse pleural thickening

Once considered separate entities, these conditions are part of a spectrum of inflammatory response to inhaled asbestos fibres that have traversed the lung and lodged in the pleura. Asbestos pleurisy may present as an acute illness with pain, fever and dyspnoea, and may be misdiagnosed as infective. Most, but not all, are characterised by a bloody pleural effusion. Many episodes are asymptomatic. The latency from first exposure is highly variable but may be <10 years. Some episodes may resolve with little legacy, while others progress to diffuse pleural thickening (DPT). Asymptomatic asbestos pleurisy is believed to be the precursor of other cases of DPT. Asbestos pleurisy is frequently recurrent and bilateral, leading to bilateral DPT. Unlike plaques, DPT commonly causes restricted ventilation and, hence, dyspnoea. Plaques and DPT can be difficult to distinguish. Radiologically, the costophrenic angle is obliterated in DPT; pathologically, DPT involves the visceral pleura while plaques are confined to the parietal surface.

Asbestosis

Asbestosis is sometimes erroneously used as a term to describe all types of asbestos-related disease, whereas it is properly defined as interstitial fibrosis due to asbestos. It occurs with significantly heavy exposure to asbestos, such as in shipyard laggers and joiners, not with casual contact. As asbestos use has reduced dramatically, so the incidence of asbestosis has fallen steeply. Cases are virtually confined to older males who encountered asbestos decades ago. There is controversy as to whether asbestosis progresses after removal from exposure or develops many years after exposure. Much of the interest in asbestosis is now medicolegal. The principal issue faced by pneumologists in practice is whether a case of interstitial lung disease is idiopathic pulmonary fibrosis (IPF) or asbestosis. Occupational exposure to asbestos may suggest asbestosis but a working knowledge of industrial processes is needed to assess the relevance of this. The presence of pleural plaques may be supportive but IPF can occur in such patients. Radiological features may help, as does review of progression over time, if such data are available.

The Helsinki criteria were developed in 1997 to assist with evaluating such cases. They include pathological features. A lung biopsy is rarely appropriate as the clinical management is not affected in most cases. Post mortem analysis may assist in medicolegal assessment.

There is a high incidence of lung cancer in patients with asbestosis – around 30% in some series. There is controversy as to whether asbestos exposure alone increases the risk of cancer.

Coal

Unlike asbestos, the mining and use of coal continues on a colossal scale, with >7 billion tonnes produced worldwide in 2011. There have been big changes in world demographics, with greatly reduced mining in the UK and huge production in China. Many European countries have significant coal industries. Dust control measures have been successful in reducing coal-related disease but new cases still occur. The number of miners employed in the industry has reduced, serving to reduce the numbers of exposed individuals, but the potential for problems has increased because of higher
dust levels produced by increased mechanisation of production.

Coal workers’ pneumoconiosis

Simple coal workers’ pneumoconiosis (CWP) is the accumulation of coal dust, predominantly in centrilobular macules 2–5 mm in diameter, often more in the upper zones. Despite the dramatic macroscopic appearances observed post mortem, and equally marked radiographic findings, simple CWP itself causes no symptoms or lung function abnormality. Symptoms such as dyspnoea require investigation for alternative diagnoses.

Progressive massive fibrosis (PMF) is associated with the presence of larger (>1 cm) nodules pathologically and radiologically. PMF occurs with greater dust exposure, and improved control measures have led to a marked decline in its prevalence. PMF is also associated with impaired lung function, principally restriction.

Caplan’s syndrome is the finding of large (0.5–5 cm) nodules in miners with rheumatoid arthritis. The nodules are not profuse and no effect is seen on lung function.

Chronic bronchitis and emphysema are caused by coal dust. Bronchitis is manifested by cough and sputum. Centrilobular emphysema is demonstrated post mortem in coal miners, especially when simple CWP is present. Airway obstruction due to this (and compounded by smoking) is the main cause of disability in miners with simple CWP.

Silicosi

Silicon is the second most abundant element on earth. Silica (silicon dioxide) and silicaceous compounds are ubiquitous, and are encountered in a wide variety of industrial processes including mining and quarrying, masonry and construction, and foundry work.

Dust control measures have led to a marked reduction in silicosis in developed countries, with only a few hundred cases in the UK, France and Germany. Many of these date from exposure many years ago. However, this situation is not global, with large numbers of new cases being recorded in China, making silicosis the most prevalent pneumoconiosis worldwide.

Simple silicosis, like simple CWP, causes little physiological disturbance or symptoms despite marked radiological changes, which are characterised by nodule formation with an upper zone predominance. With increased silica load comes an increased fibrotic response, which may become extensive and confluent. Hilar calcification (‘egg-shell’) is characteristic but not universal. Dyspnoea, accompanied by a dry cough is the usual symptom.

The lung function disturbance is variable. A restrictive defect is common with fibrotic disease but may be accompanied by obstruction that, in the early stages, may be the sole abnormality. Previously attributed to smoking, it is now recognised that silica causes emphysema, which may develop in the absence of nodular change.

Silicosis is associated with an increased risk of lung cancer. As with asbestos, it is currently undetermined as to whether this is due to silica per se or whether this is secondary to silicosis.

TB is a common complication in silicosis. Accelerated deterioration in a patient with silicosis should raise suspicion. In the past, diagnosis has often been difficult, but interferon-γ testing has helped. In South Africa, HIV infection has been shown to be synergistic with silicosis in increasing the incidence of TB.

Further reading

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 cardiorespiratory 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, their lungs are growing, their immune system is incomplete and defence 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 ageing and infections, as well as to pollutants. Air pollution has both short-term adverse effects (peak exposures) and long-term adverse effects, and these effects can involve the pulmonary system but also the cardiovascular system.

Air pollution is mostly produced by human activities. Other pollutants derive from natural sources, such as biological allergens (e.g. house dust mites, pets dander and moulds) and natural phenomena (e.g. volcanic activity and forest fires).

Recent research focuses on two broad sources:

- Motor vehicles and industrial plants
- Biomass fuels

Traffic-related air pollution is a growing concern in both developed and less-developed countries, and industrial smokestacks continue to be a major source of outdoor air pollution from the burning of fossil fuels throughout the world. However, the most threatened populations live in developing and poor countries, where air pollution reflects a combination of traditional and modern factors. Rapid
industrialisation, urbanisation and growth in vehicle use increase outdoor air pollution, and, at the same time, traditional indoor burning of solid fuels, such as coal and dung, is still widespread.

With this in mind and in view of the 2013 European ‘Year of Air’, the European Union is revising its main air pollution control policies, and the European Respiratory Society Environment and Health Committee has developed 10 concise principles for clean air that summarise the scientific state of the art and provide guidance.

Outdoor pollution

The most important outdoor pollutants derive from fossil fuel combustion. Primary pollutants directly emitted into the atmosphere are carbon monoxide, sulfur dioxide, nitrogen dioxide and particulates. Ozone is a secondary pollutant, mainly produced by chemical reaction of nitrogen dioxide 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 (which provides 70–75% of all energy in China) and vehicular traffic. Chinese mortality and morbidity associated with outdoor pollution are very high: >300,000 deaths and 20 million cases of respiratory illnesses annually. A more recent study raises the estimate of the death toll in China due to air pollution to 1.2 million.

Today, it is recognised that global warming will increase the effects of outdoor air pollution on health: it will lead to more heat waves, during which air pollution concentrations are also elevated, and during which hot temperatures and air pollutants act in synergy to produce more serious health effects than expected from heat or pollution alone.

The main effects of the more common outdoor pollutants are summarised in table 1. Exposure–response relationships for outdoor pollutants, especially particulates, 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 COPD or asthma. Long-term cumulative health effects of chronic exposure comprise an increase in mortality and morbidity 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 fetus if the mother is exposed to high levels during pregnancy (i.e. intrauterine growth retardation) and can increase respiratory neonatal mortality. Particulates, nitrogen dioxide and ozone are the most important pollutants today. The health effects of particulates are more serious for fine (particular matter with an aerodynamic diameter <2.5 μm (PM2.5)) and ultrafine (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 particulate air pollution in urban areas. Recently, much research has pointed out the negative effects of diesel exhaust exposure; people are exposed not only to motor vehicle exhausts but also to exhausts from other diesel engines (e.g. diesel trains and ships) and from power generators. In June 2012, the International Agency for Research on Cancer (IARC) classified diesel engine exhaust as carcinogenic to humans (Group 1), based on sufficient evidence that exposure is associated with an increased risk of lung cancer.

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

Table 1. Major outdoor/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><strong>Particulate matter</strong></td>
<td>Outdoor: Vehicular traffic, Woodstoves, Organic matter and fossil fuel combustion, Power stations/industry, Windblown dust from roadways, agriculture and construction, Bushfires/dust storms</td>
<td>Lung cancer</td>
</tr>
<tr>
<td></td>
<td>Indoor: Woodstoves, Organic matter and fossil fuel combustion for heating/cooking, ETS</td>
<td>Premature death, Mortality for cardiorespiratory diseases, Reduced lung function, Lower airways inflammation, Upper airways irritation</td>
</tr>
<tr>
<td><strong>Nitrogen dioxide</strong></td>
<td>Outdoor: Vehicular traffic, Power stations/industry</td>
<td>Exacerbation of asthma, Bronchial hyperresponsiveness, Increased susceptibility to respiratory infection</td>
</tr>
<tr>
<td></td>
<td>Indoor: Unvented gas/kerosene appliances</td>
<td>Lung tissue damage, Reduced lung function, Reduced exercise capacity, Exacerbation of asthma, Upper airway and eye irritation</td>
</tr>
<tr>
<td><strong>Ozone</strong></td>
<td>Outdoor: Sunlight chemical reaction with other pollutants, Vehicular traffic, Power stations/industry, Consumer products</td>
<td>Lung tissue damage, Reduced lung function, Reduced exercise capacity, Exacerbation of asthma, Upper airway and eye irritation</td>
</tr>
<tr>
<td><strong>Carbon monoxide</strong></td>
<td>Outdoor: Organic matter and fossil fuel combustion, Vehicular traffic, Woodstoves</td>
<td>Death/coma at very high levels, Headache, nausea, breathlessness, confusion/reduced mental alertness, Low birth weight (fetal exposure)</td>
</tr>
<tr>
<td></td>
<td>Indoor: Organic matter and fossil fuel combustion for heating/cooking, Woodstoves, Unvented gas/kerosene appliances, ETS</td>
<td>Death/coma at very high levels, Headache, nausea, breathlessness, confusion/reduced mental alertness, Low birth weight (fetal exposure)</td>
</tr>
<tr>
<td><strong>Sulfur dioxide</strong></td>
<td>Outdoor: Coal/oil-burning power stations, Industry/refineries, Diesel engines, Metal smelting</td>
<td>Exacerbation of respiratory diseases including asthma, Respiratory tract irritation</td>
</tr>
<tr>
<td><strong>VOCs</strong></td>
<td>Indoor: Building materials and products such as new furniture, solvents, paint, adhesives, insulation, Cleaning activities and products, Materials for offices</td>
<td>Lung cancer, Asthma, dizziness, respiratory and lung diseases, Chronic eye, lung or skin irritation, Neurological and reproductive disorders</td>
</tr>
</tbody>
</table>
significant associations of traffic with new-onset asthma, or asthma symptoms/exacerbations, in children.

Some recent studies confirming the association between urban air pollution and health status are described here.

- The Italian EpiAir project, performed in 10 cities on ~300,000 subjects aged ≥ 35 years, highlighted an increase in mortality from respiratory diseases of 2.29% (95% CI 1.03–3.58%) per 10-μg m⁻³ increase in PM₁₀ (lag 0–3 days); the increase in mortality was higher during summer.
- Data from the Cancer Prevention Study II cohort of the American Cancer Society showed an increase of 4% in mortality for respiratory diseases per 10-ppb increase in ozone concentration.
- Our team in Pisa, Italy, has reported that people living in an urban area are at higher risk of having increased bronchial responsiveness (OR 1.41, 95% CI 1.13–1.76) than people living in a rural area. Moreover, we showed long-term effects of the exposure to traffic air pollution: people residing near a major road (within 100 m) showed significantly higher risks (odds ratios ranging from 1.61 to 2.07) of persistent wheezing, dyspnoea, attacks of shortness of breath with wheezing, asthma, COPD, airway obstruction and atopy. Another Italian study, performed on children (aged 10–17 years) living in Palermo, Italy, confirmed the negative impact of heavy traffic exposure, showing significantly higher risks (odds ratios ranging from 1.39 to 1.84) of asthma, rhinoconjunctivitis and reduced lung function.

**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. Furthermore, 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 or school, and in workplaces). Conservative estimates attribute 1.5–2 million deaths per year to indoor air pollution. There is consistent evidence that exposure to indoor pollutants increases the risk of several respiratory/allergic symptoms and diseases (table 1). Relevant indoor pollution sources are environmental tobacco smoke (ETS), a common source of indoor particulates, biomass (wood/coal) fuel use, and mould/damp. Furthermore, within the western countries and in the societies that adopt western lifestyles, consumer products (i.e. computers, televisions, synthetic building materials, etc.) emit large quantities of volatile organic compounds (VOCs) and nonorganic compounds.

ETS is associated with increased risk of acute respiratory or irritation symptoms, infectious diseases, chronic respiratory illnesses, lung function reduction and even lung cancer. In children, ETS also increases the risk of sudden infant death syndrome, middle-ear disease, lower respiratory tract illnesses, wheeze and cough. ETS exposure exacerbates pre-existing asthma and increases symptom burden and morbidity. In nonsmokers, the mortality risk for respiratory diseases is about double for those living with smokers than for those who do not. Studies performed worldwide suggest higher risk for ETS exposure in females than in males. Table 2 shows the results of meta-analyses regarding the associations of ETS exposure with respiratory symptoms/diseases.

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. Indoor air pollution from biomass fuels is strongly poverty-related and represents an important risk factor for acute respiratory illness morbidity and mortality in low-income countries, especially in children and women. In China, indoor air pollution from solid fuel use is responsible for ~420,000 premature deaths annually, more than the nearly 300,000 attributed to urban outdoor air pollution in the country. A more recent study raises the estimate of the death toll in China due to
household air pollution to 1 million, close to the 1.2 million due to outdoor air pollution. The evidence that biomass use increases the risk of COPD in females and acute respiratory infections in children is very strong (about three-fold and more than three-fold higher risk in those exposed than in the unexposed, respectively). The IARC has classified the indoor combustion of coal emissions as Group 1, a known carcinogen to humans. There is strong evidence (moderate for males) that females exposed to smoke from coal fires in the home have an elevated risk of lung cancer (OR 1.9, 95% CI 1.1–3.5).

Based on meta-analyses, building dampness and mould are associated with approximately 30–50% increases in respiratory and asthma-related health outcomes. In children, a population attributable risk for asthma of 6.7% has been estimated. In adults, a pooled risk of cough by indoor mould/dampness was estimated at an odds ratio of 2.10 (95% CI 1.27–3.47). There is also evidence for an association of mould exposure with new-onset asthma and worsening of pre-existing asthma (wheezing, cough and shortness of breath) in both children and adults. Allergic symptoms are commonly related to mould exposure (sneezing; nose, mouth or throat irritations; nasal stuffiness or runny nose; and red, itchy or watery eyes).

Finally, exposure to VOCs may result in a spectrum of illnesses ranging from mild (irritations) to very severe effects, including cancer. Such exposure increases the risk for respiratory/allergic effects in infants/children, like asthma, wheeze, chronic bronchitis, reduced lung function, atopy and severity of sensitisation, rhinitis, and pulmonary infections. Many studies indicate that the effects are related to very low levels of exposure. VOC exposure also seems a significant risk factor for asthma (odds ratios ranging from 1.2 to 2.9). Many of the effects observed in children have been shown also in adults.

### 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

<table>
<thead>
<tr>
<th>Population</th>
<th>Estimated pooled risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower respiratory tract infection</td>
<td>OR 1.55 (95% CI 1.42–1.69)</td>
</tr>
<tr>
<td>2–6 years</td>
<td>OR 1.71 (95% CI 1.33–2.20)</td>
</tr>
<tr>
<td>Cough</td>
<td>OR 1.60 (95% CI 1.22–2.10)</td>
</tr>
<tr>
<td>Males</td>
<td>OR 1.68 (95% CI 1.17–2.34)</td>
</tr>
<tr>
<td>Females</td>
<td>OR 1.97 (95% CI 1.19–3.25)</td>
</tr>
<tr>
<td>Asthma onset</td>
<td>OR 1.32 (95% CI 1.24–1.41)</td>
</tr>
<tr>
<td>Children</td>
<td>OR 1.30 (95% CI 1.13–1.30)</td>
</tr>
<tr>
<td>Adults</td>
<td>OR 1.27 (95% CI 1.17–1.37)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>RR 1.15 (95% CI 1.03–1.28)</td>
</tr>
<tr>
<td>Adults</td>
<td>RR 1.31 (95% CI 1.16–1.48)</td>
</tr>
<tr>
<td>Females</td>
<td>RR 1.31 (95% CI 1.24–1.52)</td>
</tr>
<tr>
<td>North America</td>
<td>RR 1.31 (95% CI 1.24–1.52)</td>
</tr>
<tr>
<td>Asia</td>
<td>RR 1.31 (95% CI 1.16–1.48)</td>
</tr>
<tr>
<td>Europe</td>
<td>RR 1.31 (95% CI 1.24–1.52)</td>
</tr>
</tbody>
</table>

OR: odds ratio; RR: relative risk.
occur when the generation of oxidant molecules (free radicals) exceeds the available antioxidant defences. The consequence of this oxidative stress can be systemic or local inflammations thus involving the cardiopulmonary system.

The three pollutants of most concern that can cause oxidative stress include nitric oxide, which is a free radical, PM10, and ozone. The majority of human genetic association studies of air pollutants have examined ozone exposure. Ozone 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 particulates determine the potential to elicit oxidative damage. In general, the smaller the size of the particulates, the higher the toxicity through mechanisms of oxidative stress and inflammation. Nanoparticles (ultrafine particles with diameter <100 nm) are more toxic and inflammogenic 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 pollutant exposure may be higher in individuals who are genetically at risk for higher 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 for abating/reducing pollutant emissions is also important. Moreover, there is evidence that increased antioxidant intake may protect against the effects of air pollution. The role of the physician is essential in patient education on the preventive actions to reduce health effects due to 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, particularly of more susceptible individuals.

Further reading


Smoking-related diseases

Yves Martinet and Nathalie Wirth

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 other organs as well as of respiratory and cardiovascular diseases. In the European Union (EU), tobacco use kills ≥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 COPD. Given the relatively long period between time of smoking initiation (‘first puff’) and time of onset of smoking-related lung disease (≥10 years), young people who start smoking often disregard the 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 promotion.

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 during their lifetime (such as Swedish snus, for example) 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 >4000 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 and filter type), the health risks and effects of tobacco smoking are quite constant from one cigarette brand to another. Furthermore, previously labelled ‘low-tar’ and ‘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. However, these smokers have a

Key points

- Tobacco use is responsible for more than one in seven of all deaths in the EU.
- ~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.
high incidence of oral cancer. Nevertheless, their rate of respiratory disease is still higher than in nonsmokers.

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 if occasional users merely seek 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-year survival rates ranging from 10% to 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. Over the years, a shift has been observed from squamous cell lung cancer to adenocarcinoma. 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 the ages of 30, 40, 50 and 60 years, the risk of lung cancer by the age of 75 years was 2%, 3%, 6% and 10%, respectively; whereas for males who smoked up to 75 years 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 from lung cancer by sex in France, 1950–2006. Reproduced and modified from Hill et al. (2010) with permission from the publisher.](image)
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, European Respiratory Society), up to 60% of current smokers aged >65 years may suffer from COPD. Measurement of FEV₁ and its decline is the best marker of airflow limitation in COPD, and the 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 TB, 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 2002, an estimated 79,449 deaths were attributable to passive smoking from various diseases caused by

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**Figure 2.** Loss of FEV₁ in never-smokers, regular smokers and smokers giving up at ages 45 and 65 years. Reproduced and modified from Fletcher et al. (1977) with permission from the publisher.
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 figure 3.

Further reading


Tobacco dependence is a disease that would be of little consequence if it were not for the 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 when lung and other respiratory cancers are excluded. Smoking is linked causally or as an important risk factor for COPD, emphysema, asthma, and respiratory infections that include TB. Nevertheless, to speak of smoking as an occupational or environmental disease is perhaps not entirely accurate. However, without doubt, 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. However, second-hand smoke remains the most significant indoor pollutant, especially in homes and motorised vehicles.

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 have been incorporated in the Framework Convention for Tobacco Control (FCTC), which is the first medical treaty from the World Health Organization (WHO) that has been ratified by 176 countries and the European Community (EC). The WHO has also proposed a strategy, MPOWER as defined in table 1, for the implementation and monitoring of these mechanisms. 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 and the protection from exposure and product regulation by various means, are also important. Such tobacco control policies were recently modelled to tease out individual effects on current and future trends in tobacco consumption rates and lung cancer death rates, employing previously validated simulation models, e.g. SimSmoke models. It is also agreed that full information, concerning the dangers of smoking, need to be made common knowledge through sustained, mass-media
campaigns. The value of health warnings, especially graphical images, 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, promotion and sponsorship are banned. A step further would be to have plain packaging. 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 it is challenging. Even more challenging is the fact that the cost for other evidence-based interventions in the pursuit of tobacco control are usually much less than those for treatment. However, tobacco-dependency treatment is much more cost-effective than other chronic conditions, such as hypercholesterolaemia or hypertension, in terms of quality-adjusted life years (QALYs). Effective treatments are available, are very cost-effective and compare favourably with treatment of other diseases in this regard. Despite this, interest in supplying this service seems 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 argument for free choice 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 world’s population 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 improved and cheaper treatments can be developed to make this possible in the future. A recent controlled trial demonstrated the efficacy of a low-priced product, namely, cytosine in smoking cessation. 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 other 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. To achieve such standards, training of health professionals in the treatment of tobacco dependence is crucial.

**Table 1. Definition for MPOWER**

| Monitor tobacco use |
| Protect people from tobacco use |
| Offer help to quit tobacco use |
| Warn about the damages of tobacco |
| Enforce bans on tobacco advertising, promotion and sponsorship |
| Raise taxes on tobacco products |

Evidence-based treatments

Effective and cost-effective treatments for tobacco dependence 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 the optimal; however, these considerations need to be further defined along with their 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 the doubles success rate. Varenicline and buproprion also have established success rates. Varenicline seems to be more effective than NRT, while...
bupropion 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 knowledgeably by physicians. Tønnesen et al. (2007) recently reviewed the evidence for smoking cessation, concluding that with the most optimal drugs and counselling a 1-year abstinence rate of ~25% can be expected for smoking cessation. This compares very favourably with the treatment of any other chronic relapsing disease. Caponnetta et al. (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, e.g. alcoholism and depression. They also point out the complex relationship with previous attempts and of course the importance of motivation to quit. The motivational chart in figure 1 clearly outlines the importance of different stages of motivation before finally quitting smoking.

In addition, evidence suggests that attempts to quit are more frequent in subjects with high baseline BMI and low weight concerns. Innovative approaches, such as brief isometric exercise and the cognitive technique of body scanning, may be effective for reducing the desire to smoke and withdrawal symptoms in temporarily abstaining smokers. The importance of targeting specific groups, such as pregnant women and mentally ill patients, also lack adequate evidence in support of what works and what does not work in treating tobacco dependence.

Conclusion

The treatment of tobacco dependence benefits from the knowledge, experience and training of clinicians. This is not provided in medical schools at the undergraduate level. We expect that the structure of training for the management of this disease, and

![Diagram](image_url)
particularly its treatment, will improve and increase in the short term. Knowledge of general tobacco control principles also need to be addressed if we are to succeed in this important endeavour.

Further reading

- Currie LM, et al. (2012). The effect of tobacco control policies on smoking prevalence and smoking-attributable deaths in Ireland using the IrelandSS simulation model. Tob Control [In press DOI: 10.1136/tobaccocontrol-2011-050248].
Physiological response to altitude

The low barometric pressure at altitude results in reduced inspiratory oxygen tension and $P_{aO_2}$. 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 $P_{aCO_2}$ 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 $>1600$ 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

In table 1, different forms of acute and chronic altitude-related illness are summarised. Acute mountain sickness (AMS) is the most common altitude-related illness. It affects 10–40% of lowlanders rapidly ascending to 3000 m and 40–60% at 4500 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.

Key points

- A low barometric pressure at altitude results in reduced inspired oxygen tension and $P_{aO_2}$.
- Hypoxaemia triggers adaptive physiological responses termed acclimatisation.
- Respiratory acclimatisation includes hyperventilation and periodic breathing, which typically prevails during sleep.
- AMS, HACE and HAPE 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, if necessary, drugs.
If additional neurological signs such as ataxia, cognitive deficits and impaired vigilance develop, a 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 1500–2500 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 3500 m but occurs in 2–4% of mountaineers within hours to 4 days after arrival at 4500 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 2). Pulmonary vasodilators such as nifedipine or phosphodiesterase inhibitors (sildenafil)

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**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-year-old female resting after a climb at 6850 m. Reproduced and modified from Bloch et al. (2010) with permission from the publisher.**
lower pulmonary artery pressure. If descent is impossible and oxygen unavailable, a hyperbaric bag may be lifesaving.

Table 2 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. High-altitude pulmonary hypertension is another condition affecting long-term residents at altitude >2500 m. It causes dyspnoea, exercise intolerance and signs of right heart failure with oedema but erythrocytosis is not a feature.
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, $P_aO_2$ may drop to low levels at altitude so the use of supplemental oxygen should be considered. It is reasonable that patients with severe disease (FEV₁ < 50% predicted) with $S_aO_2$ < 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, as the metabolic acidosis induced by the drug may further stimulate ventilation thereby worsening dyspnoea and promoting respiratory failure.

**Asthma** A reduced allergen burden with increasing altitude can be expected at >1500 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 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 OSAS patients residing at sea level and travelling to moderate altitude (>1600 m) experience an exacerbation of sleep apnoea with pronounced hypoxaemia and frequent central events. Sleep quality is worse at altitude and daytime testing shows impaired vigilance and elevated blood pressure. Combined treatment with CPAP and acetazolamide is 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.

Further reading

There are three main groups at risk of diving-related diseases:

- 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 figure 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 an oxygen fraction of 2–5% at depths of ≥100 m.

Physical work under water is demanding. It requires evaluation of normal ventilatory capacity and physical work capacity by exercise testing. 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 the 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.

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 diver’s career may preclude further 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 of lung rupture or pulmonary barotrauma. Any processes in the lung associated with airway obstruction or 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 (\(200\) cmH\(_2\)O). 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 deepest 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 the 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 \textit{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 FEV1.

Treatment of diving related disease and hyperbaric oxygen therapy

Arterial gas embolism and decompression sickness, which are caused by free gas in the tissues, should be treated promptly with recompression and hyperbaric oxygen. The rationale is to reduce bubble radius by increasing ambient pressure and to facilitate diffusion of inert gas out of the bubbles by increasing oxygen tension. The US Navy Treatment Tables are the most commonly used reference. Normobaric oxygen therapy by tight fitting an oronasal mask should always be started immediately and be given during transport to a hyperbaric treatment facility. Restoration of fluid balance is important while other supportive therapy is questionable.

The oxygen exposure during treatment is relatively large and oxygen toxicity with an acute reduction in vital capacity of 10% is acceptable. This is because neurological deficits are the most common manifestations of decompression sickness and the reduction in vital capacity is largely reversible.

Hyperbaric oxygen therapy, most commonly given for 90 min daily at a pressure of 240 kPa for 20–30 days, may be beneficial for late side-effects of radiation therapy for cancer, chronic ischaemic ulcers and chronic osteomyelitis. The oxygen dose is lower than for treatment of decompression sickness but there may be a cumulative oxygen toxicity effect. These patients’ lung function should always be evaluated, as lung disease may pose a risk for arterial gas embolism in these patients. Pulmonary radiation injury is a contraindication to hyperbaric oxygen therapy.

Further reading

Radiation-induced lung disease

Robert P. Coppes and Peter van Luijk

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 present set dose (e.g. mean dose <20 Gy) already results in pulmonary complications in about one-fifth of patients.

The primary insults after radiation of the lungs seem to be vascular remodelling and an early inflammatory response termed radiation pneumonitis. These are followed by a late fibroproductive phase (fig. 1). All these pathologies may lead to compromised lung perfusion, increased vascular resistance, reduced gas-exchange interphase between the air and blood, and suboptimal blood oxygenation. Symptoms range from dyspnoea on effort to respiratory failure, oxygen dependency, right heart failure and death.

Almost immediately after irradiation, loss of endothelial cells causes vascular oedema and remodelling. This leads to pulmonary hypertension and right ventricle hypertrophy. Next to this, several inflammatory responses contribute to radiation pneumonitis. Acute alveolar and interstitial inflammation and loss of type I epithelial cells induce 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, such as leukocytes, lymphocytes, neutrophils and macrophages, is induced. Though macrophages are a hallmark, T-lymphocytes and mature dendritic cells also play an important role in radiation pneumonitis.

Radiation-induced lung disease is a consequence of:

- loss of endothelial and type I epithelial cells
- malfunction of microvasculature
- inflammatory responses
- lung fibrosis

Increased vascular permeability with protein exudation contributes to the development of radiation pneumonitis. Depending on the irradiated region and volume, the damaged pulmonary blood vessels (low dose and large volumes) or inflammatory parenchymal damage (high dose and low volumes) affect lung function to induce complications.

Following or even without prior symptomatic pneumonitis, chronic radiation-induced pulmonary fibrosis may develop depending on the irradiated lung volume. Radiation fibrosis is caused by accumulation of collagen and other extracellular matrix fibres in the interstitium under persistent cytokine stimuli in combination with arteriocapillary sclerosis.

Key points

- Radiotherapy for tumour treatment results in pulmonary complications in about 20% of patients.
- Radiation-induced lung injury involves vascular damage leading to pulmonary hypertension and develops from an early, inflammatory phase to a late fibrotic phase.
It should be noted that there are other causes of occupational-induced radiation lung disease, for example, resulting from nuclear accidents, and radon and uranium exposure (see Further Reading).

**Further reading**

The term interstitial lung disease (ILD) refers to a heterogeneous group of >200 different entities. Because the clinical presentation of most of them is similar (mostly, exertional dyspnoea and dry cough) chest HRCT, a CT technique optimised for high spatial resolution, plays a key role in the assessment of patients who are known to have, or are suspected of having, diffuse lung disease. The study of the HRCT appearance and distribution patterns allows a specific diagnosis to be made in many cases or, at least, is helpful in narrowing the differential diagnosis. For this reason, HRCT has become the imaging modality of choice in ILD. The importance of HRCT is further underlined by the fact that there is no single gold-standard diagnostic test for ILD; instead, a multidisciplinary approach, with integration of radiological, pathologic and clinical data, is considered the optimal approach.

Anatomy of the lung interstitium

Understanding of HRCT patterns of ILD requires knowledge of the anatomy of the normal lung. In the high-contrast environment of the lung, the resolution of HRCT is 0.2–0.3 mm. According to Weibel’s concept, the interstitium represents the supporting framework of the lung and is composed of connective tissue fibres that can be divided into two separate, but connected, compartments:

1. the central (or axial) compartment that surrounds the bronchovascular bundles, as they emerge from the pulmonary hila and extend peripherally to the level of respiratory bronchioles
2. the peripheral (or septal) interstitium that includes the interlobular septa and the subpleural interstitium

These two compartments are connected to each other by a fine network of septal connective tissue fibres (the intralobular interstitium).

Interlobular septa can occasionally be visible on HRCT of the normal lung, especially in the periphery of the anterior, lateral, juxta mediastinal regions of the upper and middle lobes, and in the periphery of the anterior and diaphragmatic regions of the lower zones.

The smallest anatomical unit of the lung visible on HRCT is the secondary pulmonary lobule (Miller’s lobule), which is the

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**Key points**

- Interstitial lung diseases are a heterogeneous group of entities with similar clinical presentations.
- A pattern-based approach to HRCT can help to discriminate between diseases with similar presentations, making a specific diagnosis in many cases or, at least, narrowing the differential diagnosis.
- In controversial cases, surgical biopsy might be necessary and a multidisciplinary approach (integrating clinical presentation and laboratory data, chest imaging, and lung pathology) is considered the best approach to formulate a confident diagnosis.
smallest area of lung parenchyma surrounded by connective tissue septa. Secondary pulmonary lobules are irregular polyhedral structures measuring 1.0–2.5 cm in diameter, containing roughly three to five acini and 30–50 primary lobules. Interlobular septa extend perpendicularly from the peripheral interstitium and penetrate the lung to form the boundaries of each secondary lobule. Secondary lobules are clearly demarcated in the periphery of the lung where interlobular septa are thicker, but are poorly demarcated centrally where interlobular septa are thinner and less well defined. Each lobule is supplied at its centre by a bronchiole and pulmonary artery.

Normal lung structures visible on HRCT are bronchi (down to eight generations), pulmonary arteries, pulmonary veins, interlobular septa and the visceral pleura (double layer as lobar fissures). Under normal conditions, structures such as lymphatic vessels, alveoli/acinai, capillary vessels and visceral pleura (non-fissural surface) are not visible on HRCT. The centrilobular artery (1 mm in diameter) and the intralobular acinar arteries (0.5 mm in diameter) are identifiable, whereas normal bronchioles supplying a secondary lobule (1 mm in diameter), with a wall thickness of ~0.15 mm, are beyond the resolution of HRCT.

Increased attenuation

Reticular pattern has several morphological variations, ranging from generalised thickening of the interlobular septa to honeycomb lung. The thickening of interlobular and intralobular septa, thus creating a net-like pattern, can generate this. On HRCT, this pattern is most frequently seen in the periphery extending from and perpendicular to the pleura. Septa can be classified as:

- smooth, where all interstitial compartments are thickened with a smooth profile (e.g. pulmonary hydrostatic oedema, lymphangitic carcinomatosis, pulmonary haemorrhage, pulmonary alveolar proteinosis, amyloidosis and a number of rarer conditions)
- irregular (e.g. fibrosis, lymphoma or secondary solid tumour)
- nodular, where the interstitial compartments are thickened in nodular form (‘beaded appearance’) (e.g. lymphangitic carcinomatosis, a NSIP may proceed from minimal changes to end-stage lung). Moreover, the same pattern may be present in several diseases (e.g. collagen vascular disorders). This is intuitive, as the lung can respond to injury in a limited and predictable mode, so that many different diseases may lead to similar alterations in pulmonary anatomy, resulting in overlapping imaging findings. These aspects underscore the need for a multidisciplinary approach (clinical presentation and laboratory data, chest imaging, and lung pathology) to formulate a confident diagnosis. Nowadays, the importance of this approach is widely recognised.

Lung parenchymal abnormalities can be grossly divided into those with increased or decreased attenuation (table 1). As a general rule, lung volumes are increased by processes that produce decreased attenuation (e.g. air trapping and emphysema) and decreased by processes that produce reticulation and honeycombing.

Approach to HRCT

In ILD, the identification of basic HRCT patterns plays a critical role at the beginning of the diagnostic assessment. In fact, the pattern and distribution of the HRCT lung appearance may suggest a specific diagnosis and can help to discriminate among diseases with similar morphology. The same disease may present with different HRCT patterns. This may result from its variable pathological expression (e.g. progressive systemic sclerosis with lung involvement may present with a usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP) or organising pneumonia pattern), from its temporal phase (e.g. hypersensitivity pneumonitis may be detected in its acute, subacute or chronic stage) or from its natural progression (e.g.
The end-stage fibrotic lung is characterised by a coarse reticular pattern reflecting advanced interstitial fibrosis and architecture destruction, and is commonly associated with honeycombing (e.g. UIP, asbestosis, collagen vascular disease and radiation-induced fibrosis).

Ground-glass pattern

Ground-glass opacities (GGOs) appear as hazy areas of increased opacity of the lung that are not dense enough to hide the underlying bronchial and vascular structures. It can result from alveolar filling with fluid, serum or amorphous material. The ground-glass appearance of interstitial fibrosis beyond the normal resolution of the scan obtained. A GGO pattern can be observed in a large number of ILDs, such as:

<table>
<thead>
<tr>
<th>Increased attenuation</th>
<th>Consolidation</th>
<th>Nodular</th>
<th>Consolidation</th>
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<tbody>
<tr>
<td>Reticular</td>
<td>GGO</td>
<td>Centrilobular</td>
<td>Paralymphatic</td>
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<tr>
<td>LC</td>
<td>NSIP, AIP</td>
<td>COP, LCH</td>
<td>RB-ILD, Silicosis</td>
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<td>HP</td>
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<tr>
<td>Chronic HP</td>
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<td>Sarcoidosis</td>
<td>RB-ILD</td>
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<td>Drugs</td>
<td>LIP</td>
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<tr>
<td>UIP</td>
<td>COP</td>
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<td>NSIP</td>
<td>Acute/subacute HP</td>
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<tr>
<td>CVD</td>
<td>Acute exacerbation of ILD</td>
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<table>
<thead>
<tr>
<th>Decreased attenuation</th>
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<tbody>
<tr>
<td>Centrilobular</td>
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<tr>
<td>Paralymphatic</td>
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<td>Random</td>
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<td>Cystic</td>
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<td>Honeycombing</td>
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<td>LCH</td>
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<td>UIP/IPF</td>
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<td>Fibrotic NSIP</td>
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<td>Drugs</td>
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<td>Sarcoïdosis</td>
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<td>Miliary TB</td>
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<td>Miliary fungal infection</td>
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<td>Emphysema</td>
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<td>Chronic HP</td>
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| L: lymphangitic carcinomatosis; HP: hypersensitivity pneumonitis; CVD: collagen vascular disease. |
present. This situation typically results from filling of the airspaces with fluid (e.g. oedema, blood or pus). Consolidation is a common finding; the following conditions may all manifest with consolidation:

- organising pneumonia
- chronic eosinophilic pneumonia
- lipoid pneumonia
- bronchoalveolar carcinoma (BAC)
- lymphoma

**Nodular pattern** is characterised by the presence of multiple airspace or interstitial nodules, well or poorly defined, varying in size (up to 3 cm in diameter), with or without presence of cavitation. Low-density nodules with ill-defined margins (nodular GG) may be difficult to recognise. They are commonly seen in patients with diseases primarily affecting the small airways and surrounding areas. High-density nodules with well-defined margins have a solid aspect and obscure the edges of vessels or other adjacent structures. They are more characteristic of diseases primarily affecting the interstitium. The nodular pattern may be classified as:

- centrilobular
- perilymphatic
- random

based on the relationship with the secondary pulmonary lobule. The distribution of the nodules depends on the route of arrival and on the modality of spread. Diseases caused by inhalation show nodules close to the bronchiole in the centre of lobules (centrilobular), while diseases that grow along the lymphatics are more present in the periphery of the lobules and along the fissures (lymphatic). The lesions that spread haematogenously are visible everywhere (random), sometimes in connection with blood vessels.

Centrilobular nodules can be hazy or sharply defined. HRCT features that can help in their discrimination are the distinct central location in the secondary pulmonary lobule, the respect to one another, and the fact that they appear separated by several millimetres from the pleural surfaces, fissures and interlobular septa. Ranging in size from a few millimetres to a centimetre, centrilobular nodules are usually ill defined. They can be further subcategorised on the basis of the presence of an associated ‘tree in bud’ pattern (e.g. centrilobular nodules with a Y-shaped configuration often caused by infection or aspiration). Centrilobular nodules are observed in subacute hypersensitivity pneumonitis, in RB-ILD, and less commonly in pneumoconiosis, pulmonary Langerhans’ cell histiocytosis (LCH), LIP and COP.

A perilymphatic distribution of nodules is commonly seen in patients with sarcoidosis, lymphangitic carcinomatosis, LIP and pneumoconiosis. Perilymphatic nodules are subpleural in location but may also be found along interlobular septa, interlobar fissures and bronchovascular bundles, where the lymphatics are most concentrated. Typically, they show a patchy distribution. However, in some patients with perilymphatic nodular disease, nodules can also be found in the centrilobular areas, in association with nodules more typically distributed in subpleural regions and along the interlobular septa (sarcoidosis and lymphangitic carcinomatosis).

Randomly distributed nodules are found diffusely throughout the lung parenchyma without a predominant distribution within either the secondary pulmonary lobules or the lymphatics. They may also be seen at the termination of small pulmonary arterial vessels (feeding-vessel sign). This distribution is typical of haematogenous dissemination (e.g. miliary TB, haematogenous metastasis and miliary fungal disease).

**Decreased attenuation**

**Cystic pattern** A cyst appears as a round parenchymal lucency or low-attenuating area with a well-defined interface with the normal lung. Cysts have variable wall thickness but usually display an epithelial or fibrous, thin wall (2 mm). The presence of a definable wall and the absence of residual centrilobular artery differentiate cysts from centrilobular emphysema. Cysts in the lung
usually contain air but occasionally contain fluid or solid material. The shape of the cysts depends on the mechanism of their formation, the relationship with each other and the concomitance of traction phenomena in the surrounding parenchyma. These ‘holes in the lung’ may be due to dilation of bronchial structures, abnormal distension of alveolar spaces, focal destruction of lung parenchyma or cavitation of solid lesions. The profusion of the cysts may be variable, from scattered to very numerous. The craniocaudal distribution of the lesions may help in the differential diagnosis of LCH, which usually spares the costophrenic angle while lymphangioleiomyomatosis (LAM) cysts are distributed throughout the lung. A cystic pattern can also be indicative of LIP, DIP and more rare conditions.

Honeycombing consists of cystic airspaces with thick, clearly definable walls lined with bronchiolar epithelium, predominantly in the basal and subpleural areas; the cystic spaces are typically layered along pleural surfaces, in one or more concentric layers. The cyst walls are generally 3–10 mm thick and have a uniform size. Honeycombing represents areas of destroyed and fibrotic lung tissue on histology, where the normal architecture has been lost. Frequently, they are associated with coarse reticulation, architectural distortion and traction bronchiectasis; as such, honeycombing is usually seen in patients with end-stage fibrosis. Diseases that may present with honeycombing include idiopathic pulmonary fibrosis (IPF), fibrotic NSIP, chronic hypersensitivity pneumonitis, sarcoidosis (fibrotic stages) and collagen vascular disease. A subpleural bibasilar honeycombing on HRCT has a high positive predictive value for the histologic diagnosis of UIP.

HRCT features of the most common ILD

**Idiopathic interstitial pneumonias (IIPs)** are a heterogeneous group of non-neoplastic lung diseases in which the lung parenchyma is damaged by varying patterns of inflammation and/or fibrosis. The American Thoracic Society/European Respiratory Society classification of IIPs, published in 2002 (and currently under revision), defines the morphological patterns on which clinical, radiological and pathological diagnosis of IIPs is based. IIPs include seven entities:

1. IPF, which is characterised by the morphologic pattern of UIP
2. NSIP
3. COP
4. RB-ILD
5. DIP
6. LIP
7. AIP

HRCT has gained an important role in the diagnosis and management of patients with IIP, particularly in distinguishing between UIP and NSIP, the two largest subsets of IIPs.

The typical UIP pattern on HRCT can be found in 50–70% of the biopsy-proven cases. When present, it allows a noninvasive diagnosis to be made with high accuracy, confidence and interobserver agreement. In all of the other IIPs, a confident diagnosis requires biopsy.

**Specific diseases**

**Idiopathic pulmonary fibrosis** The term IPF refers to a distinct type of chronic fibrosing pneumonia of unknown cause. It is the most common of the IIPs, accounting for about 50–60% of IIP cases. The prognosis is usually dismal, with a median survival time of 2–4 years from diagnosis.

On chest HRCT, IPF is characterised by the UIP pattern, which is predominantly subpleural with an apical–basal gradient (fig. 1). Specific findings of UIP pattern include honeycombing, peripheral reticular opacities that determine irregular interfaces between the lung and pleura, intralobular interstitial thickening with minimal GGO abnormality, traction bronchiectasis and bronchiolectasis. Lower lobe volume loss is also a common finding. In typical IPF, areas of increased density (GGO) are absent or of limited extension. When GGO is present in IPF, it usually evolves to fibrosis. If the areas of GGO exceed 30% of lung volume, alternative diagnostic hypotheses should be
considered, such as NSIP, DIP, COP, hypersensitivity pneumonitis or RB-ILD. Honeycombing can mimic the bullae of emphysema. The association of centrilobular and paraseptal emphysema with lung fibrosis, however, can be observed in heavy smokers. Honeycombing pattern is present in 80–90% of patients with UIP and is considered the strongest predictor of the diagnosis of IPF, even if it can be present in pulmonary fibrosis of other causes. As such, a definite UIP pattern on HRCT, in a patient without clinical evidence of an alternative diagnosis, is sufficient for a confident diagnosis of IPF and carries an accuracy of 80–90%. A UIP pattern can, however, occasionally have other causes, including collagen vascular diseases, chronic hypersensitivity pneumonitis, drugs (e.g. bleomycin and amiodarone) and asbestosis. In such cases, a histological confirmation of the diagnosis is required.

Nonspecific interstitial pneumonia is a pathological term used to describe interstitial inflammation and fibrosis with temporal and spatial uniformity that does not fulfill the clinical–pathological criteria of UIP, DIP or AIP. NSIP can be observed in a number of conditions, such as collagen vascular diseases, inhalation of organic/inorganic antigens, hypersensitivity pneumonitis, drug toxicity or slowly resolving acute lung injury. When no associated process can be found in a patient with a histological and radiological pattern of NSIP, the diagnosis of idiopathic NSIP is established. On HRCT, the disease is usually distributed bilaterally with basal and peripheral predominance (fig. 2). The most common feature is diffuse GGO, occurring in up to 80% of cases. GGO can be the only visible abnormality in ~30% of cases, or can be associated with peripheral irregular linear or reticular opacities in ~50% of cases. Consolidation occurs in 20% of patients. Traction bronchiectasis and micronodules can also be present. Subpleural sparing, if...
present, is a highly specific feature of NSIP. Honeycombing, a rare finding, which, if present, is usually mild compared with UIP, is only seen in patients with the fibrotic variant of NSIP. Differentiation between fibrotic NSIP and UIP requires surgical lung biopsy. At present, there is no single feature or combination of HRCT features that have high specificity for a histological diagnosis of NSIP. In fact, features of UIP and organising pneumonia may overlap with fibrotic and cellular NSIP, respectively.

**Cryptogenic organising pneumonia**
Organising pneumonia is often secondary to a known cause such as collagen vascular disease, viral pneumonia or drug reactions. The term COP, which refers to idiopathic organising pneumonia, better defines the disease previously known as bronchiolitis obliterans with organising pneumonia (BOOP), as the main abnormality is the organising pneumonia whereas the bronchiolar obstruction may be absent in up to one-third of the cases. HRCT features of COP are represented by multiple areas of consolidations, which are commonly bilateral, patchy and asymmetric, peripheral, and migrating (in up to 90% of cases) with or without GGOs (fig. 3). The lower lung zones are more frequently affected. Other HRCT findings include small centrilobular nodules, irregular lines, and the ‘atoll sign’ or ‘reversed halo sign’ representing peripheral consolidation with inner GGO. A perilobular pattern of increased attenuation has also been described in COP, which can resemble and be confused with interlobular septal thickening. The lung volumes are generally preserved. COP tends to preferentially involve the subpleural and bronchovascular regions of the lung parenchyma. Bronchial dilatation and air bronchogram associated with regions of consolidation can also be present. The imaging findings in these cases can often be mistaken for pneumonic consolidation. However, the foci of consolidation generally involve the lower lung zones and have a tendency to migrate, especially in the case of relapses, reported in one-third of cases. Few cases progress to irreversible fibrosis, probably representing the overlap between organising pneumonia and NSIP. Radiological presentation is not pathognomonic but, in the appropriate clinical setting, it allows one to suspect the correct diagnosis. HRCT may also be helpful in identifying a suitable site for biopsy.

**Respiratory bronchiolitis-associated ILD**
Respiratory bronchiolitis is part of the spectrum of smoking-related lung diseases. It is a distinct histopathological lesion found in the lungs of virtually all cigarette smokers. It usually represents an incidental finding and, as such, is of little clinical significance. Much less often, patients who are heavy smokers develop RB-ILD, a clinical–pathological entity characterised by pulmonary symptoms, abnormal pulmonary function test (PFT) results and imaging abnormalities, with respiratory bronchiolitis being the histological lesion on surgical lung biopsy. It is possible that RB-ILD and DIP are similar processes but at the opposite ends of the disease spectrum. The most common HRCT findings are centrilobular nodules, patchy GGO and thickening of the bronchial walls, which predominate in the upper lobes. The GGO abnormality of RB-ILD has been shown to represent areas of macrophage accumulation in the distal airspaces. Upper lobe emphysema is also commonly present as a result of smoking. Air trapping is frequently seen in expiratory expiration.

![Figure 3. COP. Axial HRCT scan shows multiple bilateral areas of peripheral consolidation with air bronchogram and GGO in the lower lobes.](image)
scans. A small percentage of patients have a reticular pattern in the absence of honeycombing and traction bronchiectasis. The differential diagnosis of RB-ILD includes acute hypersensitivity pneumonitis, DIP and NSIP. An important finding that may help to distinguish RB-ILD from DIP is the presence of centrilobular nodules and unusual presence of cystic formations in RB-ILD.

**Desquamative interstitial pneumonia** is a rare form of ILD. DIP is strongly associated with cigarette smoking and is considered to represent the end of a spectrum of RB-ILD. Though rarely, DIP may also occur in nonsmokers and has been related to a variety of conditions, including lung infections, exposure to organic dust and marijuana smoke inhalation. For the majority of patients, the onset of symptoms is between 30 and 40 years of age. Males are affected about twice as commonly as females. With smoking cessation and corticosteroid therapy, the prognosis is good. On HRCT, DIP is characterised by diffuse or patchy GGOs, which is caused by diffuse macrophage infiltration of the alveoli, and thickening of alveolar septa with peripheral and basal lung predominance (fig. 4). Other frequent CT findings include spatially limited irregular linear opacities, also concentrated in the peripheral and basal lung zones, and small (<2 cm) thin-walled cystic spaces, which are indicative of fibrotic changes. Despite differences in the CT appearance, imaging findings of RB-ILD and DIP may overlap and be indistinguishable from each other. Lung biopsy is required for a definite diagnosis.

**Lymphoid interstitial pneumonia** can be idiopathic, exceedingly rare, or secondary to systemic disorders, in particular Sjögren’s syndrome, HIV infection and variable immunodeficiency syndromes. LIP is more common in females than in males, and patients are usually in their fifth decade of life at presentation. HRCT shows bilateral abnormalities that are diffuse or have lower lung predominance. The dominant HRCT feature in patients with LIP is GGO attenuation, which is related to the histological evidence of diffuse interstitial inflammation (fig. 5). Another frequent finding is thin-walled perivascular cysts. They are the only finding that may be irreversible. In contrast to the subpleural, lower lung cystic changes in UIP, the cysts of LIP are usually within the lung parenchyma throughout the mid-lung zones and presumably result from air trapping due to peribronchiolar cellular infiltration. In combination with GGO, these cysts are highly suggestive of LIP. Occasionally,
centrilobular nodules and septal thickening are seen.

**Acute interstitial pneumonia** is acute respiratory distress syndrome (ARDS) of unknown cause. The HRCT features of AIP include GGO abnormalities, traction bronchiectasis and architectural distortion. The disease commonly has a symmetric, bilateral distribution with lower lobe predominance. The costophrenic angles are often spared. In the early phase of AIP, prevalent patchy GGOs are the dominant CT features and reflect the presence of alveolar septal oedema and hyaline membranes. Areas of consolidation are also present but usually they are less extensive and limited to the dependent area of the lung (fig. 6). In the early phase, airspace consolidation results from intra-alveolar oedema and haemorrhage. However, consolidations are also present in the fibrotic phase, thus resulting from intra-alveolar fibrosis. In the late phase of AIP, architectural distortion, traction bronchiectasis within areas of GGO consolidation and honeycombing are the most striking CT features and represent fibrotic change. They are more severe in the nondependent areas of the lung. This can be explained by the ‘protective’ effect of atelectasis and consolidation on the dependent areas of the lung during the acute phase of disease, which attenuate the potential damage associated with mechanical ventilation.

Although a considerable overlap of HRCT findings exists between AIP and ARDS, the presence of symmetric lower lobe abnormalities with honeycombing may be more suggestive of AIP.

**Other diseases**

**Hypersensitivity pneumonitis** is an immunologically induced inflammatory disease involving the lung parenchyma and terminal airways secondary to repeated inhalation of a variety of organic dusts and other agents in a sensitised host. Classically, it can be separated into three phases:

1. acute
2. subacute
3. chronic

depending on the temporality relative to initial exposure. A significant clinical and radiological overlap can often occur between these phases. Acute hypersensitivity pneumonitis presents within a few hours of substantial antigen exposure. HRCT scans, rarely obtained at this stage, demonstrate diffuse or patchy GGO with a geographic distribution, and mosaic perfusion areas due to air trapping (better or only recognised on expiratory scans). Subacute hypersensitivity pneumonitis occurs in response to intermittent or low-dose antigen exposure. HRCT is particularly helpful at this stage of diseases and is characterised by varying proportions of GG, poorly defined centrilobular nodules and areas of decreased attenuation, due to constrictive bronchiolitis with expiratory air trapping (fig. 7). The GGO pattern is general symmetric and diffuse but can be asymmetric. In some cases, reticulation and bronchiectasis may coexist, and may resemble NSIP. Chronic hypersensitivity pneumonitis occurs after long-term, low-dose antigen exposure and usually shows a fibrotic pattern resembling UIP or fibrotic NSIP. HRCT findings include irregular reticular opacities, small nodules, honeycombing and traction bronchiectasis.

Figure 6. AIP. Axial HRCT image from contrast-enhanced chest CT shows diffuse GGO and reticulation associated with dorsal bilateral consolidations, with relative sparing of the anterior segments.
as well as areas of air trapping and spared lobules, with a heterogeneous appearance, called the ‘head cheese sign’. The finding of small centrilobular nodules and the predominant mid-lung zones distribution on HRCT images, with sparing of the bases, help distinguish chronic hypersensitivity pneumonitis from IPF and fibrotic NSIP, which tend to affect more severely the lung bases. Open-lung biopsy is required to make a definite diagnosis in borderline cases.

Sarcoidosis is a systemic disorder of unknown cause characterised histologically by the presence of noncaseating granulomata in affected organs. Thoracic manifestations, the most common cause of morbidity and mortality, occur in 90% of the patients and 20% of them develop chronic fibrotic lung diseases. The classic presentation consists of enlarged hilar and mediastinal lymph nodes, with or without parenchymal involvement. Frequently, the diagnosis is suspected following chest radiography. The radiographic disease staging is as follows:

- Stage 0: no demonstrable abnormality
- Stage I: bilateral hilar lymphadenopathy (BHL) alone
- Stage II: BHL with lung infiltrates
- Stage III: pulmonary infiltrates without BHL
- Stage IV: lung fibrosis

Intrathoracic lymphadenopathy is present in up to 85% of patients at some point during the course of their disease. Hilar and mediastinal lymphadenopathy is better defined on HRCT, which can also allow a more detailed analysis of the nodal calcifications. Sarcoidosis can mimic a number of other diseases. As such, besides a typical manifestation, there may be several less common presentations. The disease preferentially involves the upper lung zones, although in advanced stages, it may display a diffuse distribution. The most common features are multiple nodular opacities with a typical perilymphatic distribution, which correlate with sites of granulomatous inflammation on histology (fig. 8). Nodules are clustered along the bronchovascular bundles, interlobar septa, interlobar fissures, adjacent to the costal pleural (often mimicking pleural plaques) and in the centrilobular regions. Nodules tend to predominate in perihilar and dorsal regions with relative sparing of the lung periphery. Nodules of sarcoidosis typically measure 1–5 mm but, rarely, multiple ill-defined large nodules (ranging in diameter from 1 to 4 cm) can be observed. In addition, multiple
coalescent nodules and peripheral ground-glass halos may be seen on HRCT. Occasionally, innumerable small satellite nodules may be adjacent to the large nodules, a finding termed the ‘galaxy sign’. In ~10% of patients, a confluence of granulomata may cause a compression of the alveoli and result in poorly defined bilateral parenchymal consolidations with air bronchogram; both parenchymal consolidations and large nodules may also cavitate. Furthermore, innumerable small interstitial granulomas (beyond the resolution of CT) may cause patchy GGOs on HRCT. The parenchymal abnormalities described here are still reversible and often resolve spontaneously, but they may evolve toward pulmonary fibrosis (in 20–25% of cases), which is characterised by linear opacities (radiating laterally from the hilum), fissure displacement, bronchiectasis and honeycombing limited to the upper lung zones, mainly in the dorsal regions. Expiratory CT images can show focal air trapping at any stage of the disease.

Conclusion

The term ILD refers to a large group of entities characterised by radiological findings that often overlap. Chest HRCT is the most important imaging method for the assessment of ILD owing to its sensitivity and specificity. In addition, it plays an important role in the management of specific problems, such as assessment of disease activity and potential reversibility, prediction and evaluation of response to therapy, choice of the most suitable site for lung biopsy, and follow-up. Pulmonologists have to know the basic HRCT patterns of ILD and their distribution because this can help to either make a diagnosis or narrowing the differential diagnosis.

Further reading

Sarcoidosis

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 aetiological 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 BTNL2 (butyrophilin-like 2) 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, being present in ≤70% of patients when carefully sought. According to

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.
- The decision to treat should be carefully assessed based on the 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.
their initial presentation, sarcoidosis patients can be divided into two distinct subgroups: acute and chronic. The acute form can present as classical Löfgren’s 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, European Respiratory Society and the World Association of Sarcoidosis and Other Granulomatous Disorders for the diagnosis of sarcoidosis include:

- the presence of a consistent clinical and radiological picture
- histological evidence of noncaseating 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:

1. provide histological confirmation of the disease
2. assess the extent and severity of organ involvement
3. assess whether the disease is stable or is likely to process
4. determine whether therapy will benefit a patient

Granulomas alone are never diagnostic proof of sarcoidosis.

An important step is the 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 biopsy of the bronchial mucosa. Transbronchial needle aspiration of mediastinal lymph nodes guided by endobronchial ultrasound is useful for diagnosing stage I and II sarcoidosis with a sensitivity of 83–93%. 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 can be used to classify sarcoidosis into four stages (table 2). CT scanning provides much greater detail of mediastinal and parenchymal abnormalities but is not essential for baseline study. It is indicated when diagnosis is unclear after chest radiography and clinical assessment or to detect complications of the lung disease including bronchiectasis, aspergilloma or superimposed infection.

Pulmonary function tests show only a moderate correlation with the extent of lung involvement detected on imaging. However, it is important to have initial baseline data

<table>
<thead>
<tr>
<th>Table 1. Initial evaluation for sarcoidosis</th>
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<tbody>
<tr>
<td>History (occupational and environmental exposure, symptoms)</td>
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<tr>
<td>Physical examination</td>
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<tr>
<td>Chest radiography</td>
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<tr>
<td>Pulmonary function tests: vital capacity, FEV1, TLCO</td>
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<tr>
<td>Peripheral blood counts</td>
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<td>Serum chemistries: calcium, liver enzymes, creatinine, ACE</td>
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<tr>
<td>Urine analysis</td>
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<tr>
<td>ECG</td>
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<tr>
<td>Eye investigation</td>
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<tr>
<td>Tuberculin skin test</td>
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<tr>
<td>Selection of site for biopsy</td>
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</table>

ACE: angiotensin-converting enzyme.
for evaluating the following clinical course. The most sensitive test is the diffusion capacity. The typical finding is a restriction, but up to 30% of patients show an obstructive impairment that may be associated with the involvement of the bronchial mucosa.

Cardiac involvement is a serious manifestation of sarcoidosis. Cardiac MRI is the preferred diagnostic test as it is a noninvasive and nonradioactive method for diagnosing cardiac sarcoidosis with a high sensitivity.

Pulmonary hypertension is a troublesome complication of sarcoidosis, with increased morbidity and mortality. The frequency is 5–15% in selected patients and 50–60% in patients with dyspnoea out of proportion with the pulmonary function test results. Such patients, most of them in radiographic stage IV, should undergo echocardiography as a screening test and right heart catheterisation for confirmation.

**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 or 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 years, chronic hypercalcaemia, nephrocalcinosis, African ethnic origin, progressive pulmonary sarcoidosis, nasal mucosal involvement, cystic bone lesions, neural sarcoidosis, cardiac sarcoidosis, pulmonary hypertension 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. For patients with symptoms from a single organ, topical therapy may be appropriate for anterior eye or for skin involvement. Otherwise, initial therapy is still based on systemic 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 usually do not require therapy with corticosteroids.

For patients with chronic disease requiring years of therapy, alternatives to corticosteroids include methotrexate, azathioprine and hydroxychloroquine, all given usually in combination with low-dose corticosteroids. For refractory sarcoidosis patients, new therapeutic approaches have begun to emerge through the use of immunomodulatory agents. Based on

<table>
<thead>
<tr>
<th>Stage</th>
<th>Findings</th>
<th>Frequency %</th>
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<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>IB</td>
<td>Signs of fibrosis</td>
<td>5–10</td>
</tr>
</tbody>
</table>

BHL: bilateral hilar lymphadenopathy.
current understanding of pathogenic mechanisms, these are tumour necrosis factor-α-blocking drugs, such as infliximab, thalidomide and pentoxifylline. Lung transplantation can be considered for severe or end-stage pulmonary sarcoidosis.

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 years 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%.

Further reading

Idiopathic interstitial pneumonias (IIPs) represent a heterogeneous group of disorders with different clinical and histological features, and different prognosis. They can be considered as inflammatory disorders of the interstitium. Extrapulmonary involvement does not occur. The cause and pathogenetic mechanisms responsible for IIPs have not been elucidated. The first stage of the pathological process consists in the recruitment of inflammatory cells in the interstitium, leading to injury of the epithelial and alveolar cells, and the subsequent abnormal wound healing response, particularly due to the fibroblasts. Nowadays, the dysregulation of fibroblasts and an excessive deposition of extracellular matrix are considered the cardinal points of the pathogenesis of the IIPs.

Because of the poor comprehension of the underlying pathogenetic mechanisms, there is no therapeutic intervention able to affect the cellular and molecular target responsible for the disease and change its course.

The most recent American Thoracic Society (ATS) and European Respiratory Society (ERS) classification of the IIPs includes seven different diseases identified by a typical histological pattern: NSIP, cryptogenic organising pneumonia/bronchiolitis obliterans organising pneumonia, acute interstitial pneumonia, respiratory bronchiolitis/interstitial lung disease, desquamative interstitial pneumonia/alveolar macrophage pneumonia and lymphoid interstitial pneumonia.

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.

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, cryptogenic organising pneumonia/bronchiolitis obliterans organising pneumonia, acute interstitial pneumonia, respiratory bronchiolitis/interstitial lung disease, desquamative interstitial pneumonia/alveolar macrophage pneumonia and lymphoid interstitial pneumonia.
- 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.

Epidemiology

The incidence of the IIPs has been estimated at seven to 11 cases per 100 000 persons and the prevalence ranges between two and 29 cases per 100 000 persons. The disease typically affects adults, with a peak after the sixth decade of life; incidence is higher in males and in smokers (Coults et al., 1994). There is a familial variant of idiopathic pulmonary fibrosis (IPF)/usual interstitial pneumonia (UIP) that accounts for 0.5–3% of cases of IIP; this form is indistinguishable from the nonfamilial forms except that patients tend to be younger.

Pathogenesis

The pathogenetic mechanisms of the IIPs are not completely clear; there are various
hypotheses relating to the initial stimulus responsible for the pathogenetic process, such as exposure to toxic substances or viral infections. Independently of the initial cause, the inflammatory–fibrotic process of UIP is characterised by an injury of the alveolar epithelial cells, destruction of the subepithelial basement membrane and subsequent abnormal cicatrisation with an 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 transforming growth factor (TGF)-β, tumour necrosis factor (TNF)-α, platelet-derived growth factor (PDGF), connective tissue growth factor, integrin-mediated intercellular adhesion molecules, proteases and oxygen radicals. Deficiency of interferon (IFN)-γ may contribute to activation and perpetuation of the fibroblastic process. Histologically, the presence of fibroblastic foci is typical of 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 mode of transmission is not known; it is probably autosomal dominant with variable penetrance 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 antagonist or TNF-α may be involved.

**Physiology**

The physiological aberrations in IIPs are typical of a restrictive pattern and include reduced lung volumes (vital capacity and TLC) and normal or increased expiratory flow rates. TLCO is typically reduced, indicating interstitium damage and, thereby gas exchange impairment (Chetta et al., 2004). A further consequence of this alteration is the hypoxaemia, which is accentuated with exercise. Late in the course of the disease, severe hypoxaemia may also be observed at rest; hypercapnia may be present as well.

**Clinical features and diagnosis**

The initial symptoms of IIPs are hidden and insidious: persistent nonproductive cough and progressive dyspnoea. In most patients, physical examination reveals end-inspiratory rales (velcro type). The course of the disease may vary depending the variant of IIP; in UIP, the prognosis is extremely severe and the course of the disease is rapid, even if some patients stabilise after an initial period of decline. Respiratory failure appears in 3–8 years and the mean survival from the onset of the disease is around 3–5 years. 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 IIP is the result of an integrated and multidisciplinary process, requiring cooperation of the clinician, the radiologist and the pathologist. International guidelines state that histology is useful for diagnosis. Surgical lung biopsy shows higher diagnostic value than transbronchial biopsy and bronchoalveolar lavage. However, it is invasive with potential risks and, sometimes, patients may present clinical and physiological contraindications to surgery. In some cases, an acute exacerbation of the

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**Table 1: Classification of IIPs**

<table>
<thead>
<tr>
<th>IPF/UIP</th>
<th>Desquamative interstitial pneumonia/ alveolar macrophage pneumonia</th>
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<tbody>
<tr>
<td></td>
<td>Respiratory bronchiolitis/interstitial lung disease</td>
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<tr>
<td>Acute interstitial pneumonia</td>
<td></td>
</tr>
<tr>
<td>Cryptogenic organising pneumonia/ bronchiolitis obliterans organising pneumonia</td>
<td></td>
</tr>
<tr>
<td>NSIP</td>
<td>Lymphoid interstitial pneumonia</td>
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disease may follow surgery, leading to a decline in general condition.

HRCT has become a crucial tool for the diagnostic process and allows an accurate and objective follow-up of the disease. HRCT images consistent with IIP represent one of the most important ATS/ERS/Japanese Respiratory Society (JRS)/Asociación Latinoamericana de Tórax (ALAT) guideline diagnostic criteria. HRCT features are often typical of the disease and, given the high-quality evidence regarding HRCT specificity for the recognition of a histopathological UIP pattern, surgical lung biopsy is not essential. In the appropriate clinical setting, the presence of a UIP pattern on HRCT is sufficient for the diagnosis of IPF (fig. 1).

In particular, in case of UIP, HRCT images show a heterogeneous distribution with a predilection for the peripheral, especially subpleural and basilar, regions of the lung. The main radiologic feature in UIP is honeycombing, i.e. cystic radiolucencies as an expression of severe and irreversible fibrotic conversion of the parenchyma. Secondary features include coarse reticular opacities, thickened bronchial walls, bronchiectasis and bronchiolectasis.

Nonspecific interstitial pneumonia (NSIP) is characterised by the presence of ground-glass areas, as a sign of an active inflammatory process. The main aspects to consider for differential diagnosis of UIP or NSIP are the geographic and temporal histological and radiological heterogeneity, the high concentration of fibroblastic foci and honeycombing in the UIP form.

Cellular analyses of bronchoalveolar lavage (BAL) and transbronchial lung biopsy can be useful in the diagnosis of certain forms of IIPs (Meyer et al., 2012).

Natural history and exacerbations

The course of the disease is characterised by a progressive pulmonary function decline, leading to worsening of general condition and death (fig. 2). A subset of patients develop an accelerated and usually fatal course, showing an extremely rapid decline; this condition is known as acute exacerbation.

The criteria for defining an exacerbation are:

- progressive dyspnoea during the last 30 days
- new pulmonary infiltrates in chest radiographs

![Figure 1. Diagnostic algorithm for IPF. ILD: interstitial lung disease; MDD: multidisciplinary discussion. Reproduced and modified from Raghu et al. (2011) with permission from the publisher.](image1)

![Figure 2. Natural history of IPF. Reproduced and modified from Raghu et al. (2011) with permission from the publisher.](image2)
worsening of hypoxaemia with a reduction in oxygen tension >10 mmHg;
absence of pulmonary infection supported by negative BAL
absence of any other cause, such as HF, pulmonary embolism or conditions that 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 IIP and may be present in 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 as a precautionary measure. Lung biopsy shows diffuse alveolar damage; however, the invasiveness of the procedure is a limiting factor and only a 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, which is not clear yet, 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 and neutrophilia in BAL) may be consistent with a viral infection; however, the pathogen has not been identified.

Treatment

IIP treatment is one of the most controversial aspects in the field of the diffuse infiltrative lung diseases. Poor understanding of the pathogenetic mechanisms underlies the ineffectiveness of the current treatment options.

The initial pathogenetic theory considering IIP as an inflammatory process makes reasonable the use of anti-inflammatory drugs, such as corticosteroids, which are considered first-line drugs. Later, cytotoxic and immuno-suppressive agents have been used, usually in combination with corticosteroids.

The most recent developments in the field identify the initial phase of the disease as alveolar epithelial cell injury 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 dysregulation. Thus, the fibroproliferative process becomes the therapeutic target, and new drugs that arrest the proliferation of fibroblasts and the deposition of extracellular matrix are being testing (Bouros et al., 2005).

The increasing clinical awareness of IPF has resulted in the recent publication of guidelines for the accurate diagnosis of IPF and recommendations for its management. The recommendations for diagnosis and treatment intervention in the new ATS/ERS/JRS/ALAT guidelines are evidence-based and eliminate the bias from expert opinions and ongoing practices in the management of IPF.

Anti-inflammatory drugs. Although corticosteroids have been considered the mainstay of IPF treatment for decades, 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 used 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 individual characteristics of patients. In the case of responders with clinical and radiological improvement,
prolonged maintenance therapy with low-dose, alternate-day prednisone may be established to reduce the chance of recrudescence. In the case of exacerbation, 2 mg·kg⁻¹·day⁻¹ of methylprednisolone for 14 days should be administered, depending on individual clinical response.

Given the lack of any scientific evidence of proven benefit, especially a dose–response effect, corticosteroid treatment should not be used in patients at high risk for adverse effects, such as elderly patients.

When the inflammatory component dominates, prompt corticosteroid treatment may lead to a significant improvement and, sometimes, to complete resolution of the disease. Desquamative interstitial pneumonia/alveolar macrophage pneumonia, acute interstitial pneumonia and cryptogenic organising pneumonia/bronchiolitis obliterans organising pneumonia are the IIPs forms with the highest rate of response to steroid therapy.

The new guidelines recommend that patients with IPF should not be treated with corticosteroid monotherapy.

Azathioprine and cyclophosphamide are the most frequently used second-line drugs, alone or in combination with corticosteroids. Currently, there is poor information regarding their efficacy. A possible adjunctive synergic effect is unconfirmed.

Azathioprine is the most frequently used cytotoxic agent and is usually well-tolerated. Its metabolism leads to the production of mercaptopurine, which is similar to purine, and inhibits DNA synthesis. Azathioprine is administered p.o., usually in combination with low-dose corticosteroids; the 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. During treatment with azathioprine, haemachrome and liver function should be monitored; in fact, azathioprine causes bone marrow suppression and hepatotoxicity. There are no clinical trials that confirm a certain benefit of combination (corticosteroids plus azathioprine) therapy. Given the minor toxicity compared with cyclophosphamid, azathioprine should be administered in patients with symptomatic or progressive disease for 6 months unless adverse effects that suggest interruption or modification of the treatment appear. A more prolonged treatment is reserved only in patients with a clinical response or complete remission of the disease.

Cyclophosphamide is usually used as a second-line drug for patients who presented adverse effects from high-dose corticosteroid therapy. It is an alkylating agent that activates the liver microsomal system and inhibits DNA synthesis; it has a marked effect on lymphocytes, thus it is used as an immunosuppressive agent. The route of administration is usually oral or intravenous but it can also be administered by intramuscular injection. Generally, cyclophosphamide is used combined with low-dose corticosteroids. Principal adverse effects are bone marrow suppression, haemorrhagic cystitis, nausea and vomiting. Scientific evidence confirming the efficacy of cyclophosphamide in IIP treatment is lacking; no clinical benefit regarding survival and progression of the disease has been reported.

Cyclosporine is a fungal peptide that exerts potent immunosuppressive effects; it inhibits T-lymphocyte proliferation by inhibiting the release of IL-2. It causes some important adverse effects, especially renal, hepatic and gastrointestinal effects. Cyclosporine is rarely used for IIP treatment and its use is limited for selected patients awaiting lung transplantation. There are no clinical trials showing that cyclosporine therapy is of benefit.

The new guidelines recommend that patients with IPF should not be treated with cyclosporine. Moreover, combination therapy with corticosteroid and immunomodulator therapy should not be recommended in IPF patients.

**Novel therapeutic strategies** The use of novel drugs in IIP treatment is suggested by the
new pathophysiological theory that recognises the fibroproliferative process plays a central role.

IFN-γ is a novel biological antifibrotic drug with a number of inhibitory effects on fibroblasts. In the literature, there are only few studies relating to the real efficacy of IFN-γ, either alone or in combination therapy with low-dose corticosteroids. Neither Ziesche et al. (1999) nor Raghu et al. (2004) reported any statistically significant differences in the primary outcome variables, such as disease progression, mortality and functional deterioration. However, patients with mild-to-moderate disease presented better, statistically significant survival. Although IFN-γ may represent a useful therapeutic tool in selected patients, additional data supporting its efficacy are needed.

The new guidelines recommend that patients with IPF should not be treated with IFN-γ.

Colchicine inhibits the synthesis of collagen and suppresses some 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. The new guidelines recommend that patients with IPF should not be treated with colchicine.

D-penicillamine is a thiolic compound that interferes with collagen turnover, inhibiting collagen synthesis and deposition by interrupting cross-linking of collagen molecules. There are no clinical controlled trials showing any benefit of D-penicillamine therapy. Given the frequency adverse effects, D-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-α, and inhibits TGF-β-stimulated collagen synthesis. Moreover, it decreases synthesis of extracellular matrix and blocks the mitogenic effect of profibrotic cytokines. Azuma et al. (2005) published the results of a double-blind, randomised, placebo-controlled trial but no statistically significant difference in desaturation during the 6-min walk test (6MWT) was found; however, a positive treatment effect with pirfenidone was demonstrated in secondary end points, such as vital capacity and prevention of acute exacerbation of the disease. In fact, successive studies showed that pirfenidone preserves vital capacity and improves progression-free survival time better than placebo. The new guidelines recommend that the majority of patients with IPF should not be treated with pirfenidone but this therapy may be a reasonable choice in a minority of patients.

Experimental models in vitro and in vivo showed that angiotensin-converting enzyme inhibitors and statins possess antifibrotic properties. However, there is no evidence of survival improvement in treated patients.

There is evidence that oxidant agents production increases in IIP. In particular, neutrophils, macrophages and fibroblasts release oxidant agents, such as reactive oxygen species, hydrogen peroxide and superoxide anions. These factors, added to the reduction of antioxidants, facilitate fibroblast dysregulation and deposition of extracellular matrix.

N-acetylcysteine (NAC) is derived from the amino acid cysteine. It is considered a precursor of glutathione (GSH) and stimulates GSH synthesis. GSH has strong antioxidant properties, as it removes free oxygen radicals and decreases hydrogen peroxide. The route of administration is oral at a dose of 1800 mg·day⁻¹ added to conventional therapy with corticosteroids and azathioprine. A significant difference in the rate of decline of FVC and TlCO has been described in patients treated with NAC; however, no difference was observed in mortality.

A recent study showed that increased risks of death and hospitalisation were observed in patients with IPF who were treated with a combination of prednisone, azathioprine, and NAC, as compared with placebo.
The new guidelines recommend that the majority of patients should not be treated with NAC monotherapy or with combination corticosteroid, azathioprine and NAC therapy, but this therapy may be reasonable in a minority of patients.

Endothelin 1 (ET-1) is a potent mitogen for endothelial and smooth muscle cells. ET-1 is strongly upregulated in patients with IIP and is mainly expressed in epithelial cells. Some studies have suggested that inhibition of ET-1 could have antifibrotic effects. Bosentan is a nonselective ETA and ETB receptor antagonist which is used in patients with pulmonary hypertension, and it could delay the progression of IIPs. The Bosentan Use in Interstitial Lung Disease (BUILD)-1 trial showed that bosentan was not superior to placebo in the 6MWT, and the effects of bosentan treatment on health-related quality of life and dyspnoea in the all-treated population were minimal. Similarly, in the BUILD-3 trial, no treatment effects were observed on health-related quality of life or dyspnoea (King et al., 2011). The new guidelines recommend that patients with IPF should not be treated with bosentan.

TNF-α has been found to be significantly elevated in bleomycin-induced pulmonary fibrosis. TNF-α stimulates a series of cytokines, such as TGF-β and IL-5, and modifies eosinophil recruitment in the parenchyma. Antibodies against TNF-α and soluble TNF-α receptor antagonists have been found to reduce the fibrotic process in animals. A recent study showed that BIBF 1120 at a dose of 150 mg twice daily was associated with a trend toward a reduction in the decline in lung function compared with placebo, with fewer acute exacerbations and preserved quality of life (Richeldi et al., 2011).

The typical fibroproliferative process in IIP seems to be related to inflammation and vascular injury. Indeed, endothelium damage causes exposition of the intimal tissue to the circulation and this is strongly pro-thrombotic. Pulmonary embolism is one of the most common causes of death in IIP patients and D-dimer levels often increase in exacerbations of the disease (Castro et al., 2001). In a prospective study, Kubo et al. (2005) evaluated the role of thrombotic events in the natural history of the disease and survival improvement in IIP patients receiving oral anticoagulant therapy. 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 exacerbation-free days did not differ between the two groups. The mechanisms underlying better survival in patients treated with anticoagulant therapy are unclear. Certainly, extravascular deposition of fibrin and thrombotic events play a main role in the fibroproliferative process and acute lung injury.

The new guidelines recommend that the majority of patients with IPF should not be treated with anticoagulants but this therapy may be a reasonable choice in a minority of patients.

The study by Lee et al. (2011) showed an apparent survival benefit associated with medications to suppress the acidity of the gastric juice, given as gastro-oesophageal reflux (GOR) therapy. This observation is consistent with an increasing body of evidence supporting the concept of silent microaspiration as a result of abnormal GOR in the pathogenesis of IPF. If GOR therapy improves survival in patients with IPF, then other treatment interventions to decrease and/or control GOR should include aggressive conservative measures with altered eating, drinking and sleep habits/behavioural patterns, decrease in abdominal girth, and/or laparoscopic anti-reflux.
surgery. However, further studies are needed to confirm these data.

**Lung transplantation** is the only option that definitely improves survival in IIP patients and the only option for patients who respond poorly to medical therapy. IIPs represent the second most frequent disease that requires lung transplantation. It is extremely important to decide when to list a patient for transplantation. Given the legal complexity of 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 2). The new guidelines recommend that appropriate patients with IPF should undergo lung transplantation.

Unfortunately, many patients die while awaiting transplantation because of the poor availability of donor organs. Post-operative mortality in transplanted patients is high, because of rejection, infections and other complications. 2- and 5-year survival rates following single lung transplantation are ~70% and ~50%, respectively.

**Stem cell-based therapy** Given the recent advances in IPF pathogenesis, new therapeutic models are being investigated, focusing on the cellular and molecular mechanisms underlying the disease. In particular, alveolar epithelial cell injury arises from an abnormal accumulation of fibroblasts and deposition of extracellular matrix, resulting in distortion of lung parenchyma architecture. Therefore, lung tissue regeneration, remodelling and repair mechanisms could represent new potential therapeutic targets.

The discovery that stem cells can contribute to the formation of differentiated cell types, especially after injury, justifies the experimental use of stem cells in tissue regeneration. It is believed that stem cells play a central role in cell injury and fibrotic process; however, their role is still controversial. In particular, the mechanisms of cell recruitment to site in case of tissue damage are not completely clear. Therefore, embryo or adult stem cells transplantation could be a valid novel therapeutic option in pulmonary fibrosis. Official data confirming the efficacy and applicability of this treatment are lacking; furthermore, the importance of immunosuppressive therapy before stem cells transplantation is unclear, as the data are poor.

### Further reading


### Table 2. International Society for Heart and Lung Transplantation guidelines

| For referral | Radiographic or histological evidence of UIP irrespective of vital capacity  
Histological evidence of fibrotic NSIP |
| For listing | Radiographic or histological evidence of UIP and any of the following:  
TlCO <39% pred  
≥10% reduction in FVC in the last 6 months  
Oxygen saturation <88% during 6MWT  
Honeycombing on HRCT (fibrosis score >2)  
Histological evidence of NSIP and any of the following:  
TlCO < 35% predicted  
≥10% reduction in FVC or  
≥15% in TlCO in the last 6 months |
Eosinophilic diseases

Andrew Menzies-Gow

The exact role of the eosinophil in health 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 systemic diseases, such as hypereosinophilic syndrome (HES) (table 1).

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 airway inflammation without the variable airflow obstruction or airway 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 PC_{20} (provocative concentration causing a 20% fall in FEV1) of \textless 16 mg/mL and \textgreater 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 of the treatment of eosinophilic bronchitis. Inhaled corticosteroids produce a significant improvement in symptoms as well as 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 IL-5.
Acute and chronic eosinophilic pneumonia

Acute eosinophilic pneumonia presents as an acute febrile illness of <1 month’s duration and predominately affects cigarette smokers. The average age at presentation is 30 years with symptoms of dyspnoea, cough, myalgia and fever. 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 females 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 along with elevated inflammatory markers. The majority of patients have infiltrates visible on chest radiography and they are peripherally distributed in about two-thirds of cases (fig. 1).
HRCT 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 allergic bronchopulmonary aspergillosis, HES and Churg–Strauss syndrome, which should be excluded at the time of diagnosis.

**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:

- blood eosinophilia $>1500$ cells per mm$^3$ for $\geq 6$ months
- absence of an underlying cause for the eosinophilia
- end organ damage due to the eosinophilia

Idiopathic HES can occur at any age but tends to develop in the 30s or 40s 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, and present with 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.

Dulohery et al. (2011) reported the frequency of pulmonary HES and associated clinical and radiologic features. In their case series of 49 patients, 24% had parenchymal lung involvement, which most commonly consisted of patchy ground-glass opacities and consolidation; one patient exhibited numerous pulmonary nodules. 27% had asthma. Most patients with pulmonary involvement of HES improved and no deaths were observed.

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 (FIP1-like protein 1–platelet-derived growth factor receptor-alpha). Historically, these patients 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 (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.

Further reading

Drug-induced respiratory disease

Philippe Camus and Philippe Bonniaud

Drug-induced respiratory disease (DIRD) is a relatively common, generally unpredictable set of complications of therapy with or exposure to one of >700 distinct drugs (www.pneumotox.com).

Drugs account for about 3% of all interstitial lung disease (ILD) cases and about 8–10% of acute lung injury (ALI) cases are due to drugs, mainly chemotherapy and amiodarone. The biologics (erlotinib, dasatinib, gefitinib, imatinib and nilotinib), monoclonal antibodies (abciximab, adalimumab, bevacizumab, cetuximab and infliximab) and etanercept can cause mechanism-based or idiosyncratic adverse respiratory reactions. Irradiation, inhaled or injected substances of abuse, excipients and vehicles, herbals, and vaccines can also cause respiratory injury. Iatrogenic non-drug-induced complications include the adverse consequences of catheters, and medical, imaging and surgical procedures (these are not covered here). The diagnosis of DIRD is mainly one of exclusion (table 1).

Aetiologies other than drugs must be carefully excluded, including the pulmonary manifestations of the underlying illness when present, and opportunistic infections due to Pneumocystis jiroveci or other fungi, parasites, viruses or bacteria. Patients exposed to methotrexate, chemotherapy agents or immunosuppressive drugs including prolonged corticosteroid therapy, tumour necrosis factor (TNF)-α antagonists, rituximab, and those who have received radiation therapy to the chest, or are stem cell or lung transplant recipients are particularly exposed to the risk of developing opportunistic respiratory infections.

Key points

- DIRD is not uncommon, and can involve the larynx, major and lower airways, lung, pleura, pulmonary circulation, neuromuscular system and haemoglobin. Chemotherapy agents, amiodarone, ACE inhibitors, NSAIDs and β-blockers pose particular risk of adverse respiratory effects.
- Some DIRDs cause acute life-threatening respiratory distress, requiring immediate management.
- The clinical, imaging and pathological expression of DIRD may closely resemble that of illnesses of other causes or that occur idiopathically. Pathology is rarely specific for drug aetiology.
- Diagnosing DIRD requires a high degree of awareness, up-to-date knowledge and ruling out of other causes, particularly infection, using BAL and appropriate tests.
- Stopping the drug is often followed by improvement in symptoms, signs and imaging. Care should be taken to avoid relapse of the condition for which the drug was given.
- Corticosteroid therapy is reserved for severe cases and where dechallenge does not produce satisfactory improvement; duration varies with drug and pattern.
- Generally, rechallenge with the drug is discouraged as severe relapse can occur.
Drugs history is now included in the workup of any patient with ILD and the same should apply to other patterns of drug-induced respiratory involvement (table 3). Overall, the greatest incidence is with chemotherapy agents including bleomycin (up to 50%, depending on the drug regimen and which diagnostic test is used to diagnose it), angiotensin-converting enzyme inhibitors (ACEIs), amiodarone (2-4%), methotrexate (0.5–1%), mineral lipids (paraffin) in the elderly, mammalian target of rapamycin (mTOR) inhibitors, nitrofurantoin, TNF-α antagonists, tyrosine kinase inhibitors (TKIs),

<table>
<thead>
<tr>
<th>Table 1. Checklist for diagnosing and managing DIRDs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Emergent management</strong> should be placed ahead of causality assessment while managing acute drug-induced emergencies such as anaphylaxis, bronchospasm, asphyxia, diffuse white-out, bleeding, tamponade, pulmonary hypertension, respiratory muscle paralysis or methaemoglobinemia.</td>
</tr>
<tr>
<td>Maintain a high degree of awareness. Two main questions arise:</td>
</tr>
<tr>
<td>1) Could new and otherwise unexplained signs and symptoms (respiratory and/or nonrespiratory) be due to a drug or drugs? Check Pneumotox by drug names.</td>
</tr>
<tr>
<td>2) Which pattern of involvement may result from the drug the patients is on? Check Pneumotox by patterns.</td>
</tr>
<tr>
<td>Take complete history and list current or past exposure to any medication, abused substance, or herbal, chemical or physical agent.</td>
</tr>
<tr>
<td>Retrieve and review any pre-therapy imaging and pulmonary function, if available.</td>
</tr>
<tr>
<td>Review the possibility of respiratory involvement from any underlying disease present (connective tissue disease including rheumatoid arthritis, malignant conditions, etc.).</td>
</tr>
<tr>
<td>Correlate time on each specific drug and timing of exposure (delay between first exposure and onset of signs and symptoms). This can vary from minutes with anaphylaxis or bronchospasm, to months or years with ILD.</td>
</tr>
<tr>
<td>Attempt to define the pattern of involvement (using clinical features, imaging, HRCT, BAL and diuresis) in a noninvasive, conservative way. A lung biopsy is rarely indicated as the procedure carries its own morbidity/mortality and may yield nonspecific findings. A matching table of drugs and pathology patterns is available on Pneumotox (pattern XV) and in table 2.</td>
</tr>
<tr>
<td>Correlate each drug with pattern of involvement in the patient (see Further Reading and Pneumotox)</td>
</tr>
<tr>
<td><strong>Differential:</strong> evaluate the possibility of underlying disease or coincidental illness (including heart failure or an opportunistic infection in the immunodepressed) versus drug-induced disease</td>
</tr>
<tr>
<td>Most in vitro tests have fallen out of favour except the unusual drug-induced ANA, ANCA and anti-HNE.</td>
</tr>
<tr>
<td>Discontinue drug, underlying condition permitting. Cover with a substitute drug if needed. Expect improvement in hours, weeks or more depending on drug and pattern.</td>
</tr>
<tr>
<td>Decide on corticosteroid therapy. Corticosteroid therapy is indicated depending on severity, extensity of involvement and response to drug discontinuance.</td>
</tr>
<tr>
<td>Organise follow-up for resolution of signs, symptoms, pulmonary physiology and imaging.</td>
</tr>
<tr>
<td>Consider rechallenge only if drug is vital, or with the purpose of desensitisation or induction of tolerance, preferably if documented in the literature. Make sure the patient will never get re-exposed to the culprit drug.</td>
</tr>
</tbody>
</table>

HNE: human neutrophil elastase.
radiation therapy, drugs of abuse including heroin and cocaine, levamisole, and liquid silicone. As drugs may target any subsystem of the respiratory apparatus, varied clinical and imaging presentations may ensue. DIRD can be in the form of ILD, noncardiogenic pulmonary oedema, ALI/acute respiratory distress syndrome (ARDS), alveolar haemorrhage, lung nodules, stridor and asphyxia, catastrophic bronchospasm,

Table 2. Main imaging–pathological patterns of DIRDs

<table>
<thead>
<tr>
<th>Pattern on chest radiograph or CT</th>
<th>Causal drugs</th>
<th>Pathology correlate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse haze Ground-glass opacity</td>
<td>Drugs that cause interstitial pneumonia (NSIP-like) Chemotherapy agents</td>
<td>Interstitial inflammation Early/mild pulmonary oedema, alveolar haemorrhage or DAD</td>
</tr>
<tr>
<td>Localised ground-glass opacity</td>
<td>Radiation therapy</td>
<td>Early mild radiation lung injury (interstitial oedema, cell sloughing, cell debris)</td>
</tr>
<tr>
<td>Diffuse white-out</td>
<td>Drugs that produce acute ILD, pulmonary oedema, eosinophilic pneumonia, DAD or DAH*</td>
<td>Dense cellular interstitial pneumonitis with or without eosinophilia Acute pulmonary oedema Alveolar haemorrhage</td>
</tr>
<tr>
<td>Disseminated ground-glass opacity with a mosaic pattern of distribution</td>
<td>Drugs that cause interstitial pneumonia</td>
<td>Cellular interstitial pneumonia DIP</td>
</tr>
<tr>
<td>Bilateral perihilar alveolar opacities with a batwing pattern of distribution</td>
<td>Drugs that cause pulmonary oedema, DAD or DAH</td>
<td>Pulmonary oedema DAD DAH</td>
</tr>
<tr>
<td>Subpleural areas of consolidation</td>
<td>Drugs that cause pulmonary eosinophilia or OP</td>
<td>Eosinophilic pneumonia OP</td>
</tr>
<tr>
<td>Opacities with a recognisable segmental or lobar pattern of distribution</td>
<td>Amiodarone Statins Paraffin</td>
<td>Phospholipidosis OP Exogenous lipid pneumonia</td>
</tr>
<tr>
<td>Miliary pattern</td>
<td>BCG therapy Methotrexate Sirolimus</td>
<td>Granulomatous reaction</td>
</tr>
<tr>
<td>Area of consolidation A mass</td>
<td>Drugs that cause OP or eosinophilic pneumonia Amiodarone Paraffin</td>
<td>OP Eosinophilic pneumonia Phospholipidosis Amiodaronoma Paraffinoma</td>
</tr>
<tr>
<td>Wandering opacities</td>
<td>Drugs that cause OP or PIE</td>
<td>OP Eosinophilic pneumonia</td>
</tr>
<tr>
<td>Multiple nodular opacities</td>
<td>Irradiation for breast carcinoma Amiodarone Bleomycin</td>
<td>APT features OP Areas of nodular fibrosis</td>
</tr>
<tr>
<td>Pulmonary fibrosis Low lung volumes</td>
<td>Chemotherapy agents Amiodarone Nitrofurantoin</td>
<td>Pulmonary fibrosis NSIP-fibrotic or UIP pattern</td>
</tr>
</tbody>
</table>

NSIP: nonspecific interstitial pneumonia; DIP: desquamative interstitial pneumonia; OP: organising pneumonia; BCG: bacille Calmette–Gue´rin; UIP: usual interstitial pneumonia. #: see appropriate pattern at www.pneumotox.com
<table>
<thead>
<tr>
<th>Pattern</th>
<th>Pathophysiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenchymal lung disease</td>
<td>Interstitial/alveolar inflammation/filling</td>
</tr>
<tr>
<td>Interstitial lung diseases</td>
<td>Influx/persistence of inflammatory cells</td>
</tr>
<tr>
<td>Endogenous lipid pneumonia (phospholipidosis)</td>
<td>Disordered phospholipid catabolism</td>
</tr>
<tr>
<td>Exogenous lipid pneumonia</td>
<td>Accumulation of nondigestible oil and oil-laden macrophages in alveolar spaces</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>Scarring</td>
</tr>
<tr>
<td>Diffuse pulmonary calcification</td>
<td>Precipitation of calcium in pulmonary interstitium</td>
</tr>
<tr>
<td>Foreign body reaction</td>
<td>Granulomas around drug or excipients</td>
</tr>
<tr>
<td>Pulmonary nodules</td>
<td>Circumscribed areas of OP or fibrosis</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
<td></td>
</tr>
<tr>
<td>Noncardiogenic pulmonary oedema</td>
<td>Increased permeability of alveolar barrier to fluid</td>
</tr>
<tr>
<td>Cardiogenic pulmonary oedema</td>
<td>Raised pulmonary venous pressure due to myocardial injury</td>
</tr>
<tr>
<td>ALI/ARDS</td>
<td>Increased permeability of alveolar capillary barrier to fluid and proteins</td>
</tr>
<tr>
<td>Transfusion-related ALI</td>
<td>Immune-mediated blood reaction to anti-HLA antibodies of donor origin. Neutrophil sequestration</td>
</tr>
<tr>
<td>Pulmonary haemorrhage</td>
<td></td>
</tr>
<tr>
<td>DAH</td>
<td>Synchronous capillary bleeding usually from disordered coagulation, low platelets or capillaritis</td>
</tr>
<tr>
<td>ANCA-associated DAH</td>
<td>ANCA/activated neutrophil-mediated capillaritis and consequent bleeding</td>
</tr>
<tr>
<td>Airway involvement</td>
<td></td>
</tr>
<tr>
<td>Bronchospasm/asthma</td>
<td>Subverted prostaglandin/leukotriene handling</td>
</tr>
<tr>
<td>Obliterative bronchiolitis</td>
<td>Acceleration of bronchiolitis from the underlying disease?</td>
</tr>
<tr>
<td>Cough</td>
<td>Bradykinin-mediated?</td>
</tr>
<tr>
<td>Foreign body bronchiolitis</td>
<td>Airway-centred reaction against drug or vehicle</td>
</tr>
<tr>
<td>Large airway involvement or closure</td>
<td></td>
</tr>
<tr>
<td>Angio-oedema</td>
<td>Bradykinin-mediated?</td>
</tr>
<tr>
<td>Haematoma causing UAO</td>
<td>Localised bleeding causing compression</td>
</tr>
<tr>
<td>Pulmonary vasculopathy</td>
<td></td>
</tr>
<tr>
<td>Pulmonary thromboembolism</td>
<td>Excessive coagulation</td>
</tr>
<tr>
<td>Pulmonary arterial hypertension</td>
<td>Serotonin-based?</td>
</tr>
<tr>
<td>Pulmonary vasculitis/capillaritis</td>
<td>Drug-induced ANCA s</td>
</tr>
<tr>
<td>Fat/lipid/silicone embolism</td>
<td>Increased capillary permeability. Bypass of foreign fluid through the lung, causing brain injury</td>
</tr>
<tr>
<td>Foreign body vasculopathy</td>
<td>Granulomatous reaction around foreign drug-associated material</td>
</tr>
<tr>
<td>Pattern</td>
<td>Pathophysiology</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Cement/mercury embolism</td>
<td>Lodging of acrylate or metallic mercury in the distal pulmonary circulation</td>
</tr>
<tr>
<td><strong>Pleural/pericardial involvement</strong></td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>Pleural inflammation</td>
</tr>
<tr>
<td>Pleural thickening/fibrosis</td>
<td>Scarring/fibrosis</td>
</tr>
<tr>
<td>Pleural effusion and drug lupus</td>
<td>Autoimmune-mediated?</td>
</tr>
<tr>
<td>Haemothorax</td>
<td>Drug-induced disordered coagulation</td>
</tr>
<tr>
<td>Chylothorax</td>
<td>PDGFR inhibition?</td>
</tr>
<tr>
<td>Serositis</td>
<td>Autoimmune-mediated?</td>
</tr>
<tr>
<td>Haemopericardium</td>
<td>Drug-induced disordered coagulation</td>
</tr>
<tr>
<td>Pleuritic chest pain</td>
<td>Pleural inflammation</td>
</tr>
<tr>
<td>Pleuroparenchymal fibroelastosis</td>
<td>Scarring, elastic fibre type</td>
</tr>
<tr>
<td>Pleural mass or masses</td>
<td>Scarring around foreign material (talc)</td>
</tr>
<tr>
<td><strong>Mediastinal involvement</strong></td>
<td></td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Unknown</td>
</tr>
<tr>
<td>Mediastinal lipomatosis</td>
<td>Central fat distribution</td>
</tr>
<tr>
<td>Fibrosing mediastinitis</td>
<td>Scarring, usually radiation induced</td>
</tr>
<tr>
<td><strong>Neuromuscular involvement</strong></td>
<td></td>
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<tr>
<td>Respiratory muscle weakness/paralysis</td>
<td>Myoneural presynaptic blockade of acetylcholine release</td>
</tr>
<tr>
<td>Ventilatory depression/apnoea</td>
<td>Opiate effect on central ventilatory oscillator</td>
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<tr>
<td>Respiratory muscle/myopathy</td>
<td>Corticosteroid-induced muscle wasting</td>
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<tr>
<td><strong>Acquired haemoglobinopathy</strong></td>
<td></td>
</tr>
<tr>
<td>Methaemoglobinaemia</td>
<td>Haemoglobin poisoning via iron oxidation</td>
</tr>
<tr>
<td><strong>Systemic syndromes</strong></td>
<td></td>
</tr>
<tr>
<td>DRESS</td>
<td>T-cells, HHV6 or HHV8</td>
</tr>
<tr>
<td>Antiphospholipid antibody syndrome</td>
<td>Unknown</td>
</tr>
<tr>
<td>Drug-induced lupus</td>
<td>Drug-triggered autoimmunity</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Some due to drug-induced IgE release</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td>Reaction to foreign (e.g. murine) proteins</td>
</tr>
<tr>
<td>Eosinophilic granulomatosis with polyangiitis</td>
<td>Unknown</td>
</tr>
<tr>
<td>Immune reconstitution syndrome</td>
<td>Exaggerated reaction to microorganisms once immune cells repopulate tissues</td>
</tr>
<tr>
<td>Polymyositis/dermatopolymyositis</td>
<td>Unknown</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Unknown</td>
</tr>
<tr>
<td>Systemic vasculitis</td>
<td>Drug-induced ANCA-mediated?</td>
</tr>
</tbody>
</table>
cough, pulmonary hypertension, pleural effusion, cardiac tamponade, haemothorax, neuromuscular blockade, or haemoglobinopathy.

Life-threatening presentations include anaphylaxis, acute laryngeal angio-oedema (usually from ACEIs), catastrophic bronchospasm (typically from nonsteroidal anti-inflammatory drugs (NSAIDs) or $\beta$-blockers), acute methotrexate pneumonitis, minocycline- or tobacco-related acute eosinophilic pneumonia, tocolytic- or chemotherapy-induced pulmonary oedema, chemotherapy-induced ALI or ARDS, anticoagulant-induced diffuse alveolar haemorrhage (DAH), large volume-occupying pleural effusions, cardiac tamponade, methaemoglobinaemia, neuromuscular paralysis and systemic conditions such as DRESS (drug reaction with eosinophilia and OP). These presentations, particularly when they occur in the emergency room or intra- or perioperatively, portend immediate severity and require prompt evaluation.

Management is aimed at restoring airway patency, maintaining oxygenation and reversing drug-induced inflammation and oedema using drug withdrawal and corticosteroid therapy. Further compounding these issues, drugs can cause cardiac injury, which may cause heart failure and can impact the lung and pleura (table 3).

### Pathophysiology: mechanisms

Mechanisms in DIRD are summarised in table 3. With a few drugs (e.g. chemotherapy agents and amiodarone), reactions may correspond to a dose-related cytopathic mechanism. Identification of a threshold dosage may then enable risk reduction. However, most drug reactions are idiosyncratic and unpredictable, occurring in only a few predisposed individuals, possibly with a predilection in those who harbour a distinct pharmacokinetic trait. Several drugs in a given family produce a stereotyped pattern of involvement (e.g. $\beta$-blockers, NSAIDs and bronchospasm, NSAIDs and eosinophilic pneumonia, chemotherapy and pulmonary oedema or ALI-ARDS/diffuse alveolar damage (DAD), anticoagulants and DAH, and ergots and pleural involvement), suggesting a reaction linked to the pharmacological effect of the drug, even though the pharmacophores differ. Drug disposition in the lung may be a relevant factor for toxicity. Amiodarone and its metabolite concentrate in lung, causing toxicity to lung cells. The slow efflux of these compounds from the lung may explain both the slow resolution of amiodarone pulmonary toxicity (APT) and relapses of the condition even when amiodarone is discontinued, at a time when corticosteroid therapy is being tapered. The pulmonary metabolism of nitrofurantoin, cyclophosphamide, mitomycin, bleomycin and paraquat in designated lung cells.
generates reactive oxygen species, which cause cell stress and death, pulmonary inflammation, and/or fibrosis. The heterogeneous distribution of activating enzymes in lung may account for the selective targeted alveolar or bronchiolar injury seen with certain drugs. Drug-induced asthma is largely non-IgE-dependent. Small incremental doses of NSAIDs or aspirin can be given to asthmatics who are intolerant to these drugs to induce a state of tolerance that can be maintained on continued exposure to the medication. Unusual cases of respiratory injury result from deposition of drug excipients in the small airways and pulmonary arterioles, causing reactive foreign body obstructive granulomas that cause obstruction to airflow or pulmonary hypertension. Amiodarone, radiation and chemotherapy agent toxicity is potentiated by molecular oxygen. Patients must be spared unnecessary association of these factors. Patients on chemotherapy for malignant conditions or who receive amiodarone in the long term may exhibit a time- or dose-related decrease in TLCO thought to reflect subclinical toxicity, without necessarily annunciating the development of clinical disease. In that setting, risk-to-benefit evaluation of drug discontinuation or maintenance is indicated in each patient.

Clinical presentation

Drugs can cause injury when administered by the oral, intravenous, intramuscular, inhaled, pleural, dermal, intrathecal, intracoronary or gynaecological route. DIRD can also develop following delivery in organs situated upstream of the lung (e.g. vertebrae, brain, liver and oesophagus). A high index of suspicion is warranted. Drugs should be a diagnostic consideration in any patient with otherwise unexplained symptoms, abnormal pulmonary physiology or new radiographic findings while being treated with a compatible drug or set of drugs. Some adverse reactions develop within minutes of exposure, suggesting causality (e.g. β-blocker-induced bronchospasm, and chemotherapy- or tocolytic-induced pulmonary oedema). For many drugs, there may be a delay of weeks, months or years before symptom presentation. Presenting symptoms include a nonproductive cough, dyspnoea, wheezing, cyanosis, fever, rigors and malaise. Acute bronchospasm, angio-oedema, cardiovascular collapse, shock, stridor, hoarseness, wheezing, haemoptysis or acute chest pain are less common presentations. Other features include a cutaneous rash, lymph-node enlargement, myositis, livedo reticularis, skin necrosis, hepatitis or other deep-seated organ involvement. Rare patients present with a systemic picture reminiscent of the lupus erythematosus (lupus-inducing agents), granulomatous polyangiitis (propylthiouracil), eosinophilic granulomatous polyangiitis (leukotriene receptor antagonists) or dermatopolymyositis (statins). Severity of DIRD is linked to the acuteness of presentation, extent and location of the pathological process, and reversibility upon drug discontinuance or under the influence of therapy. Life-threatening presentations include anaphylactic shock, upper airway angioedema and closure, acute ILD, pulmonary infiltration with eosinophilia (PIE), organising pneumonia, noncardiogenic pulmonary oedema or alveolar haemorrhage, catastrophic bronchospasm, large pleural effusions, tamponade, methaemoglobinemia, apnoea, and respiratory paralysis. Drug withdrawal, if followed by abatement of signs and symptoms, supports the drug aetiology. The risk of rechallenge should be balanced against the merit of securing the diagnosis, as fatal reactions may ensue.

Many clinical situations are inextricably complex, particularly in ILD patients who are exposed to several possible causal drugs, who have received radiation therapy, or in whom DIRD cannot be confidently separated from underlying disease-related pulmonary involvement or from an infection. Oncology patients who are receiving chemotherapy, TKIs, mTOR inhibitors and/or radiation therapy, or those with rheumatoid arthritis who receive combination therapy with corticosteroids...
and/or anti-TNF antibody therapy exemplify these difficulties. Careful assessment of each drug’s causality and meticulous exclusion of an infection are required using molecular techniques on bronchoalveolar lavage (BAL) fluid. Notwithstanding that, patients may progress without a firm diagnosis despite exclusion of an infection, withdrawal of the suspect drug, corticosteroids and empiric antibiotic therapy. Diagnosing drug-induced ILD is also difficult in patients with autoimmune conditions, or in recipients of solid organ or stem cell transplants who receive long-term treatments with cytotoxic agents, immunosuppressive drugs, rituximab and corticosteroids.

**Imaging**

Imaging is most useful in patients presenting with pulmonary opacities. Patterns and correlates are shown in Table 2.

The extent of involvement seen on imaging roughly correlates with gas exchange. HRCT discloses inter- and intralobular septal thickening, disseminated lobular opacities, faint or dense ground-glass shadowing, or alveolar filling. Pleural effusion denotes severe ILD or pulmonary oedema, or occurs in isolation as a complication of therapy with one or more of ~60 different drugs. Amiodarone pulmonary toxicity takes the form of asymmetric pulmonary opacities, areas of condensation that may be electron-dense due to the two iodine atoms per amiodarone molecule, a density with recognisable segmental distribution or, rarely, shaggy lung nodules. Early ‘chemotherapy lung’ corresponding to DAD and ALI is in the form of a diffuse haze or ground glass. Late chemotherapy lung resembles pulmonary fibrosis. Eosinophilic pneumonia can manifest with lung opacities, having a preferentially subpleural distribution. Acute nitrofurantoin lung is in the form of diffuse haze and small pleural effusions, while the chronic form of the disease shows scattered peribronchovascular zonal consolidation. Organising pneumonia may present with characteristic migratory opacities on serial chest films or diffuse involvement.

Mediastinal or hilar lymphadenopathy characterises those cases with a drug-induced sarcoid-like reaction. Pulmonary opacities in exogenous lipid pneumonia exhibit low attenuation numbers, and pulmonary arteries and their branches are discernible within the involved area. Radiation pneumonitis develops preferentially in the area of the radiation beam, although current stereotactic body irradiation tends to produce circumscribed whorled foci of radiation pneumonitis. Inferring pathology from the pattern seen on imaging should be interpreted with caution. Fatty mediastinal deposits suggest corticosteroid therapy. Embolism of acrylic cement or mercury can be visualized as branched vascular densities on unenhanced CT. An air–fluid level or pneumothorax can be a complication of chemotherapy-induced tumoural cavitation.

**BAL, pathology and other tests**

BAL is indicated to rule out an infection (particularly *P. jiroveci*) via stains, cultures and reverse transcriptase PCR. BAL can also indicate which cell type (*i.e.* lymphocytes, eosinophils or neutrophils) is increased, and whether atypical cells or phospholipid-laden (foamy) alveolar macrophages are present. BAL is useful to diagnose methotrexate pneumonitis, drug-induced eosinophilic pneumonias, APT and chemotherapy lung. BAL cell numbers normalise as patients improve. The BAL in exogenous lipid pneumonia contains stainable mineral lipids free in the BAL fluid and within vacuoles in alveolar macrophages.

Drugs can cause virtually any known pattern of ILD, including: cellular or fibrotic nonspecific interstitial pneumonia; eosinophilic pneumonia; ALI or DAD; classic or acute fibrinous organising pneumonia; interstitial granulomas; alveolar haemorrhage; pulmonary capillaritis or vasculitis; desquamative, giant-cell or lymphocytic-interstitial pneumonia; a usual interstitial pneumonia or pulmonary alveolar proteinosis pattern; and diffuse pulmonary calcification. These are not specific to the drug aetiology. Only phospholipidosis and exogenous lipid pneumonia are suggestive
enough to point to the drug aetiology. While examination of a lung biopsy sample helps eliminate a condition other than drugs, including an infection, a risk–benefit analysis is not available and mortality is significant, especially in the hypoxaemic or immunodepressed. A conservative approach is advised, where drug dechallenge is the usual first step.

No in vitro test of monocyte cell migration in the presence of a drug or metabolite has demonstrated utility in DIRD, and these can be misleading. Certain phenotypic traits may indicate an increased risk of developing DIRD. However, these tests are not widely available.

Monitoring of drug levels in plasma can be helpful to track aspirin over-dosing, or exposure to illicit opiates or levamisole.

Specific reactions

**Parenchymal lung disease**  Methotrexate pneumonitis typifies acute fulminant drug-induced ILD, a condition that can be produced by ~70 other drugs. The condition develops with no forewarning symptoms in patients on long-term methotrexate, typically those with rheumatoid arthritis. A background of pre-existing ILD is a risk factor. The disease manifests with cough, fever, dyspnoea and diffuse pulmonary opacities, sometimes with rapidly progressive white-out and hypoxaemic respiratory failure. Lymphocytes dominate in the BAL. The main differential is *Pneumocystis* or another opportunistic infection that needs to be ruled out using the BAL. Methotrexate pneumonitis may also follow less severe a course with faint pulmonary opacities on imaging. Rarely, pulmonary fibrosis develops following an episode of methotrexate lung. Corticosteroid therapy is indicated in severe cases.

Pulmonary eosinophilia is a common pattern of reaction to one of >150 drugs. Other causes of pulmonary infiltrates and eosinophilia must be ruled out, including parasitic infestation. There is bilateral shadowing in the context of peripheral and BAL eosinophilia. Acute eosinophilic pneumonia is a severe form of PIE with acute respiratory failure. Characteristic causal drugs include NSAIDs, antibiotics (e.g. minocycline), abused drugs and recent uptake of tobacco smoking. Rechallenge is contraindicated, as relapse will almost inevitably occur. Severe systemic presentations characterised by a cutaneous rash and deep-seated organ involvement are termed DRESS or anticonvulsant syndrome.

APT is a distinctive condition that develops insidiously over months or years into treatment with amiodarone in ~3% of patients. High dosages and advanced age increase the risk of developing the condition. APT takes the form of asymmetric areas of pneumonitis or consolidation that can be electron-dense on HRCT, as is liver tissue. Pulmonary function is restrictive in nature. Foamy cells in the BAL are suggestive but not diagnostic of APT. Other APT presentations include ground-glass shadowing, lung nodules, pulmonary fibrosis or pleural effusion. Amiodarone withdrawal may not be sufficient for APT to resolve due to the high affinity and persistence of amiodarone in lung tissue. Corticosteroid therapy often is indicated to speed up recovery. Severe APT can occur after thoracic surgery, particularly in oxygen-exposed patients in the form of an ARDS picture. Prognosis is guarded.

About 150 drugs can cause NCPE (noncardiogenic pulmonary oedema), including the chemotherapeutic agents taxanes and gemcitabine, blood products, tocolytics, and aspirin. Severity ranges from transient pulmonary infiltrates following each course with the drug to acute pulmonary oedema or an ARDS picture. Chemotherapy lung takes 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 more recent evidence implicating TKIs (cetuximab, erlotinib, gefitinib and pemetrexed). On pathology, there is modest interstitial inflammation and oedema, a reactive epithelium, and areas of ALI or DAD. The condition may improve upon drug discontinuance and corticosteroid therapy. In more advanced
cases, an ARDS picture develops. Late cases present irreversible pulmonary fibrosis.

Drug-induced organising pneumonia resembles cryptogenic organising pneumonia or organising pneumonia of other causes. It is in the form of migratory opacities, a fixed opacity or mass, or diffuse shadowing with respiratory failure. Main causal agents include amiodarone, interferons, minocycline, rituximab, statins and breast radiation therapy. Drug withdrawal is followed by improvement while failure to recognise the drug aetiology exposes to the risk of relapses. Corticosteroid therapy is reserved for severe organising pneumonia cases or those with equivocal effect of drug dechallenge.

Interferons, anti-TNF agents and a few other drugs may cause pulmonary infiltrates and lymphadenopathy, and a granulomatous pattern of reaction mimicking sarcoidosis. A confirmatory biopsy and interferon-γ test for TB may be indicated to rule out an infection.

Drug-induced DAH is best diagnosed by BAL, which shows bloodier return on sequential aliquots. Anticoagulants, thrombolytic agents, abciximab and other antiplatelet agents, propylthiouracil, and cocaine (among 70 other drugs) can cause the syndrome. DAH is with or without capillaritis. Rarely, alveolar haemorrhage occurs as a manifestation of drug-induced anti-neutrophil cytoplasmic antibody (ANCA) vasculitis (mainly propylthiouracil- or levamisole-induced).

Pulmonary fibrosis can occur as a complication of treatments with chemotherapy agents, amiodarone and irradiation (then conforming to the radiation portal). Patients present with dyspnoea, diffuse linear or streaky opacities and volume loss on imaging. In contrast to interstitial pulmonary fibrosis, honeycombing is unusual. The condition may stabilise with or progress despite drug discontinuance. Response to corticosteroid therapy is often limited. A few patients have received a lung transplant.

Corticosteroid therapy is indicated in severe drug-induced ILD, preferably if an infection is reasonably excluded and wherever drug withdrawal is not followed by improvement.

**Airway involvement** Angio-oedema classically occurs with ACEIs and it is more common in middle-aged or elderly African-American women. The condition may develop within hours of the first administration of the drug or it occurs months or years into an uneventful treatment, in the form of rapidly progressive breathing difficulty due to upper airway oedema and narrowing. Oedema of the lips, tongue, mouth floor, arytenoids and larynx has been reported, but the thoracic trachea is typically spared. Yearly incidence is ~1%, which makes it a significant cumulative risk in patients treated with these medications over the long term. Some patients develop the condition after airway manipulation or the trauma of intubation. About 40% of the patients are admitted to an intensive care unit (ICU) and mechanical ventilation is indicated in about 10%. Emergent identification and maintenance of upper airway patency is essential.

Orotracheal intubation is indicated in severe cases. Short of stabilising the airway, emergent tracheostomy may be required, with significant attending risks. Although patients improve upon drug discontinuance, close follow-up is necessary as a rebound phenomenon can occur in the first 24-48 h. Patients should not be re-exposed to any ACEI, or grave relapse can occur. Angiotensin receptor II blockers should be given prudently, as a few patients will cross-react.

Catastrophic bronchospasm may follow exposure to as little as one tablet of NSAID, aspirin or nonselective β-blockers (among 120 other drugs). The accident occurs within minutes, with a predilection for aspirin-sensitive individuals, atopics and asthmatics. About 15% of ICU-admitted asthma attack cases are triggered by exposure to such drugs. Insufflated heroin has recently emerged as a significant cause of severe bronchospasm and urine drug screening is indicated. Rechallenge with the culprit drug inevitably leads to relapse with a risk of hypoxic brain damage and death.

Lone, chronic, annoying cough is a common complication of treatments with ACEI.
Incidence depends on which ACEI is used. It may be difficult to make sure when exactly the cough started with respect to when the ACEI was started. When in doubt, dechallenge is indicated. The cough remits with drug discontinuation, except if it was revealing an underlying lung condition.

Rare cases of penicillamine-induced obliterative bronchiolitis have been reported. These may reflect acceleration of underlying small airway disease related to the background connective tissue disease. Obliterative bronchiolitis can complicate herbal therapy with the Asian Sauropus shrub leaf, or be a manifestation of graft versus host disease or lung rejection in stem-cell and lung transplant recipients, respectively.

Foreign-body bronchiolitis has been described in a few subjects who intentionally inhaled cosmetic talc.

**Pleura** Nearly 60 drugs can injure the pleura, including ergolines and dasatinib. Involvement is in the form of a free-flowing exudate with or without eosinophilia, or a serosanguineous effusion. Lupus-inducing drugs can cause drug lupus, which manifests with pleuritis, pleural or pleuropericardial effusion, and circulating and pleural antinuclear antibody (ANA). Anti-TNF agents (infliximab, etanercept and adalimumab) and interferons may also cause lupus. Sometimes, anti-double stranded DNA antibodies are present as well. Signs, symptoms and ANA resolves upon discontinuation of the drug.

All ergots are notable for the insidious development of bilateral pleural thickening with or without an effusion, causing dyspnoea, chest pain, audible friction rubs and restrictive lung dysfunction. There is definite but slow improvement upon discontinuation of the drug.

**Pulmonary vasculopathy** This condition is mostly is in the form of pulmonary hypertension analogous to primary pulmonary hypertension. Iatrogenic pulmonary hypertension may follow treatments with amphetamine-like anorectics (fenfluramine and benfluorex) or
dasatinib. Pulmonary hypertension in drug abusers stems from injection of crushed tablets, or results from stimulant (amphetamine) use or abuse.

**Methaemoglobinaemia** is a drug-induced state of ferric (rather than ferrous) iron oxidation in haemoglobin. Methaemoglobin is a poor oxygen carrier. Clinical presentation is slate-grey cyanosis, a low $S\text{pO}_2$, and a normal measured $P\text{aO}_2$ and calculated $S\text{aO}_2$. Actual measurement of methaemoglobin is indicated in patients exposed to a causative drug, mainly benzocaine, dapsone, nitrites and nitric oxide.

**Further reading**

- Camus P. The Drug-Induced Respiratory Disease Website. www.pneumotox.com
Pulmonary embolism

Massimo Pistolesi

Despite the recent advances in prevention and diagnostic imaging, pulmonary embolism remains a major health problem. The incidence of this pathological condition is as high as one in 1000 cases per year in the general population. Early diagnosis is fundamental as 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 >100,000 people die each year of pulmonary embolism.

Several points are summarised below concerning the diagnostic strategies to be adopted in patients with clinical suspicion of pulmonary embolism that have been highlighted and brought to the attention of the scientific community by recent scientific publications, expert reviews and international guidelines.

Key points

- Although early treatment is highly effective, pulmonary embolism is underdiagnosed and, therefore, remains a major health problem.
- Diagnostic strategy should be based on clinical evaluation of the probability of pulmonary embolism.
- The NPVs and PPVs of diagnostic tests for pulmonary embolism are high when the results are concordant with the clinical assessment.
- Additional testing is necessary when the test results are inconsistent with clinical probability.

General rules for the diagnostic work-up of patients clinically suspected of pulmonary embolism

- Pre-test clinical probability of pulmonary embolism should be objectively assessed in each patient.
- D-dimer should be determined if pre-test probability of pulmonary embolism is low or intermediate.
- Diagnostic imaging of the chest should be used to assess post-test probability of pulmonary embolism in most patients. Further testing is necessary when the post-test probability of pulmonary embolism is neither sufficiently low nor sufficiently high to permit therapeutic decisions.
- Diagnostic strategies of pulmonary embolism can differ significantly in different clinical contexts and special conditions.

Pre-test clinical probability of pulmonary embolism

A thorough clinical evaluation is the key step in raising the suspicion of the disease and setting up appropriate diagnostic strategies. A recent study has shown that the vast majority of patients with pulmonary embolism has at least one of four symptoms which, in decreasing order of frequency, are:

1. sudden onset dyspnoea
2. chest pain
3. fainting (or syncope)
4. haemoptysis

Although the diagnostic yield of individual clinical symptoms, signs and common laboratory tests is limited, the combination of these variables, either by empirical
assessed in each patient with suspected pulmonary embolism before any further objective testing occurs. Future research is needed to develop standardised models, of varying degrees of complexity, which may find applications in different clinical settings to predict the probability of pulmonary embolisms.

D-dimer

Plasma D-dimer levels are elevated in the presence of simultaneous activation of coagulation and fibrinolysis. Consequently, a normal D-dimer level has a high NPV for pulmonary embolism or deep vein thrombosis (DVT). However, endogenous fibrin production may be increased in a wide variety of conditions including, cancer, inflammation, infection, pregnancy and chronic illnesses. Elevated plasma D-dimer levels have, for this reason, a low positive predictive value (PPV) for pulmonary embolism and DVT.

The value of D-dimer measurement in the diagnostic work-up of each patient must be considered according to the determined clinical probability of pulmonary embolism and the sensitivity of the particular method of D-dimer measurement employed. A negative D-dimer test result, measured by any method, in combination with a low probability clinical assessment, excludes pulmonary embolism with accuracy. An intermediate clinical probability also would exclude pulmonary embolism with reasonable certainty if D-dimer was measured by a high-sensitivity ELISA. It has been shown that the 3-month risk of pulmonary embolism 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 a high probability of pulmonary embolism, a concomitant negative D-dimer test does not exclude pulmonary embolism.

The number of patients with suspected pulmonary embolism in whom D-dimer must be measured to exclude one pulmonary embolism episode ranges between three in the emergency department and ≥10 in hospitalised patients. It then
appears recommendable to consider D-dimer measurement in the diagnostic work-up of pulmonary embolism only in outpatients or in patients in the emergency department with low or intermediate levels of clinical probability.

The sensitivity of D-dimer testing for pulmonary embolism increases with the extent of pulmonary embolism. D-dimer concentrations are the highest in patients with pulmonary embolism involving the pulmonary trunk and lobar arteries and with

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**Table 1. Clinical probability scoring systems**

<table>
<thead>
<tr>
<th>Wells score</th>
<th>Geneva score</th>
<th>Pisa score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs and symptoms of DVT</td>
<td>Recent surgery</td>
<td>High</td>
</tr>
</tbody>
</table>
| Heart rate 
  $\geq100$ beats min$^{-1}$                                              | Previous PE or DVT | Intermediate                                                               |
| Immobilisation of surgery                                                  | Older age          | Low                                                                       |
| Previous DVT or PE                                                         | Hypocapnia         |                                                                           |
| Haemoptysis                                                               | Hypoxaemia         |                                                                           |
| Malignancy                                                                | Tachycardia        |                                                                           |
| PE more likely than an alternative diagnosis                              | Plate-like atelectasis |                                                           |
| Low                                                                       | Hemidiaphragm elevation |                                                                       |
| Intermediate                                                               | Low                | $\leq 4$                                                                  |
| High                                                                       | Intermediate       | $5–8$                                                                    |
|                                                                            | High               | $\geq 9$                                                                  |

PE: pulmonary embolism.
perfusion scan defects involving >50% of the pulmonary circulation.

**Diagnostic imaging of the chest: post-test probability of pulmonary embolism**

In recent years, the contribution of CT angiography (CTA) to the diagnosis of pulmonary embolism has 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 pulmonary embolism, 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 of 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. Several recent papers have shown a positive yield rate of CTA of <10% in patients who are clinically suspected of pulmonary embolism. This may indicate that the wide availability of CTA has led to an overuse of the technique as a screening procedure for pulmonary embolism in the emergency department. It has been suggested that a substantial number of CTAs could be avoided by adhering to the information derived from clinical evaluation and D-dimer testing.

Perfusion (Q') lung scanning was introduced 40 years ago as the first chest imaging method for the diagnosis of pulmonary embolism. A normal Q' scan excludes pulmonary embolism (high sensitivity and high NPV), whatever the pre-test clinical probability. However, Q' scanning was thought to be poorly specific (low PPV) for pulmonary embolism because all common pulmonary diseases (infections, neoplasms and COPD) can produce decreased blood flow to the affected regions. Ventilation (V') scanning was added to Q' scanning 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 for diagnosing pulmonary embolism is at variance with the notion that ventilation is shifted away from embolised lung regions. The concept that deadspace ventilation is not significantly increased in the course of pulmonary embolism was widely held in respiratory pathophysiology before the V'/Q' scanning approach was developed, as 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 a high-probability V'/Q' scan (Q' defects without matching V' abnormalities) lacks sensitivity in diagnosing pulmonary embolism, as it fails to identify 59% of pulmonary embolism patients (sensitivity 41%, specificity 97%). The combination of clinical probability and V'/Q' scan results either confirms or excludes pulmonary embolism 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 pulmonary embolism when featuring wedge-shaped (segmental) perfusion defects or not compatible with pulmonary embolism when featuring defects other than wedge-shaped or normal perfusion. When compared with the original PIOPED protocol, the PISA-PED approach has several advantages:

1) Q' scanning either confirms or excludes the clinical suspicion of pulmonary embolism (thus virtually eliminating nondiagnostic examinations)

2) the sensitivity of lung scintigraphy is greatly increased (86% versus 41%) but with minor reduction of specificity (from 97% to 93%)

3) the combination of clinical probability and Q' scanning results confirms or excludes pulmonary embolism in ~80% of patients.
More recently, the diagnostic performance of \( Q' \) scanning for pulmonary embolism 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 ‘pulmonary embolism present’, ‘pulmonary embolism 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 NPVs, with no nondiagnostic readings for the \( Q' \) scan (table 2). Accordingly, in 2012, the Society of Nuclear Medicine revised the practice guidelines for lung scintigraphy, reporting that ‘The modified PIOPED II and PISAPED criteria using information from chest radiograph and perfusion scans have been shown to perform equivalently to those including ventilation scintigraphy, with fewer nondiagnostic studies’.

### Diagnostic strategies in different clinical contexts and special conditions

Most clinicians and diagnostic radiologists feel more comfortable with an anatomical demonstration of whether a clot is present than assessing the probability of pulmonary embolism by looking at \( V'/Q' \) mismatches (PIOPED) or evaluating the shape of a perfusion defect (PISA-PED). Furthermore, contrary to scintigraphy, in most hospitals, CTA is available 24 h a day, 7 days a week. However, CTA cannot be performed in the whole population of patients suspected of pulmonary embolism. As shown in the PIOPED II trial, 50% of the recruited patients did not undergo CTA because of documented contraindications, such as renal failure, abnormal creatinine levels, allergy to the contrast agent, possible pregnancy, critical illness, requirement of ventilator support or recent myocardial infarction. In all these conditions, \( Q' \) scanning could be the preferred alternative approach to the diagnosis of pulmonary embolism. This approach is particularly important for reproductive-age female patients in whom the breast irradiation dose from CTA can be minimised by using the \( Q' \) scan as the first imaging test. It has been recently shown that contrast medium-induced nephropathy is at least as common as a diagnosis of pulmonary embolism after CTA.

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.

### Conclusions

The choice of a diagnostic strategy for pulmonary embolism depends on the pre-test clinical probability of pulmonary embolism, 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 pulmonary embolism, 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 pulmonary embolism 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 pulmonary embolism is suspected in routine clinical practice. Scintigraphy can be considered the preferred alternative chest imaging technique for patients with

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**Table 2. Predictive value of multidetector CTA and \( Q' \) scanning from retrospective evaluation of PIOPED II data**

<table>
<thead>
<tr>
<th>Imaging test</th>
<th>PPV</th>
<th>NPV</th>
<th>Nondiagnostic</th>
</tr>
</thead>
<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>
</tbody>
</table>

Data are presented as %.
contraindication to CTA. If scintigraphy is used, eliminating the V′ scan can reduce cost and radiation load with gain in diagnostic yield.

Further reading

Pulmonary vasculitis

Georgios Margaritopoulos and Athol U. Wells

The principles of diagnosis and management are broadly similar across the individual pulmonary vasculitides, subdivided 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
- to select a level of treatment appropriate to disease severity

Granulomatosis with polyangiitis (GPA) (the entity formerly known as Wegener’s granulomatosis) and Churg–Strauss syndrome (CSS) are the most frequent exemplars of life-threatening anti-neutrophil cytoplasmic antibody vasculitides (AAVs).

Epidemiology and pathogenesis

GPA is the third most prevalent systemic vasculitis (after giant cell arteritis and vasculitides in rheumatoid arthritis), with an annual incidence of 3–11 per million, largely affecting adults aged 30–50 years. CSS has an annual incidence of ~3 per million and mainly affects adults aged 30–50 years. In neither disorder is there a strong sex predilection.

Anti-neutrophil cytoplasmic antibodies (ANCAs) are often present in systemic vasculitides involving the small and medium-sized vessels, including CSS, GPA and microscopic polyangiitis (MPA). ANCAs are subcategorised as cytoplasmic, perinuclear or atypical, and are directed primarily against proteinase-3 in GPA (cytoplasmic) and against myeloperoxidase in CSS (perinuclear), although all ANCA patterns have been reported in both disorders. In vitro and animal data suggest that ANCAs 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 GPA.

Clinical presentation

Vasculitis should be suspected in diffuse alveolar haemorrhage. Haemoptysis is often absent or scant. 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

Key points

- Haemoptysis is often scant 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.
presenting with breathlessness on exertion and an unexplained isolated or disproportionate reduction in TLCO; 2) in patients with features of an underlying systemic vasculitis, such as GPA, 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.

### Churg–Strauss syndrome

The American College of Rheumatology (ACR) 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 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, granulomata and tissue eosinophilia. Pulmonary infiltrates on chest imaging are more common than pulmonary nodules (which very seldom cavitate). Pleural disease is present in 50%. The diagnostic role of ANCA continues to be debated. ANCAs, usually perinuclear ANCAs (p-ANCAs), are present in up to two-thirds of patients, but also occur in many other nonvasculitic autoimmune and infectious conditions.

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**Table 1. Classification of pulmonary vasculitis**

<table>
<thead>
<tr>
<th>Vasculitis</th>
<th>Frequency of lung involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
</tr>
<tr>
<td>Large vessel</td>
<td></td>
</tr>
<tr>
<td>Giant-cell arteritis</td>
<td>Rare</td>
</tr>
<tr>
<td>Takayasu’s arteritis</td>
<td>Frequent</td>
</tr>
<tr>
<td>Medium-sized vessel</td>
<td></td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>Rare</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>No</td>
</tr>
<tr>
<td>Small vessel</td>
<td></td>
</tr>
<tr>
<td>Granulomatosis with polyangiitis (Wegener’s)</td>
<td>Frequent</td>
</tr>
<tr>
<td>Churg–Strauss syndrome</td>
<td>Frequent</td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td>Frequent</td>
</tr>
<tr>
<td>Henoch–Schönlein purpura</td>
<td>No</td>
</tr>
<tr>
<td>Essential cryoglobulinaemia</td>
<td>No</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
</tr>
<tr>
<td>Rheumatological</td>
<td></td>
</tr>
<tr>
<td>Pulmonary–renal (e.g. Goodpasture’s syndrome)</td>
<td></td>
</tr>
<tr>
<td>Relapsing polychondritis</td>
<td></td>
</tr>
<tr>
<td>Behçet’s syndrome</td>
<td></td>
</tr>
<tr>
<td>Chronic infection</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
</tr>
</tbody>
</table>

* #: Chapel Hill international consensus nomenclature; #: with variable medium-sized vessel involvement.

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ERS Handbook: Respiratory Medicine
Thus, neither the presence nor the absence of p-ANCAs is diagnostically definitive and is no more than a useful ancillary finding increasing or decreasing the diagnostic likelihood.

**Granulomatosis with polyangiitis**

The classic historical GPA triad consisted 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 and tends to occur before specific pulmonary manifestations of GPA are apparent. 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 that 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: cytoplasmic ANCAs (c-ANCAs) are not present in all cases (especially when GPA is confined to the lungs), and are also found in other vasculitides, chronic bacterial infections and cryoglobulinaemia.

Among vasculitides, MPA, a necrotising vasculitis affecting small to medium-sized vessels, is the main clinical mimic of GPA. Although pulmonary involvement is less frequent than in GPA, 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 GPA.

**Diagnosis of vasculitis**

A confident diagnosis requires histological confirmation or satisfaction of the requisite investigations.

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**Table 2. Useful investigations for suspected pulmonary vasculitis**

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Lung function tests</th>
<th>Renal function</th>
<th>Immunology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest radiography</td>
<td>Pulmonary function tests</td>
<td>Urine dipstick testing and microscopy for proteinuria, haematuria and cellular casts</td>
<td>ANCAst</td>
</tr>
<tr>
<td>HRCT</td>
<td>Arterial gases</td>
<td>Consider renal biopsy (if evidence of nephritis)</td>
<td>Anti-GBM antibodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Immune complexes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rheumatoid factor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ANAs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antiphospholipid antibodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bronchoalveolar lavage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chest CT</td>
<td>Iron-laden macrophages</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Biopsy</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Renal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Skin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lung (surgical)</td>
</tr>
</tbody>
</table>

GBM: glomerular basement membrane; ANA: anti-nuclear antibody.

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**Table 3. ACR diagnostic criteria for CSS (four out of six required)**

<table>
<thead>
<tr>
<th>Presence of asthma</th>
<th>Peripheral blood eosinophilia (&gt;10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of a neuropathy in a vasculitic pattern (e.g. mononeuritis multiplex)</td>
<td>Evidence of extravascular eosinophilia on biopsy</td>
</tr>
<tr>
<td>Transient pulmonary infiltrates</td>
<td></td>
</tr>
<tr>
<td>A history of sinus disease</td>
<td></td>
</tr>
</tbody>
</table>

Among vasculitides, MPA, a necrotising vasculitis affecting small to medium-sized vessels, is the main clinical mimic of GPA. Although pulmonary involvement is less frequent than in GPA, 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 GPA.
number of clinical criteria. However, many patients with vasculitis have features overlapping between diagnostic entities with transient or non-fulfilment 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 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 GPA 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 with limited involvement. In localised pulmonary GPA and CSS alike, the outcome is much better than with multiorgan involvement. In CSS, the prognosis worsens strikingly with two or more extrapulmonary complications (5-year 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 GPA, and to renal failure, cerebrovascular involvement and gastrointestinal disease in CSS (with 10% of deaths accounted for by lung disease).

Treatment

Remission induction therapy of AAVs should be dictated by disease extent and severity (Table 4).

In limited disease there are limited data supporting the use of oral steroids as monotherapy and/or a single cytotoxic agent such as methotrexate, azathioprine and mycophenolate mofetil.

In early generalised disease, oral cyclophosphamide and steroids are the cornerstones of treatment. 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.

In generalised active disease, oral cyclophosphamide and intravenous methylprednisolone have generally been used. However, oral cyclophosphamide (2.0 mg·kg⁻¹·day⁻¹) and intravenous cyclophosphamide (600 mg·m⁻², at 3 to 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

Table 4. EUVAS classification clinical features

| Limited isolated upper airway disease |
| Early generalised end-organ involvement that lacks a clear or immediate threat to organ function |
| Generalised active end-organ involvement with clinically significant impairment of organ function |
| Severe immediate threat of organ failure or death |
| Refractory disease that has failed to respond to conventional therapies |
| Remission (maintenance): no evidence of ongoing vasculitic activity |

EUVAS: European Vasculitis Study Group.
much less likely to provoke haemorrhagic cystitis and subsequent malignancy, based on long-term systemic lupus erythematosus data. Importantly, in multicentre controlled trials, rituximab given weekly for 4 weeks was found to be as efficacious as oral cyclophosphamide in inducing remission (including a patient with alveolar haemorrhage) and has a particular role in patients with relapsing disease that is poorly controlled by traditional immunosuppressive therapy.

In severe disease with diffuse alveolar haemorrhage or renal failure, plasma exchange should be considered early together with high doses of intravenous methylprednisolone and oral cyclophosphamide. The early use of rituximab is strongly recommended in this difficult clinical scenario and if disease is overtly life-threatening at presentation, initial combination therapy using all three agents should be considered, especially when plasma exchange is not readily available.

In refractory disease, intravenous immunoglobulin and anti-thymocyte globulin have been variably efficacious.

Following initial treatment, less intense long-term therapy is almost invariably required. Standard maintenance treatment has consisted of azathioprine (2.0 mg·kg⁻¹·day⁻¹), usually with in combination with low-dose corticosteroid therapy. Methotrexate (25 mg per week) is as efficacious as azathioprine. However, relapse is more prevalent with the use of mycophenolate mofetil and this agent should, therefore, be considered only in patients intolerant of azathioprine and methotrexate. Maintenance therapy should be continued for a ≥18 months but in many cases, prolonged maintenance therapy is required, sometimes for decades or longer.

Prophylactic co-trimoxazole (trimethoprim 160 mg/sulphamethoxazole 800 mg three times a week) is often used with prolonged intense immunosuppression, to reduce the risk of opportunistic Pneumocystis jiroveci infection. In GPA, co-trimoxazole therapy has been efficacious in localised respiratory tract disease and may have an ancillary role in maintaining remission.

Further reading

Pulmonary hypertension is defined as an increase in mean pulmonary arterial pressure ($mP_{pa}$) $\geq 25$ mmHg at rest as assessed by right heart catheterisation. According to values of pulmonary wedge pressure ($P_{pw}$), pulmonary hypertension can be pre-capillary ($P_{pw} \leq 15$ mmHg) or post-capillary ($P_{pw} > 15$ mmHg).

Pulmonary hypertension can be classified into five groups according to pathological, pathophysiological and therapeutic characteristics. Despite comparable elevations of $mP_{pa}$ in the different clinical groups, the underlying mechanisms, diagnostic approaches, and prognostic and therapeutic implications are completely different.

The clinical classification of pulmonary hypertension is shown in table 1. Group 1 relates to pulmonary arterial hypertension (PAH), corresponding to idiopathic, heritable and associated PAH. The term familial PAH has been replaced by heritable PAH because specific gene mutations have been identified in sporadic cases with no family history, mainly because of the low penetrance of the causal mutations. Heritable forms of PAH include clinically sporadic idiopathic PAH with germline mutations (mainly in the bone morphogenetic protein receptor II ($BMPR2$) gene as well as the activin receptor-like kinase type-1 ($ALK1$) or endoglin genes) 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 accounts 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 characteristics with PAH but also demonstrate a number of differences.

Key points
- Pulmonary hypertension is defined as an increase in $mP_{pa}$ $\geq 25$ mmHg at rest as assessed by right heart catheterisation.
- PAH is a rare condition characterised by chronic pre-capillary pulmonary hypertension 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 pre-capillary pulmonary hypertension ($mP_{pa} \geq 25$ mmHg and $P_{pw} \leq 15$ mmHg).
- Recent advances in the management of PAH include prostaglandins, ERA and PDE5 I.
- Lung transplantation is an option for severe patients deteriorating despite medical treatment.
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 pulmonary hypertension, 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 pulmonary hypertension are those complicating left heart diseases (group 2) and pulmonary diseases (group 3).

All forms of pulmonary hypertension have some common pathological features regardless of their aetiology:

- Medial hypertrophy of muscular and elastic arteries
- Dilation and intimal atheromas of elastic pulmonary arteries
- Right ventricular hypertrophy

### Table 1. Updated clinical classification of pulmonary hypertension (PH)

<table>
<thead>
<tr>
<th>1 PAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Idiopathic PAH</td>
</tr>
<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>
</tr>
<tr>
<td>1.2.3 Unknown</td>
</tr>
<tr>
<td>1.3 Drug and toxin induced</td>
</tr>
<tr>
<td>1.4 APAH</td>
</tr>
<tr>
<td>1.4.1 Connective tissue diseases</td>
</tr>
<tr>
<td>1.4.2 HIV infection</td>
</tr>
<tr>
<td>1.4.3 Portal hypertension</td>
</tr>
<tr>
<td>1.4.4 Congenital heart disease</td>
</tr>
<tr>
<td>1.4.5 Schistosomiasis</td>
</tr>
<tr>
<td>1.4.6 Chronic haemolytic anaemia</td>
</tr>
<tr>
<td>1.5 Persistent PH of the newborn</td>
</tr>
</tbody>
</table>

| 1’ PVOD and/or pulmonary capillary haemangiomatosis |

| 2 PH due to left heart disease |
| 2.1 Systolic dysfunction |
| 2.2 Diastolic dysfunction |
| 2.3 Valvular disease |

| 3 PH due to lung diseases and/or hypoxia |
| 3.1 COPD |
| 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 CTEPH |

| 5 PH with unclear and/or multifactorial mechanisms |
| 5.1 Haematological disorders: myeloproliferative disorders, splenectomy. |
| 5.2 Systemic disorders, sarcoidosis, pulmonary Langerhans’ cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis |
| 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders |
| 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis |

APAH: associated PAH. Reproduced from Simonneau et al. (2009) with permission from the publisher.
In addition to the aforementioned pathological changes common to all forms of pulmonary hypertension, 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. In the early 2000s, the prevalence of idiopathic PAH was about 6 per million in the French Registry and its incidence was 2 per million per year. Median survival of idiopathic PAH was 2.8 years 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 progressive, fatal diseases 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 pulmonary hypertension (group 2: left heart diseases; group 3: pulmonary diseases), distinguishing group 4 (CTEPH) and, finally, making the diagnosis and recognising 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, pulmonary hypertension is found unexpectedly on transthoracic echocardiography requested for another indication.

If noninvasive assessment is compatible with pulmonary hypertension, clinical history, symptoms, signs, ECG, chest radiograph, transthoracic echocardiogram, pulmonary function tests (including nocturnal oximetry if required) and 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 pulmonary hypertension seems ‘out of proportion’ to their severity, less common causes of pulmonary hypertension should be sought. Ventilation/perfusion lung scanning should be considered. If the 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 CT of the chest, right heart catheterisation and selective pulmonary angiography. HRCT of the chest may also

![Figure 1. A typical plexiform lesion in a patient with idiopathic PAH. The lesion is located at an arterial branching point.](image-url)
show signs suggestive of group 1’ (PVOD). If the 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 haemodynamic 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. New York Heart Association (NYHA) functional class is a simple clinical parameter of major prognostic value.

<table>
<thead>
<tr>
<th>Functional class</th>
<th>Description</th>
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</table>
| I                | Patients with PH but without resulting limitation of physical activity  
                    Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near syncope |
| II               | Patients with PH resulting in slight limitation of physical activity  
                    They are comfortable at rest  
                    Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope |
| III              | Patients with PH resulting in marked limitation of physical activity  
                    They are comfortable at rest  
                    Less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope |
| IV               | Patients with PH with inability to carry out any physical activity without symptoms  
                    These patients manifest signs of right heart failure  
                    Dyspnoea and/or fatigue may even be present at rest  
                    Discomfort is increased by any physical activity |

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 and PAH associated with anorexigen use are the most likely to exhibit an acute positive response and to profit from long-term 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 NYHA functional class II...
Avoid excessive physical activity (I-C)
Avoid pregnancy (I-C)
Psychosocial support (IIa-C)
Influenza and pneumococcal infection vaccination (II-C)

**Initial therapy**

<table>
<thead>
<tr>
<th>WHO-FC I–III</th>
<th>CCB (I–C)</th>
</tr>
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<tbody>
<tr>
<td>Sustained response (WHO-FC I–II)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Continue CCB</td>
<td></td>
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</table>

**Vasoreactive**

**Nonvasoreactive**

<table>
<thead>
<tr>
<th>WHO-FC I–II</th>
<th>WHO-FC III</th>
<th>WHO-FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-A</td>
<td>Ambrisentan, bosentan, Sildenafil</td>
<td>Ambrisentan, bosentan, Sildenafil, Epoprostenol i.v., iloprost inhaled</td>
</tr>
<tr>
<td>I-B</td>
<td>Tadalafil</td>
<td>Tadalafil, Treprostinil s.c., inhaled</td>
</tr>
<tr>
<td>IIa-C</td>
<td>Iloprost i.v., treprostinil i.v.</td>
<td>Ambrisentan, bosentan, Sildenafil, tadalafil, Iloprost inhaled and i.v.</td>
</tr>
<tr>
<td>IIb-B</td>
<td>Beraprost</td>
<td></td>
</tr>
</tbody>
</table>

**Inadequate clinical response**

- Sequential combination therapy (IIa-B)
- Oral anticoagulants: IPAH, heritable PAH and PAH due to anorexigens (IIa-C)
- APAH (IIa-C)
- Diuretics (I-C)
- Oxygen (I-C)
- Digoxin (II-C)

**General measures and supportive therapy**

| Expert referral (I-C) |

**Supervised rehabilitation (II a-B)**

**Avoid pregnancy (I-C)**

**General measures and supportive therapy**

| Acute vasoreactivity test (I-C for IPAH) (IIb-C for APAH) |

**BAS (I-C) and/or Lung transplantation (I-C)**

**Inadequate clinical response**

**Figure 2. Evidence-based treatment algorithm for PAH patients (for group 1 patients only). Level of recommendation and evidence have been evaluated in the European Society of Cardiology/European Respiratory Society European Guidelines and shown in red. 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. $^{*}$: to maintain $P_{ao2}$ $\geq 8$ kPa (60 mmHg); $^{*}$: under regulatory review; $^{+}$: IIa-C for WHO-FC II.**
should be treated with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 inhibitor (PDE5 I). Nonresponders to acute vasoreactivity testing or acute responders who do not respond to chronic calcium channel blocker therapy should be considered candidates for treatment with either an ERA, a PDE5 I or a prostanoid. As head-to-head comparisons between 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 \textit{i.v. eprostenol in NYHA functional class III patients, because of its survival benefits. Continuous }\textit{i.v. eprostenol 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, a prostanoid plus an ERA, a prostanoid plus a PDE5 I or a triple combination therapy. 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.

Further reading

Pleural effusion

Robert Loddenkemper

Key points

• Pleural effusions may present as primary manifestations of many diseases. However, most often, they are observed as secondary manifestations or complications of other diseases.
• Cardiac failure is the main cause of pleural effusions. Of noncardiac causes, parapneumonic effusions are commonest, followed by malignant pleural effusions and pleural effusions due to pulmonary embolism.
• Small pleural effusions can be detected best by ultrasound (or CT).
• Pleural effusion can, in the majority of cases, be diagnosed by case history, clinical presentation, imaging techniques and examination of pleural fluid.
• The most important laboratory parameter of pleural fluid is total protein, distinguishing trans- from exudates.
• Biopsy procedures such as closed-needle biopsy or medical thoracoscopy/pleuroscopy may be necessary to confirm or exclude malignant or tuberculous causes.
• Treatment depends upon the underlying disease.
• Local treatment options include therapeutic thoracentesis, chest-tube drainage, chemical pleurodesis and, rarely, surgical interventions.

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 36%, of which ~75% are of bacterial and 25% of viral origin. Malignant pleural effusions follow in 18% of cases, half of which are caused by lung or breast cancer. Pleural effusion is secondary to pulmonary embolism in 14% of cases, to liver cirrhosis in 5% and to gastrointestinal diseases, mainly pancreatitis, in 2% of cases. Many other possible causes, such as collagen vascular diseases like rheumatoid arthritis and systemic lupus erythematosus as well as several drugs (www.pneumotox.com), play an important role in differential diagnosis. Often, pleural effusions are observed after abdominal surgery, liver transplantation or coronary artery bypass surgery/pericardiectomy.

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 (normal production estimated at 15 mL·day^-1 in a 60-kg person). 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 or nephrotic 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 a diffuse increase of capillary permeability, due to localised ruptures (e.g., blood vessels, lymphatic vessels, lung abscess or 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 predominantly in patients aged >60 yrs.

The most common clinical 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. CT and MRI have very similar sensitivities, but require more advanced technology and are therefore much more expensive. However, if pulmonary embolism is suspected, CT angiography is the preferred test.

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. At least if the effusion is small, thoracentesis should 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

![Diagram of Diagnostic Approach to Pleural Effusions](image-url)
even permits a clear diagnosis. The most important criteria are appearance, protein content and cellular components. In the 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 the total protein content in the effusion, for which a threshold value of 30 g·L⁻¹ differentiates a transudate from an exudate. However, this value is not exclusive, and additional parameters such as lactate dehydrogenase (>200 U·L⁻¹) or cholesterol (>0.55 mmol·L⁻¹ (60 mg·dl⁻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, TB or malignant effusion, or oesophageal perforation. Elevated levels of N-terminal pro-brain natriuretic protein (NT-proBNP) (in pleural fluid and/or blood) are characteristic of effusions caused by cardiac failure.

Markedly elevated amylase values are observed in acute pancreatitis and pancreatic pseudocysts, oesophageal perforation and, occasionally, in malignant effusions.

Haemothorax is characterised by purely bloody effusions and haematocrit values that exceed those in peripheral blood by >50%.

In chylothorax, increased triglycerides distinguish chylous from pseudochylous effusions. Although nonspecific, adenosine deaminase and T-cell-based interferon-γ release assays may allow support the diagnosis of TB as the cause of lymphocytic pleural effusions.

Diagnostic testing for the infecting organisms that cause pleural effusion is indicated in parapneumonic effusions/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 and dyspnoea), treatment of the underlying diseases, prevention of pleural fibrosis with

<table>
<thead>
<tr>
<th>Table 1. Investigative parameters of pleural effusion</th>
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<tbody>
<tr>
<td><strong>Obligatory</strong></td>
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<tr>
<td>Appearance</td>
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<tr>
<td>Total protein</td>
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<tr>
<td>Cell differentiation (cytology)</td>
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<tr>
<td><strong>Optional</strong></td>
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<tr>
<td>Glucose (pH)</td>
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<tr>
<td>Lactate dehydrogenase</td>
</tr>
<tr>
<td>Cholesterol</td>
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<tr>
<td>NT-proBNP</td>
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<tr>
<td>Triglycerides</td>
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<tr>
<td>Amylase</td>
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<tr>
<td>Bilirubin</td>
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<tr>
<td>Creatinine</td>
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<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 and parasites</td>
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<tr>
<th>Table 2. Light’s criteria for exudates</th>
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<tr>
<td>Effusion concentration</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Total protein</td>
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<tr>
<td>Lactate dehydrogenase</td>
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ERS Handbook: Respiratory Medicine
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.

Further reading

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 possibly ruptured oesophagus with diminished chest wall integrity can cause free air in the pleural space, as can, 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 according to 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.

In the North American population, incidence varies from 6–7 per 100 000
males to 1–2 per 100,000 females. Bilateral pneumothoraces occur in <10% of patients. Recurrences are observed in 42% of patients, usually within 2 years. 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.

CT imaging is generally not necessary unless abnormalities are noted on the plain chest radiograph or further evaluation is required (e.g., of 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 need 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 most often results 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. Occasionally, the patient

<table>
<thead>
<tr>
<th>Table 1. Classification of pneumothorax</th>
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<tbody>
<tr>
<td><strong>Spontaneous</strong></td>
</tr>
<tr>
<td>Primary (healthy individuals)</td>
</tr>
<tr>
<td>Secondary (underlying pulmonary disease)</td>
</tr>
<tr>
<td>COPD</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Neoplasm</td>
</tr>
<tr>
<td>Catamenial</td>
</tr>
<tr>
<td>Miscellaneous</td>
</tr>
<tr>
<td><strong>Traumatic</strong></td>
</tr>
<tr>
<td>Blunt</td>
</tr>
<tr>
<td>Penetrating</td>
</tr>
<tr>
<td><strong>Iatrogenic</strong></td>
</tr>
<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.
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 importance of sympysis 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.

Indications for surgery in primary spontaneous pneumothorax are presented in Table 2.

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.

The 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.

Table 2. Indications for surgery in primary spontaneous pneumothorax

<table>
<thead>
<tr>
<th>First episode</th>
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<tbody>
<tr>
<td>Prolonged air leak</td>
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<tr>
<td>No re-expansion of the lung</td>
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<tr>
<td>Bilateral pneumothoraces</td>
</tr>
<tr>
<td>Haemopneumothorax</td>
</tr>
<tr>
<td>Occupational hazard (flight personnel, divers)</td>
</tr>
<tr>
<td>Absence of medical facilities in isolated area</td>
</tr>
<tr>
<td>Tension pneumothorax</td>
</tr>
<tr>
<td>Associated single large bulla</td>
</tr>
<tr>
<td>Individual indication</td>
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<tr>
<th>Second episode</th>
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<tbody>
<tr>
<td>Ipsilateral recurrence</td>
</tr>
<tr>
<td>Contralateral recurrence after a first pneumothorax</td>
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</table>

Figure 4. Specimen of an apical bulla resected by stapler.
Apical parietal pleurectomy can be performed easily using this technique with modern endo-scissors and forceps. However, a single-centre randomised study of 787 patients shows that pleurodesis can be achieved with talc poudrage even in young patients with a lower morbidity, less surgical time and no significant differences concerning recurrence of pneumothorax.

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.

COPD is the most common cause of secondary pneumothorax (fig. 6 and table 3). It occurs typically in patients aged >50 years 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. 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, CT 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 health.
condition. Other options, such as chemical pleurodesis, autologous blood injection and permanent fistula drainage can be considered in individual cases.

Conclusion

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 thoracoscopic surgery is the safest approach with excellent long-term results.

Further reading

Mediastinitis

Pierre-Emmanuel Falcoz, Nicola Santelmo and Gilbert Massard

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 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 periodontal, retropharyngeal and peritonsillar abscesses. According to Wheatley et al. (1990), the most common primary oropharyngeal infection is odontogenic (25 out of 43 cases), with mandibular or molar abscesses being the second and third most common primary infections, respectively.

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 spreads from neck to mediastinum along three primary routes: via the retropharyngeal space, the perivascular space and the pre-tracheal 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 (loss of anatomical structure), gravity and negative intrathoracic pressure.

Pathogens involved

DNM is a polymicrobial process with anaerobic organisms being the most

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 intravenous antibiotics as well as early and aggressive surgical drainage.
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 often acting 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

The anamnesis of mediastinitis is as follows.

- Phase I: periodontal or peritonsillar abscess treated by simple antibiotic therapy
- Phase II: erythema and oedema of the neck with or without 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 the 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 the diagnostic study of choice for patients in whom DNM is suspected. Indeed, CT scan findings have been proven to confirm 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

The 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, and feeding jejunostomy

The decision on the type of surgical drainage to be employed is a crucial one. Classically, four approaches have been reported:

1. transcervical
2. standard posterolateral thoracotomy
3. median sternotomy
4. transthoracic via subxyphoid or clamshell incision

A 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. Ideally, CT or, failing that, ultrasound-guided percutaneous drainage 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 of 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, the superior vena cava, oesophagus, and 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. The 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. Further drainage should be carried out if necessary either surgically or by percutaneous drainage.

Further reading


Various neuromuscular diseases (NMDs) 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 to 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 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 mucus 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 (PFTs) should be performed routinely during the evaluation of patients with NMD. Because of the inadequacy of inspiratory muscle function, PFTs generally reveal the pattern of a restrictive ventilatory defect, with the following characteristics:

- preserved TLC until a far-advanced stage of the disease;
- elevated residual volume;
- reduced vital capacity (VC); and
- preserved functional residual capacity.

When VC falls below 55% predicted, 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 ≥ 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 cmH₂O) or a high positive maximal

Key points

- NMD have a range of causes, but common principles apply to their treatment.
- Treatment focuses on ventilatory assistance and assisted coughing techniques.
expiratory pressure result (≥ +90 cmH2O) 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 >270 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% pred or MIP below 30% pred, daytime arterial blood gas analysis should be performed.

Sleep study All patients with NMD should be monitored carefully for the presence of SDB. Nocturnal oximetry alone is inadequate to detect sleep apnoea and hypoventilation. In addition, criteria defining significant desaturations remain controversial. Overnight polysomnography (PSG) or respiratory polygraphy is advisable for patients who develop symptoms and signs of sleep–wake abnormality or nocturnal respiratory failure. It has been suggested that PSG or respiratory polygraphy 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 for long-term ventilatory treatment.

Management

**Long-term noninvasive positive pressure ventilation** In recent years, the approach to care in neuromuscular respiratory failure 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, even noninvasively; and

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.

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**Table 1. NMDs affecting respiratory function**

<table>
<thead>
<tr>
<th>Site of lesion</th>
<th>Specific disorders</th>
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</thead>
<tbody>
<tr>
<td>Anterior horn cell</td>
<td>Amyotrophic lateral sclerosis</td>
</tr>
<tr>
<td></td>
<td>Poliomyelitis</td>
</tr>
<tr>
<td></td>
<td>Type I SMA, intermediate SMA</td>
</tr>
<tr>
<td>Peripheral nerve and/or nerve</td>
<td>Guillain–Barré syndrome</td>
</tr>
<tr>
<td>roots</td>
<td>Charcot–Marie–Tooth disease</td>
</tr>
<tr>
<td>Neuromuscular junction</td>
<td>Congenital myasthenia</td>
</tr>
<tr>
<td>Muscle</td>
<td>Duchenne/Becker muscular dystrophy</td>
</tr>
<tr>
<td></td>
<td>Limb-girdle muscular dystrophy (especially types 2C-2F-2I)</td>
</tr>
<tr>
<td></td>
<td>Facioscapulohumeral muscular dystrophy</td>
</tr>
<tr>
<td></td>
<td>Congenital muscular dystrophy</td>
</tr>
<tr>
<td></td>
<td>Congenital myotonic dystrophy</td>
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<tr>
<td></td>
<td>Acid maltase deficiency</td>
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<tr>
<td></td>
<td>Congenital myopathy</td>
</tr>
<tr>
<td></td>
<td>Mitochondrial myopathy</td>
</tr>
<tr>
<td></td>
<td>Bethlem myopathy</td>
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</table>

SMA: spinal muscular atrophy.
As a consequence, increasing numbers of NMD patients with advanced respiratory impairment are now being successfully treated by long-term noninvasive positive pressure ventilation (NPPV), usually in the home setting. The noninvasive administration of positive pressure ventilation requires a positive pressure ventilator delivering pressurised gas to the lungs through an interface via the nose or mouth, or both. In recent years, manufacturers have developed a new generation of microprocessor-controlled ventilators aimed at combining a minimum warranted alveolar ventilation with maximal patient comfort. 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 effort is unable to sustain adequate alveolar ventilation, causing chronic-stable or slowly progressive respiratory failure.

Indications for NPPV therapy in chronic NMD are symptoms (such as fatigue, dyspnoea, morning headache) and one of the following physiological criteria.

- Significant daytime carbon dioxide retention ($P_{aCO_2} > 50$ mmHg)
- Nocturnal oxygen desaturation ($S_{aO_2} < 88\%$ for at least five consecutive minutes)

- $FVC < 50\%$ pred or MIP < 60 cmH$_2$O (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 round-the-clock (>20 h) ventilatory support

These conditions usually require an invasive application of mechanical ventilation 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-day$^{-1}$. 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 respiratory failure 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), and 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.

Examinations required in the assessment of respiratory function in patients with NMD are:

- checklist of symptoms and signs;
- VC sitting or standing, and lying;
- maximal inspiratory and expiratory pressures;
- cough peak expiratory flow;
- arterial blood gases, if symptoms present; and
- PSG or respiratory polygraphy, if symptoms or nocturnal respiratory failure present.

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Approach to acute respiratory illness

The onset of acute respiratory failure, due to the combination of inspiratory, expiratory or bulbar innervated muscle dysfunction leading to inadequate cough and inability to handle oropharyngeal secretions, is a crucial event in the advanced stage of most NMD and a major cause of death, unless mechanical ventilation is used. Respiratory tract infection is the most common precipitating factor, potentially aggravating inspiratory muscle weakness and promoting atelectasis and pneumonia. A list of potential precipitating factors is presented in table 2.

A noninvasive approach to the management of respiratory tract infections causing acute respiratory failure, 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 techniques have been demonstrated to be effective in facilitating the elimination of airway secretions. Additionally, mechanical insufflation–exsufflation has been shown to effectively mobilise mucous secretions and has been proposed as a complement to manually assisted coughing techniques in the prevention of pulmonary morbidity (fig. 1).

Mechanical insufflation–exsufflation 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. For NMD patients who still require endotracheal intubation and invasive mechanical ventilation, preventive application of NPPV after extubation may provide a clinically important advantage by averting the need for re-intubation or tracheostomy, and shortening their stay in the intensive care unit.

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.

Table 2. Potential causes of acute respiratory failure in NMD patients

<table>
<thead>
<tr>
<th>Common</th>
<th>Less common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection/acute bronchitis</td>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>Sedatives and hypnotics</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>Tracheal haemorrhage (patients with tracheostomy)</td>
</tr>
</tbody>
</table>

Further reading


Chest wall disorders

Pierre-Emmanuel Falcoz, Nicola Santelmo and Gilbert Massard

There is a large and diverse group of congenital abnormalities of the thorax that manifest as deformities and/or defects of the anterior chest wall. Depending on the severity of the case, there may be cardiopulmonary (tolerance to exercise) or psychological implications.

This diverse group includes:
- Pectus excavatum or ‘funnel chest’
- Pectus carinatum or ‘keel chest’
- Poland syndrome
- Cleft sternum

Among these, pectus excavatum and pectus carinatum are the two most common chest wall abnormalities.

Pathogenesis

Over the years, the theories concerning the pathogenesis of pectoral 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.

Pectus excavatum is a recessively inherited chest wall deformity with an occurrence of 0.3% of all births (9:1 predominance in males). In patients with pectus excavatum, the normally 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 indications for surgery may be summarised as follows.
- Aesthetic (psychological repercussion)
- Symptom
- Exercise intolerance, decreased endurance or exercise-induced asthma
- Body images issues (CT scan)
- Pain
- Abnormal/low FVC, FEV₁ or maximum voluntary ventilation
- Decreased oxygen pulse, oxygen uptake or V’E
- Echocardiogram: compression of right atrium/right ventricle (rare)
- CT Haller index >3.0
- Calliper measurement depth >2.5 cm

Pectus carinatum In pectus carinatum, 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 indications for surgery may be summarised as follows.

- Aesthetic (psychological repercussion)
- Pain
- Frequent injury
- Body image issues
- Abnormal pulmonary function testing

**Surgical treatment**

**Pectus excavatum** 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 used).

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 performed by means of minimally invasive surgery, and based on the skeleton's malleability and the remodelling capacity of the thorax. The technique consists of the implantation of a retrosternal steel bar that modifies the concavity of the sternum while maintaining the contour of the reformed thorax, all by means of two small incisions on each side of the thorax. In terms of chest wall kinematics, the Nuss procedure increases chest wall volume by 11% without affecting chest wall displacement or rib cage configuration.

**Pectus carinatum** The repair of pectus carinatum, including exposure, detachment of the pectoralis muscles, transverse osteotomy and resection of the deformed cartilages, is largely identical to that described in pectus excavatum. Operative correction requires double bilateral chondotomy parasternally and at points of transition to the 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 ≥6 months).

**Controversies**

Some controversies do need to be mentioned. First, concerning pectus excavatum, there has never been a randomised controlled trial comparing the results of the two most common surgical procedures. The meta-analysis by Nasr et al. (2010) comparing the Nuss procedure and the Ravitch technique repair suggested no differences with respect to overall complications, length of hospital stay or time to ambulation. 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 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 pectoral 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.

**Conclusion**

Chest wall abnormalities (pectus excavatum and pectus carinatum) 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 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.

Further reading

Pathology and molecular biology of lung cancer

Sylvie Lantuéjoul, Lénaïg Mescam-Mancini, Barbara Burroni and Anne McLeer-Florin

Lung cancer prognosis is poor, with a global survival rate, all stages combined, of ~15%, mainly because most cases are surgically unresectable at the time of diagnosis. However, the discovery in 2004 of EGFR (epidermal growth factor receptor) mutations in a subset of adenocarcinomas, leading to a specific clinical response to tyrosine kinase inhibitors (TKIs), has raised high hopes towards development of targeted therapies (Travis et al., 2011). Lung tumours in nonsmokers are the seventh cause of death by cancer worldwide and are more readily observed in women, especially in Asia. These tumours are characterised by the presence of a ‘driver’ mutation – translocation or amplification of an oncogene – leading to constitutive stimulation of cell proliferation and anti-apoptotic signalling pathways in the tumour cells (fig. 1) (Weinstein et al., 2008).

ErbB family

The ErbB family comprises EGFR (also known as ErbB1 or HER1), ErbB2 (HER2 or Neu), ErbB3 (HER3) and ErbB4 (HER4).

EGFR gene mutations lead to activation of the Ras/mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinase (PI3K)/AKT downstream pathways. These mutations are found in 50% of adenocarcinomas in Asian patients and only 15% of Caucasian patients (West et al., 2012). They mostly arise in nonsmoking women with papillar or lepidic adenocarcinomas, according to the new World Health Organization (WHO) classification of lung adenocarcinoma (Travis et al., 2011), that are thyroid transcription factor (TTF)1 positive (Shigematsu et al., 2006). In 85% of cases, these activating mutations correspond to a deletion in exon 19 (39%) or a point mutation (L858R) in exon 21 (46%), and confer sensitivity to the EGFR TKI gefitinib (marketed as Iressa by AstraZeneca, London, UK) and erlotinib (Tarceva; Genentech–Roche, San Francisco, CA, USA), which are US Food and Drug Administration (FDA)-approved for the treatment of mutated metastatic non-small cell lung carcinomas (NSCLCs) (Uramoto et al., 2007). Conversely, insertion in exon 20 is correlated with primary resistance to EGFR TKIs, and the T790M mutation is associated with secondary resistance (Cheng et al., 2012). Antibodies raised against the exon 19-deleted form (del746–750) (clone 6B6; Cell Signaling Technology (Danvers, MA, USA) monoclonal antibody (mAb) 2085) and the exon 21-mutated form (L858R) (clone D38B1; Cell Signaling Technology mAb 3197) are in development for diagnosis by immunohistochemistry, with sensitivities ranging from 40% to 100% and specificities from 88% to 100% (Kitamura et al., 2010).

Key points

- Lung cancer prognosis is poor, most cases being surgically unresectable at the time of diagnosis.
- Driver mutations, translocations or amplifications are involved in lung oncogenesis, and have led to a molecular classification of lung tumours.
Mutations of HER2 and HER4 are rare (2–4%). HER2 mutations (exon 20) arise in nonsmoking Asian women, and could confer sensitivity to trastuzumab and pan-EGFR/HER2 inhibitors (lapatinib, BIBW29952, neratinib, etc.) (Brabender et al., 2001).

KRAS and BRAF

KRAS mutations are observed in up to 30% of adenocarcinomas. KRAS and EGFR mutations are mutually exclusive (Shigematsu et al., 2006), and KRAS mutations are associated with a resistance to EGFR TKIs.

BRAF is a downstream effector of RAS. The BRAF V600E mutation is the most frequent (50%), before G469A (39%) and D594G (11%). They are observed in 3% of NSCLCs. Mutations other than V600E are more common in smokers; V600E is more common in women with micropapillar adenocarcinoma of poor prognosis. These mutations could confer sensitivity to MEK (MAPK kinase) inhibitors (Paik et al., 2011).

ALK

In 2007, ALK (anaplastic lymphoma kinase) (chromosome 2p23) and EML4 (echinoderm microtubule-associated protein-like 4) (2p21) gene rearrangement was identified in NSCLC (Soda et al., 2007). Other ALK partners have been reported, such as TFG (TRK-fused gene), KIF5B (kinesin family member 5B) and KLC1 (kinesin light chain 1) (Takeuchi et al., 2012; Togashi et al., 2012). These rearrangements are observed in 3–7% of NSCLCs and are mutually exclusive with EGFR and KRAS mutations. Patients with ALK rearrangement are often young, light smokers or nonsmokers at an advanced stage with frequent pleural localisations (Soda et al., 2007). ALK-positive tumours are mostly TTF1-positive adenocarcinomas with signet-ring cells (Rodig et al., 2009). A favourable response with the FDA-approved small molecule ALK and Met inhibitor crizotinib (PF-02341066) has been obtained in phase I/II clinical trials. FISH (fluorescence in situ hybridisation) remains

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**Figure 1.** Druggable genetic abnormalities (mutation, amplification and rearrangement) in pulmonary a) adenocarcinomas and b) squamous cell carcinomas in Caucasian patients.
the gold-standard technique for diagnosis but this technique is costly and time-consuming, and several authors have suggested pre-screening by immunohistochemistry (fig. 2a and b) with two antibodies (clone 5A4 (Abcam, Cambridge, UK) and D5F3 (Cell Signaling Technology)) presenting high sensitivities and specificities (92–100% and 99–100%, respectively) (McLeer-Florin et al., 2012).

**ROS1 and RET**

ROS1 (c-Ros oncogene 1, 6q22) rearrangements have been detected in 0.9–1.7% of NSCLCs (Bergethon et al., 2012; Takeuchi et al., 2012) and RET (Ret proto-oncogene, 10q11.2) rearrangements are observed in 1.2% of adenocarcinomas. Both types of rearrangements arise in young light smoking or nonsmoking patients with adenocarcinomas, and seem to be mutually exclusive with EGFR mutations or ALK rearrangements. Crizotinib could target ROS1 rearranged tumours and vandetanib, a VEGFR (vascular endothelial growth factor receptor), EGFR and Ret inhibitor, could inhibit RET-rearranged tumour cell proliferation (Takeuchi et al., 2012).

**MET**

In lung cancer, the c-Met pathway, including PI3K/AKT/mammalian target of rapamycin (mTOR), Ras/MEK/MAPK, Src and STAT (signal transducer and activator of transcription), is activated either via ligand (hepatocyte growth factor (HGF)) or receptor overexpression, MET gene amplification, mutations, or alternative splicing (Feng et al., 2012). Various scores for c-Met overexpression and MET amplification have been proposed (fig. 2c and d). MET amplification seems to be correlated with a poor outcome (Cappuzzo et al., 2009), and c-Met phosphorylation with the development of brain metastases and primary and acquired resistance to EGFR TKIs (Benedettini et al., 2010).

**PIK3CA**

The PIK3CA gene is mutated in 3.6% of squamous cell carcinomas (SCCs) and 2% of adenocarcinomas with an acinar or papillary histology (Samuels et al., 2005). Mutations affect exons 9 and 20, and amplification of the 3q25–27 genomic region containing PIK3CA (3q26) is detected in 10% NSCLC. In SCC, 3q26 amplification is reported in 40% of cases. These mutations or amplifications are not exclusive with those of EGFR and KRAS. Various PI3K inhibitors are under development, some also targeting mTOR (Heist et al., 2012).

**FGFR1**

Amplification of FGFR1 (fibroblast growth factor receptor 1, 8p12) has recently been discovered in 20% of SCCs and 3.4% of adenocarcinomas (Weiss et al., 2010). Inhibition of FGFR1 by a pan-FGFR TKI, PD173074, is being evaluated in a phase I trial (www.clinicaltrials.gov identifier NCT00979134).

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**Figure 2. Examples of ALK and c-Met changes in NSCLC.** a) Immunohistochemical expression of ALK fusion protein (Abcam clone 5A4). b) ALK gene rearrangement demonstrated by break-apart FISH (Vysis LSI ALK Dual-Color Break Apart Rearrangement Probe; Abbott Molecular, Des Plaines, IL, USA) showing typical split signals (red and green) in the same ALK-rearranged tumour as in a). c) Immunohistochemical expression of c-Met protein (clone SP44; Ventana Medical Systems, Oro Valley, AZ, USA). d) MET gene amplification demonstrated by SISH (silver in situ hybridisation) (black: MET gene; red: chromosome 7 centromere) (Ventana Medical Systems).
Conclusion

Historically, lung cancer classification and treatment were based on tumour histology. Recent discovery of driver mutations in genes encoding tyrosine kinases have led to a molecular classification of lung tumours, allowing the emergence of a personalised, targeted therapy, and improved outcomes.

Further reading

Lung cancer is the most common cause of cancer-related mortality worldwide for both males and females, with a global 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 approximately 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. However, in recent years, an increasing number of never-smoking patients present with a lung cancer, often females with adenocarcinoma histology. A number of other factors may affect the risk of developing lung cancer, such as underlying acquired lung diseases (COPD and pulmonary fibrosis) and environmental exposures, often synergistically with smoking (asbestos, radon, metals, ionising radiation including previous radiotherapy, fine dust air pollution 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 (EGFR, KRAS, c-MET, BCL2, etc.), deletions and/or mutations in tumour suppressor genes (TP53, RB1 and genes on chromosome 3p) or altered telomerase activity.

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 and facial oedema), Pancoast syndrome (pain, Horner sign and hand muscle atrophy).
In addition, paraneoplastic effects of lung cancer are common: hypercalcaemia (nausea, lethargy and dehydration), syndrome of inappropriate antidiuretic hormone (hyponatraemia), hypertrophic osteoarthropathy (clubbing and periosteal proliferation of tubular bones), dermatomyositis, haematological manifestations (anaemia, leukocytosis and thrombocytosis), hypercoagulability, Cushing’s syndrome and 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 metastases are the liver (pain and constitutional symptoms), adrenal glands, bones (pain) and brain (headache, paresis and 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 (PET) with $^{18}$F-2-fluoro-2-deoxy-D-glucose (FDG) (enhanced uptake of FDG is seen in tumours) or contrast-enhanced CT. For most lesions, pathological documentation is needed: peripheral sampling of tissue by bronchoscopy (nowadays assisted by endobronchial ultrasound), fine-needle aspiration by CT guidance or, sometimes, surgical sampling by video-assisted thoracoscopy.

Historically, very small diagnostic samples were sufficient to make the pathological diagnosis of either non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC). One of the major recent advances in chemotherapy and molecular targeted therapy has been the use tissue-based predictive factors for treatment efficacy (e.g. nonsquamous histology for pemetrexed, activating EGFR mutation for gefitinib or erlotinib and EML4–ALK translocation mutation for crizotinib). This has largely changed the role of the pulmonologist in the diagnostic process and reversed the evolution of diagnosis based on ever smaller samples to one based on ever less invasive techniques. In order to respond to the increasing demand for larger amounts of tissue to perform additional immunohistochemistry, fluorescence in situ hybridisation or mutation testing, it now important to maximise the number of biopsies at bronchoscopy, to make cell blocks of the cytological samples obtained at endobronchial ultrasound-guide transbronchial needle aspiration (EBUS-TBNA) or to use larger core needles when taking a CT-guided transthoracic biopsy.

**Staging**

Staging, the process of determining the extent of lung cancer, is crucial for the
prognosis and choice of treatment. The stage is defined by the international TNM (tumour, node, metastasis) classification. The most recent version, adopted since 2010, is applicable to NSCLC, SCLC and carcinoid tumours. The combination of T, N, and M descriptors determines the overall disease stage: stage I (localised tumour and 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) (table 1).

Staging is a stepwise process. For all patients, the minimal noninvasive staging will include a detailed medical history (smoking habits, occupational history, intra- and extrathoracic and paraneoplastic symptoms, and performance status), a physical examination (e.g. careful auscultation and percussion may suggest the presence of atelectasis, pleural effusion or large airway obstruction, liver enlargement may indicate hepatic metastases, etc.), blood testing and a contrast-enhanced CT from the adrenal gland to the lung apex. According to symptoms and locoregional spread, CT or MRI of the brain, bone scintigraphy, or other tests may be appropriate.

Patients with a potential for radical treatment (i.e. no evident metastatic disease or major comorbidity) will usually need additional tests. They will benefit from FDG-PET or fusion FDG-PET-CT, which improve staging of locoregional lymph node and distant spread (e.g. PET may indicate unexpected metastases in up to 20% of patients).

In nonmetastatic patients, the exact definition of locoregional spread will help to choose the best type of multimodality treatment (i.e. how to combine chemotherapy, surgery and radiotherapy). Detailed invasive locoregional staging often is indicated for that purpose, as the value of CT to ascertain the nature of mediastinal lymph nodes is limited: pooled positive predictive value 50% and negative predictive value 80%. Addition of PET has improved these figures to 80% and 90%, respectively. Based on a recent landmark randomised trial, endoscopic staging has taken over the role of mediastinoscopy as initial test in most patients. Endoscopic lymph node staging consists of EBUS-TBNA (for paratracheal nodes 2R, 2L, 4R and 4L, subcarinal node 7, and hilar nodes 10R, 10L, 11R and 11L) and/or oesophageal ultrasound-guided fine-needle aspiration (for left paratracheal nodes 4L and 5, subcarinal node 7, paraoesophageal nodes 8 and 9, and hilar nodes 10R and 10L) (fig. 2). These techniques can reduce the need for baseline surgical staging by 70%. Endoscopic staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
<th>5-year survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Surgical resection (adjuvant chemotherapy for large</td>
<td>58–73</td>
</tr>
<tr>
<td></td>
<td>tumours)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radiotherapy if medically inoperable</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Surgical resection and adjuvant chemotherapy</td>
<td>36–46</td>
</tr>
<tr>
<td></td>
<td>Radiotherapy if medically inoperable</td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>Surgical or nonsurgical combined-modality treatment</td>
<td>24</td>
</tr>
<tr>
<td>IIIIB</td>
<td>Nonsurgical combined-modality treatment</td>
<td>9</td>
</tr>
<tr>
<td>Advanced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Chemotherapy and/or targeted agents</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

Table 1. Major staging groups, preferred treatment patterns and expected 5-year survival rates for NSCLC

Data from Goldstraw et al. (2007).
may lead to false-negative results in ~20% of the cases; therefore, a negative test result in a patient suspected of having lymph node disease should be completed by an adequate surgical procedure. Another important advantage of using endoscopic techniques upfront is that mediastinoscopic staging can be reserved as the most accurate technique for assessment of lymph node staging after induction treatment.

**Functional assessment**

All patients need an ECG and basic pulmonary function tests, such as FEV₁ and FVC. In patients scheduled for radical treatment (surgical or nonsurgical...
combined-modality treatment), a more detailed functional evaluation is needed, especially as many patients have co-existing smoking-related cardiopulmonary disease. To determine the volume of lung that can be removed and to identify patients at risk of post-operative complications, each patient should undergo pulmonary function testing: lung volumes and TLCO. Post-operative respiratory failure rarely occurs if the predicted post-resection FEV1 and TLCO are more than 30–40% of the normal values.

Additional cardiopulmonary exercise testing with ergospirometry is indicated when baseline FEV1 or TLCO values are <80% predicted. In this group, patients who reach their target heart rate and exercise capacity and who have a maximal oxygen uptake ($V'_O_2\text{max}$) >15 mL·kg$^{-1}$·min$^{-1}$ are less likely to have post-operative complications or mortality. If the $V'_O_2\text{max}$ is between 10 and 20 mL·kg$^{-1}$·min$^{-1}$, quantitative pulmonary perfusion scanning may be used to calculate more precisely the estimated post-operative values and the proportion of lung that can be removed. Moreover, patients with a baseline oxygen saturation of <90%, those who desaturate more than 4% during exercise testing or those with $P_aCO_2 >45$ mmHg have a greater likelihood of post-operative complications.

Apart from pulmonary function evaluation, assessment of other comorbid conditions, such as heart disease (echocardiography and coronary tests), renal insufficiency and diabetes, may be warranted.

Further reading

Most patients with lung cancer present in advanced stages of disease and cannot be cured by surgery or radiation therapy. In metastatic disease, the focus of treatment is palliation of symptoms and maintenance of quality of life. Systemic treatment with chemotherapy and with newer ‘targeted’ therapies form the basis of treatment in stage IV, and can significantly improve symptoms, and improve both progression-free and overall survival. Whereas chemotherapy involves the use of substances with nonspecific cytotoxic and antiproliferative properties, molecular biological therapy aims at more specific targets that are usually more active than normal.

Depending on the clinical situation, either a single chemotherapeutic agent or a doublet may be given. If the patient is fit enough for chemotherapy, a platinum-based doublet is used. Differences in tumour histology and molecular biology are increasingly taken into account when planning systemic therapy, in particular for non-small cell lung cancer (NSCLC).

In earlier stages of disease, systemic chemotherapy 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).

**Key points**

- Due to the interdisciplinary nature of lung cancer treatment, decision-making should take place in structured tumour boards.
- Performance status is an important parameter in treatment decision-making.
- The side-effects of chemotherapy vary between agents and should be taken into account during treatment planning.
- Endobronchial techniques are an important tool in the palliation of lung cancer patients.
- First-line treatment of advanced NSCLC, adjuvant chemotherapy and chemotherapy for radiochemotherapy is mostly a platinum-based doublet.
- The individualisation of treatment based on histology and molecular biology, in particular the EGFR mutation and EML4–ALK fusion, is of increasing importance in NSCLC.
- SCLC generally responds well to initial chemotherapy.
- Prophylactic cranial irradiation has an important role in the treatment of SCLC.
How to treat a patient is dependent 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 (WHO)/Eastern Cooperative Oncology Group (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, cyclophosphamide and vincristine. In SCLC, 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

<table>
<thead>
<tr>
<th>Table 1. The major side-effects of chemotherapeutic agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nausea and vomiting</strong></td>
</tr>
<tr>
<td>Cisplatin is highly emetogenic</td>
</tr>
<tr>
<td>Prophylactic antiemetics should be given to all patients receiving chemotherapy</td>
</tr>
<tr>
<td>Delayed nausea and vomiting may occur days after administration</td>
</tr>
<tr>
<td>Commonly used antiemetics include dexamethasone, serotonin antagonists and neurokinin-1 inhibition</td>
</tr>
<tr>
<td><strong>Neutropenia</strong></td>
</tr>
<tr>
<td>Severe neutropenia refers to peripheral neutrophil counts &lt;500 cells·μL⁻¹</td>
</tr>
<tr>
<td>Reverse isolation in hospitalised patients with severe neutropenia may reduce the risk of nosocomial infections</td>
</tr>
<tr>
<td>Febrile neutropenia refers to elevated oral or axillary temperature (≥38°C for ≥1 h or &gt;38.2°C one-time measurement) in the setting of severe neutropenia, and should be treated with intravenous antibiotics</td>
</tr>
<tr>
<td>The prophylactic use of granulocyte colony-stimulating factors can be considered in those at increased risk of developing febrile neutropenia</td>
</tr>
<tr>
<td><strong>Anaemia</strong></td>
</tr>
<tr>
<td>Consider transfusion in symptomatic patients or those with very low haemoglobin</td>
</tr>
<tr>
<td>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><strong>Neuropathy</strong></td>
</tr>
<tr>
<td>Most commonly caused by the taxanes and vinorelbine</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
</tr>
<tr>
<td>Multifactorial</td>
</tr>
<tr>
<td>Malnutrition, anaemia and depression commonly play a role</td>
</tr>
</tbody>
</table>
progresses quickly after chemotherapy, second-line treatment is usually recommended. Inclusion in clinical trials or best supportive care alone 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 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 most NSCLC patients with metastases or malignant pleural effusion, although its

<table>
<thead>
<tr>
<th>Cisplatin</th>
<th>Highly emetogenic (appropriate use of anti-emetics is essential) Nephrotoxic: avoid in patients with reduced GFR Pre-hydration (≥500 mL NaCl 0.9% per 50 mg cisplatin) reduces the risk of nephrotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>Consider as alternative to cisplatin in elderly patients or those with contraindications to cisplatin, dosed at AUC</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>May cause neuropathy or neutropenia 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 with radiotherapy due to increased side-effects</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>Short (10-min) infusion time Effective in patients with nonsquamous cell NSCLC and mesothelioma The risk of myelosuppression can be significantly reduced by vitamin B&lt;sub&gt;12&lt;/sub&gt; (1000 IU i.m. every 9 weeks) and folate (0.35–1 mg day&lt;sup&gt;-1&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Premedication to prevent allergic reaction is required (dexamethasone and 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; i.m.: intramuscular.

| Table 3. The WHO/ECOG scale |
|-------------------------------|---------------------------------|
| WHO/ECOG performance status | Description                     |
| 0                             | Patient is fully active and unrestricted in daily activities |
| 1                             | Patient cannot carry out physically strenuous activities but is able to care for self and carry out light work |
| 2                             | Patient is ambulatory and can care for self but is unable to work Up and about for >50% of waking hours |
| 3                             | Patient is limited in self-care activities and confined to bed or chair for >50% of waking hours Completely disabled Cannot care for self Totally confined to bed or chair |
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 four to six 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. First-line treatment with targeted therapies (see later) is an option for some patients.

Second/third-line chemotherapy in NSCLC generally involves monotherapy with a chemotherapeutic agent (docetaxel for all NSCLC histologies and pemetrexed for nonsquamous histology) or the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) 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 with an alternative medication (switch maintenance) or with one of the original substances (continuation maintenance) may be beneficial, perhaps especially for patients who did not respond particularly well to first-line chemotherapy (stable disease patients compared to partial/complete responders).

**Targeted therapies** The role of targeted therapies in NSCLC is growing rapidly. At the moment, especially in adenocarcinoma, in ~50% of the tumours, we can detect a so-called driving mutation. Unlike traditional chemotherapeutics, which interfere with cell division in all rapidly dividing cells, targeted therapies attempt to inhibit cell activity more selectivity at the level of growth factor receptors and intracellular signalling cascades.

EGFR is involved in signalling cascades leading to cell division and proliferation. In tumour cells, mutations in and overexpression of the EGFR gene or 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 TKIs that inactivate the intracellular portion of 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, may cause resistance. Response to EGFR inhibitors is also associated with certain clinical characteristics (female patients, nonsmokers, adenocarcinoma and Asian ethnicity). Erlotinib is approved as a second- or third-line therapy in NSCLC regardless of EGFR mutation status but should only be given in the first line if an activating EGFR mutation is present. Gefitinib is only approved for use in patients with a documented activating mutation in EGFR. First-line treatment with erlotinib has been demonstrated to improve progression-free survival in European patients harbouring...
EGFR mutation compared with first-line chemotherapy.

Usually, a secondary resistance develops during treatment with erlotinib or gefitinib, which is, among others, caused by MET amplification or resistance mutations in EGFR. For this situation, further treatment in clinical trials would be possible.

Further treatable growth-activating targets are ALK (anaplastic lymphoma kinase) gene rearrangements, which occur in approximately 3–5% of NSCLC, especially in adenocarcinoma. EML4 (echinoderm microtubule-associated protein-like 4)–ALK fusion is especially found in patients with NSCLC. Crizotinib is a TKI of MET, c-Ros and ALK. Phase II data have shown these tumours to be highly sensitive to the ALK TKI crizotinib. Crizotinib is approved for the treatment of EML4–ALK-positive NSCLC in the USA and Europe.

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 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 plus paclitaxel was shown to provide a survival benefit, whereas the combination of bevacizumab with cisplatin plus gemcitabine only showed a benefit in progression-free survival.

Bevacizumab can cause severe haemoptysis, seen in a 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 is given. The data in the literature are not adequately elaborated; in practice, more than six cycles are often 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, 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. The general supportive/palliative measures are applied additionally as needed.

Palliative radiation provides symptomatic relief in patients with brain and bone metastases. Pleurodesis is an option for patients with recurrent malignant pleural effusions.

Further reading

Despite the progress made in thoracic oncology over the past 30 years, surgical treatment based on anatomical resection with complete mediastinal lymph node dissection remains the mainstay of cure 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 stereotaxic radiotherapy and radiofrequency ablation; these treatments are not yet scientifically validated and ignore lymphatic spread (see later). 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; this is of weak clinical relevance for the individual patient, given that treatment of 20 patients is needed to save one at 2 years. The result deteriorates in the long term, and long-term complications of chemotherapy appear in survivors. In summary, to date, the best possible surgery needs to be performed in operable patients. Classic resection by open thoracotomy is increasingly challenged by VATS (video-assisted thoracoscopic surgery) in the case of small tumours. Generalisation of screening programmes with low-dose CT is expected to increase considerably accrual of small, T1 tumours in the future (National Lung Screening Trial Research Team, 2011).

Work-up of the patient should include a check-up of fitness according to European Respiratory Society/European Society of Thoracic Surgeons (ESTS) guidelines.

The aim of this section 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 of early-stage lung cancer, it seems adequate to restrict this label to patients with reasonable chances of 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 years, which is comparable to the worst N1. Furthermore, resectable T4N0 disease, such as selected cases of Pancoast tumours or main carinal invasion, may achieve a 5-year 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% to 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-year survival rates vary between 35% and 50%. Besides a difference between T1N1 and T2N1, there is a very dissimilar survival pattern according to the intra- or extralobar location of the N1 node. Intralobar N1 is credited with 5-year survival close to 55%, whereas in extralobar N1 it reaches only 35% (table 2).

For stage IIIA-N2, survival rates at 5 years are considerably lower and range from 15% to 25%. However, minimal N2 is a subgroup with a possible survival rate of 35% at 5 years. There is a small subset of completely resectable IIIA-T4No disease (Pancoast tumours, main carina involvement) that can achieve a survival of close to 50% at 5 years.

The large majority of patients with stage IIIB are inoperable and global survival at 5 years is <5%.

Quality requirements: the surgeon and the institution

Thoracic oncologic surgery is a specialised medical activity. Well-trained thoracic surgeons working in high-volume units obtain the best results.

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 1583 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 <10 resections during the observation period.

Hospital volume and its impact on post-operative mortality A review of data from the Medicare registry between 1994 and 1999

| Table 1. Survival following stage I disease: independent factors of prognosis |
|-----------------------------|-------------------|-----------------|--------|--------|
|                             | Yes %             | No %            | p-value| Relative risk |
| Pneumonectomy              | 53 %             | 62.7            | 0.031  | 1.55   |
| Angio-invasion              | 54.5             | 61.9            | 0.029  | 1.85   |
| Atherosclerosis            | 46.3             | 64.3            | 0.017  | 1.55   |

Data from Thomas et al. (2002).
revealed that operative mortality following lobectomy varied from 6.4% in a low-activity centre (fewer than nine 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%, respectively.

We may conclude that a high hospital volume warrants the necessary routine not only of the operating surgeon, but also of the surrounding team.

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 2118 patients operated upon in one of 76 hospitals over a 10-year period, divided into quintiles according to hospital volume. Operative mortality ranged from 3% at high- to 6% at low-volume units; operative morbidity ranged 20–44%. The 5-year survival decreased from 44% at high- to 33% at low-volume centres.

This study suggests that appropriate decision-making is enhanced by routine.

Qualification of thoracic surgeons depends on national rules in the different European countries. In an attempt at harmonisation over the European territory, the European Union of Medical Specialists has created the European Board of Thoracic Surgery certification, which may be obtained by an examination conducted every year by the ESTS.

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.

Complete anatomic resection Anatomic resection means either lobectomy or pneumonectomy with precise hilar dissection, according to the locoregional 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% to 10% following pneumonectomy. Mortality after pneumonectomy may be >10% in patients aged >70 years, 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).

Resection of less than a pulmonary lobe is not recommended as routine. The Lung

<table>
<thead>
<tr>
<th>First author</th>
<th>Patients n</th>
<th>5-year survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yano</td>
<td>78</td>
<td>64</td>
</tr>
<tr>
<td>Van Velzen</td>
<td>391</td>
<td>57</td>
</tr>
<tr>
<td>Riquet</td>
<td>256</td>
<td>53</td>
</tr>
</tbody>
</table>
Cancer Study Group (Ginsberg et al., 1995) compared lobectomy and segmentectomy (or wedge excision) for T1N0 cancer in a randomised trial. There was a drop in 5-year survival of 20% for patients subjected to segmentectomy and a three-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.

**Complete homolateral lymph node dissection**

The goals of lymph node dissection are:

1. to ascertain staging
2. to ensure complete resection of the disease

Staging is important at the individual level to set prognosis and to define the most appropriate treatment strategy. At 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. CT 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 histological 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:

- random sampling of nodes
- complete node dissection

Obviously, only complete dissection appears to be serious and reliable. The arguments are as follows.

In patients with pathological stage I-No 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 compared sampling and dissection in each single case of 248 resections. Sampling identified 52% of resections as 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 and oesophagus). On the right side, it includes lower oesophageal nodes within the pulmonary ligament, subcarinal space and paratracheal space. On the left side, it includes the pulmonary ligament, subcarinal space, aortopulmonary window, phrenic nodes and subaortic nodes up to the left tracheobronchial angle.

Formal lymph node dissection does not increase the post-operative complication rate. There is increasing evidence for a positive effect on survival. An initial 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-year 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

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 for 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 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.

What is the impact of minimally invasive surgery?

Minimally invasive major resections, such as lobectomy and, more recently, segmentectomy, performed by VATS, are increasingly offered to patients with small tumours. The common end-points are that, while operative mortality is similar to that of open procedures, there is a significant decrease of complication rate and length of hospital stay. Post-operative pain is considerably lower, recovery is faster and the social cost is decreased (Whitson et al., 2008; Paul et al., 2010; Yang et al., 2012).

Oncologic concerns may be addressed as follows. Minimally invasive resection can be recommended for T1 and small T2 tumours, and achieves equivalent long-term survival rates when compared with open surgery. Evidence for N1 or N2 disease primarily orientates towards classic open surgery, except for very experienced teams. There is no doubt that a precise anatomical dissection of the hilar structures (artery, vein and bronchus) can be safely performed. A negative PET lowers the risk for mediastinal lymph node involvement; furthermore, there is a shift towards less invasive histology in the case of small tumours (adenocarcinoma with lepidic growth in particular).

Nevertheless, a careful evaluation of the mediastinum with mediastinoscopy and/or lymph node dissection is still recommended.

The demand for minimally invasive surgery will certainly be increased if lung cancer screening programmes with low-dose CT are generalised.

---

Table 3. Lymph node dissection increases survival: results of a randomised study

<table>
<thead>
<tr>
<th>5-year survival</th>
<th>268 dissections</th>
<th>264 samplings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>82.2</td>
<td>57.5</td>
</tr>
<tr>
<td>Stage II</td>
<td>50.4</td>
<td>34.0</td>
</tr>
<tr>
<td>Stage 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>

Date are presented as %. Reproduced from Wu et al. (2002), with permission from the publisher.

---

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>
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<td>31</td>
</tr>
<tr>
<td>Massard</td>
<td>70</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>Icard</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>

Data are presented as %.
Further reading

Radiotherapy for lung cancer

Luigi Moretti and Paul Van Houtte

While surgery remains the treatment of choice for early-stage disease, radiotherapy is the commonest treatment modality for lung cancer, with >50% of patients receiving radiation at some point in their disease history, either for cure or palliation. In the past, conventional radiotherapy yielded poor outcomes for early-stage patients or locally advanced disease due to the radiation techniques available. However, today, major technical advances (positron emission tomography (PET)/CT-based treatment plans, three-dimensional treatment planning, multileaf collimators, gating techniques, etc.) allow us to overcome the challenge of delivering an effective radiation dose while protecting vital organs or structures (lungs, oesophagus, heart, spinal cord, etc.). This is well illustrated by the breakthrough of stereotactic body radiation therapy (SBRT) for early-stage disease leading to impressive local control and survival (table 1).

Furthermore, the management of locally advanced non-small cell lung cancer (NSCLC) has moved to a multimodality approach including a platinum-based chemotherapy delivered concurrently with high-dose radiotherapy and surgery for selected cases. Systemic treatments (chemotherapy and targeted agents) are taking a more and more important place either for stage IV disease or in association with radiotherapy and surgery for earlier cases. Today, NSCLC is no longer considered a single disease, and pathological subtypes or receptor mutations (epidermal growth factor receptor, etc.) should be identified.

For small cell lung cancer (SCLC), definitive chemoradiotherapy is usually used for limited- or extensive-stage SCLC with a good response to chemotherapy, although surgical resection for early-stage SCLC (T1-2N0) may be considered.

**Mechanism of action**

At the cellular level, the most important effects of radiation are linked to double-stranded breaks in nuclear DNA, either by direct ionisation or by indirect formation of free radicals, formed by water radiolysis, that subsequently interact with DNA. Radiation

**Key points**

- For early-stage NSCLC patients, surgery (lobectomy or an anatomical segmentectomy with lymph node dissection) remains the standard treatment, while SBRT is indicated for medically inoperable patients.
- In locally advanced NSCLC, definitive concurrent chemoradiotherapy is preferred while surgery is used for selected cases (with induction or adjuvant chemotherapy).
- Although still controversial, post-operative radiotherapy is recommended for patients with positive surgical margins and/or pathologic N2 disease.
- The current management of SCLC includes chemoradiotherapy with or without induction chemotherapy.
- PCI is indicated for all stages of SCLC after response to primary therapy.
can also affect the processes of the cell cycle and alter cell growth. When not able to repair the damage, cell undergo several types of death, i.e. apoptosis or senescence, and are ultimately cleared by physiological normal mechanisms. Similarly, adverse effects of radiation are mainly the consequence of radiation damage to surrounding normal tissues, which were not able to repair adequately.

**Tumour radiobiology**

Tumour radiobiology is complex, as response depends not only on dose but also on individual radiosensitivity, timing, total dose, fraction size and other agents given concurrently (i.e. chemotherapy). It allows the optimisation of a radiotherapy schedule and therapeutic ratio for individual patients in regards to maximising tumour control probability and minimising normal tissue complication probability.

The biological factors that influence the response of normal and neoplastic tissues to fractionated radiotherapy are repair, redistribution, repopulation, reoxygenation and intrinsic radiosensitivity (the ‘five Rs’ of radiotherapy).

**Radiotherapy indications**

- Definitive treatment for medically inoperable stage I NSCLC using hypofractionated SBRT
- Definitive treatment for locally advanced (stage III) NSCLC and limited-stage SCLC with concurrent chemotherapy
- Prophylactic cranial irradiation in all stages of SCLC after response to primary treatment
- Post-operative radiation after surgical resection with pathologic N2 disease and T4 disease except for separate nodules in the same lobe, close/positive surgical margins and gross residual disease
- Palliation for pain, bleeding, superior vena cava syndrome, brain metastasis and cord compression

**Techniques of radiotherapy**

- External beam radiation with three-dimensional conformal radiation (3D-CRT), intensity-modulated radiotherapy or SBRT
- Intraoperative high dose rate brachytherapy (used after wedge resection, this may improve local control rates)
- Endobronchial brachytherapy (for palliation of endobronchial disease or to boost treatment after initial course of definitive 3D-CRT for primary cancer with endobronchial component or for small endobronchial-only tumour)

**Radiotherapy planning**

**NSCLC** For definitive radiotherapy, the prescribed dose depends on the target

---

**Table 1. Overall survival based on stage at presentation and treatment applied**

<table>
<thead>
<tr>
<th>Disease stage</th>
<th>Overall survival</th>
<th>Median survival</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I–II (early)</td>
<td>53–80% at 5 years</td>
<td>20–60 months</td>
<td>Surgery</td>
</tr>
<tr>
<td></td>
<td>68–77% at 5 years</td>
<td></td>
<td>SBRT</td>
</tr>
<tr>
<td>III (locally advanced)</td>
<td>9–16% at 5 years</td>
<td>13–17 months</td>
<td>Chemoradiation</td>
</tr>
<tr>
<td></td>
<td>15–22% at 3 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV (advanced)</td>
<td>30–40% at 1 year</td>
<td>8–10 months</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>SCLC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>20–30% at 5 years</td>
<td>18 months</td>
<td>Chemoradiation</td>
</tr>
<tr>
<td></td>
<td>30–40% at 3 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50% at 1 year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extensive</td>
<td>0–2% at 3 years</td>
<td>7–10 months</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td></td>
<td>27–40% at 1 year</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
volumes and the presence of organs at risk in the region that needs to be treated. In addition, local tumour control is correlated with total dose delivered and the delivery time, with a potential impact on survival.

Traditionally, the mediastinum or elective nodal area were treated with 45–50 Gy in conventional fractions (once-daily doses of 1.8–2.0 Gy), and the primary or gross tumour boosted to a total dose of ≥60 Gy. The tumour dose of 60 Gy was established as the standard of care in the old Radiation Therapy Oncology Group (RTOG) 73–01 randomised trial. Nevertheless, there was still a high rate of local failure and distant relapse. Thus, higher radiation doses have been advocated in an attempt to improve local control, either by increasing the total dose with conventional daily dose of 2 Gy or using an accelerated radiation schedule. This was only possible by changing the old concept of elective nodal irradiation to limit the radiotherapy fields to the primary tumour and involved nodes (biopsy-proven, or based on CT scan and fluorodeoxyglucose PET imaging). Another important step was the use of induction chemotherapy, which was showed to improve survival by reducing distant metastases. A concurrent schedule has been established to be superior to the induction approach both in long-term survival and local control, but with an increase in acute toxicities. Different regimens are used, usually a platinum-based doublet with a third-generation drug (i.e. paclitaxel or vinorelbine). The optimal sequence must still be defined: concurrent versus induction followed by a concurrent chemoradiation strategy. The later approach may be of interest in the case of bulky disease for the downsizing of tumour and the subsequent volume reduction in normal tissue irradiated. The place of maintenance chemotherapy, targeted agents or pemetrexed for adenocarcinoma is currently not known.

In the particular case of superior sulcus tumours, neoadjuvant concurrent chemoradiation (45 Gy) followed by surgery and adjuvant chemotherapy is the preferred approach. If initially unresectable (or after restaging), definitive concurrent chemoradiation to a dose of 63–66 Gy is indicated.

Although it remains globally controversial, post-operative radiation is generally recommended after surgical resection when a pathological report demonstrates N2 disease, extracapsular nodal extension (ECE), T4 disease, positive surgical margins or macroscopic residual disease. When post-operative radiation is indicated, the mediastinum is commonly treated with 50 Gy in 25 fractions, with an additional boost of 10 Gy on areas of ECE or bulky nodal disease. Similarly, regions of gross residual disease should be treated with 66 Gy if the normal surrounding structures allow it.

SBRT or stereotactic ablative radiation therapy (SABR) is a novel form of high-precision, image-guided radiotherapy for stage I NSCLC. This technique requires accurate patient positioning, breathing control, four-dimensional target definition and the use of multiple non-coplanar radiation beams, subsequently allowing steep dose gradients and major hypofractionation (delivering a high dose in a few fractions, approximately three to eight treatments). Indeed, high biological effective doses (>100 Gy) are required to achieve a significant improvement in local tumour control and survival in medically operable or inoperable NSCLC patients. At this moment, concurrent chemotherapy should be avoided with dose-escalated radiotherapy or SBRT until further clinical data are available.

SCLC The treatment of limited-stage SCLC includes chest radiotherapy delivered concurrently with cisplatin and etoposide during the first cycles if possible. The optimal radiation dose or schedule (one or two fractions daily) is still not known (trials are ongoing). Hyperfractionation, with fraction of 1.5 Gy twice daily to a total dose of 45 Gy, was shown to be superior to a classical 45 Gy in 5 weeks with one fraction a day, but with an increase in acute toxicities. Currently, chest radiotherapy for SCLC is similar to NSCLC, increasing the total
radiation dose (≥60 Gy) and avoiding elective mediastinal irradiation.

Prophylactic cranial irradiation (PCI) should be given for all stages of SCLC after any degree of favourable response to primary treatment. The current standard total dose is 25 Gy given in 10 fractions. No benefit was demonstrated from the use of higher doses.

Despite the fact that the rate of brain metastases is similar to that in limited-stage SCLC, the role of PCI in NSCLC remains more controversial since it was shown to reduce brain metastases but does not improve overall survival in randomised studies. Nevertheless, the development of brain metastases is common in patients with locally advanced NSCLC treated with chemoradiation and, therefore, a subgroup of patients (especially younger patients) may still benefit from either PCI or an aggressive cranial treatment after early detection of brain metastases.

Palliative radiotherapy

For relief of symptoms such as pain, haemoptysis, dysphagia and dyspnoea, different dose schedules are being used and proven adequate: 1 × 10 Gy, 10 × 3 Gy, 5 × 4 Gy, 2 × 8.5 Gy (with a 1-week interval), 13–15 × 3 Gy (daily) and 20 × 2.5 Gy (daily).

Selection of treatment should be tailored to the needs of patients, usually being centred on quality of life, and based on age, performance status, tumour burden and specific symptoms.

One schedule (10 fractions of 3 Gy) seems to be favoured among radiologists, with a good balance between palliation, 1-year survival and treatment time commitment.

For patients with good performance status and limited distant disease (e.g. oligometastatic), a definitive dose of radiation concurrent with chemotherapy may be preferred to have a sustained symptomatic improvement, and continuing good performance status.

Radiotherapy side-effects

Radiotherapy-induced toxicity is related to the volume of normal tissues surrounding the target tumour. The dose-limiting organs for chest radiation are the spinal cord, lung, oesophagus and heart. Classically, side-effects are divided into early/acute and late/chronic toxicity. These unwanted effects can be reduced using dose–volume constraints, which are modified by multiples factors, such as concurrent chemotherapy or surgery. Most of the toxicity data are derived from conventionally fractionated radiation and may not apply with SBRT in which large doses per fractions are used. Although the results are not mature yet, several studies suggested limited early toxicity after SBRT for early-stage NSCLC not close to the central structures. Toxicities should be graded using the Common Terminology Criteria for Adverse Events system (CTCAE) from the National Cancer Institute (NCI).

Common acute side-effects seen in radiotherapy for lung cancer include oesophagitis, skin irritation (dermatitis), cough, fatigue and nausea/vomiting. Most of these are resolved 2–4 weeks after radiotherapy. Acute pneumonitis can occur 1–6 months after radiation.

Delayed complications include radiation pneumonitis, pulmonary fibrosis, pericarditis, pericardial effusion, coronary artery disease, oesophageal stricture/fistula, Lhermitte’s syndrome, brachial plexopathy, rib fracture and second cancers.

Radiation pneumonitis typically occurs approximately 6–10 weeks after radiotherapy. Most patients have only radiographic changes without any clinical symptoms or functional end-point modifications. Clinical symptoms are cough, dyspnoea, hypoxia and fever. Symptomatic radiation pneumonitis can be treated with steroids after excluding an infection. Pulmonary fibrosis usually evolves 6 months to several years after treatment. Several dosimetric parameters can be used to help predict the risk of pulmonary toxicity, commonly the V20 (the total lung volume receiving at least 20 Gy) and the mean lung dose (MLD). Current
guidelines recommend a V20 below 30–35% and a MLD below 18–20 Gy. Additionally, the use of systemic chemotherapy as well as the sequencing of therapies may have a significant impact on the toxicity.

Oesophageal toxicity is globally the most common acute toxicity during chest/mediastinal radiotherapy. While oesophagitis can be severe, it is rarely a reason to stop treatment if managed adequately. Dosimetric factors that influence oesophageal toxicity include the length of oesophagus receiving beyond 40–50 Gy and the mean oesophageal dose. Again, the use of concurrent chemotherapy with thoracic radiation significantly increases severe esophagitis compared to radiation alone.

Since patients treated for locally advanced lung cancer typically have pre-existing cardiopulmonary disease, the risk of radiation-induced cardiovascular disease is rather difficult to define, especially among the few long-term survivors. After mediastinal irradiation with at least a portion of the heart receiving a relatively high dose, the most common complications are pericarditis, coronary artery disease and, less frequently, myocardial infarction. The new advances in radiotherapy techniques allow the reduction of heart volume irradiated and subsequently potentially reduce the risk of cardiac toxicity.

While rare and sometimes spectacular, Lhermitte’s syndrome (sudden electric-like shocks extending down the spine with head flexion) usually resolves spontaneously, and is not predictive for chronic myelopathy. Spinal cord radiation injury is a very rare but serious complication of radiotherapy. Accordingly, most centres use conservative spinal cord dose constraints and limit the maximum dose to 45–50 Gy.

Caution should be used in treating central lesions with SBRT as they are at increased risk of toxicity compared to peripheral lesions. In addition, tumour volume is a significant predictor of severe toxicity, which suggests limiting the use of SBRT for early-stage NSCLC. Reported complications include pneumonitis, pleural effusion, haemoptysis and rib fracture depending on initial tumour location. Accordingly, SBRT for apical lesions carries a risk of brachial plexus toxicity. Specific dose constraints are recommended for SBRT, allowing for the prediction of the risk of toxicity as well as the potential to lower this risk before treatment. Clinical data with a longer follow-up are needed to better quantify the risk of late complications associated with SBRT.

Further reading

Metastatic tumours

Elisabeth Quoix

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

They occur commonly in patients with haematological or solid tumours. In a series of 133 patients (Anderson et al., 1974), the most common primary sites appeared to be breast carcinoma (35 patients), lung cancer (32 patients), lymphomas (20 patients), Hodgkin’s disease (12 patient), ovary carcinoma (nine patients), adenocarcinoma of unknown primary tumour (six patients) and melanoma (four patients). In females specifically, 37% of malignant pleural effusions are due to breast cancer, 20% to gynaecological cancers and 15% to lung cancer (Kreisman et al., 1983). Probably, with the increase in the frequency of lung cancer in females, in the next few years, there will be a higher percentage of malignant pleural effusions secondary to lung cancer (fig. 1).

Pericardial effusions

Of 55 patients admitted in an intensive care unit with malignant pericardial effusion, 30 had a lung carcinoma as primary site, nine a breast cancer, five haematological malignancies and 11 other solid tumors (Dequanter et al., 2008).

Pulmonary metastases

The lung is a prominent site of metastasis of breast, colon, kidney, uterus, and head and neck tumours. Some otherwise rare tumours (choriocarcinoma, osteosarcoma, testicular tumour, melanoma, Ewing tumour and thyroid carcinoma) frequently metastasise to the lung. Endothoracic metastases of breast cancer are essentially pleuropulmonary (figs 2 and 3). In a review of 660 cases of breast cancers followed for a period of 5 years between 1975 and 1979, 119 endothoracic metastases were recorded.

Key points

- The thorax is a common site of metastasis from several cancers.
- It is sometimes difficult to distinguish between primary lung cancer and metastases from other primaries.
- Prognosis is linked to the underlying primary.

Figure 1. Neoplastic pericardial effusion in a patient with lung cancer.
Among them, 79 were pleural or pleuroparietal, 80 were pulmonary (lymphangitis, n=41; multiple nodules, n=34; solitary nodules, n=9; endobronchial, n=7; tumoural emboli, n=2; alveolar metastasis, n=1). 46 were hilar or mediastinal, and two were myocardial metastases (Kreisman et al., 1983).

Pulmonary metastases are also frequent in lung cancer and their prognosis appears to be of intermediate value if there is no other site involved; they are now classified as M1a in the new staging classification (Ou et al., 2008). Sometimes, pulmonary metastases may be excavated (fig. 3) and may induce pneumothorax. Some may be calcified either spontaneously (osteosarcoma, bone giant cell tumour or papillary carcinoma of the thyroid) or after treatment (Seo et al., 2001).

Endobronchial metastasis is an infrequent feature (table 1), the most frequent primary site being the head and neck (although it might be difficult to distinguish them from a primary lung cancer) and the next most common being the breast and kidney (Sorensen, 2004; Milleron et al., 1986).

It may be quite difficult if not impossible to distinguish a primary lung cancer from endobronchial metastasis on a CT image. Endobronchial metastases from melanoma often appear black on CT images. Endobronchial metastases of a kidney cancer display strong enhancement on contrast-enhanced CT images (Park et al., 2004). Whenever bronchofibroscopy is performed, there may be quite severe bleeding from the biopsy attempt; cough with haemoptysis is the most frequent symptom.
Tumoural emboli may provide similar clinical and radiological features as thromboemboli; however, peripheral tumoural microemboli are characterised by normal imaging but respiratory failure (Dizon et al., 2008; Chatkin et al., 2007). Diagnosis may be obtained by transbronchial biopsy or by videothoracoscopy; on histological examination, multiple carcinomatous emboli are visible in distal pulmonary arteries, veins and lymphatics.

Hilar and mediastinal metastatic lymph nodes

Metastatic hilar and mediastinal lymph nodes are mostly linked to an intrathoracic carcinoma. Among 565 patients, only 37 had a history of extrathoracic carcinoma in a surgical series (Riquet et al., 2009). The primary cancer was most frequently breast, with others being from the kidney, testis, prostate, thyroid and other sites. Metastasis of breast cancer to intrathoracic nodes seems to occur quite frequently. In an autopsy series by Thomas et al. (1979) of females 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

The bones of the chest are common sites of secondary lesions of lung, prostate and breast cancer, in which bone is the most common metastatic site (Costelloe et al., 2009).

Bone metastases affect 8% of patients with breast cancer. Bone scanning remains the}

<table>
<thead>
<tr>
<th>Primary tumour</th>
<th>Metastases 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>
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<td>Bladder</td>
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</tr>
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<td>Ovarian</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Prostate</td>
<td>4 (2)</td>
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</tr>
<tr>
<td>Testis</td>
<td>3 (1)</td>
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<tr>
<td>Pancreas</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Adrenal gland</td>
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</tr>
<tr>
<td>Stomach</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

Data from Seo et al. (2001).

Table 1. Endobronchial metastases: frequency by primary site

Figure 4. Left scapula osteolytic metastasis of a right upper lobe adenocarcinoma.

Figure 5. Osteolytic metastasis of the second right rib.
mainstay for detection of bone metastases. In a meta-analysis of six studies comparing bone scanning and positron emission tomography (PET) without CT in breast cancer, a pooled lesion-based sensitivity of 88% and specificity of 87% was found for bone scanning, and a sensitivity of 69% and a specificity of 98% for PET (Shie et al., 2008).

Bone is a frequent metastatic site in lung cancer (fig. 4). In a recent study of 1000 patients, 105 (10.5%) had bone metastases at diagnosis (Song et al., 2009). The sensitivity of PET/CT was 94.3% compared to 78.1% with bone scanning and the specificity was, respectively, 98.8% and 97.4%. Among the 346 bone metastases detected by PET/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 is poor anatomical resolution (fig. 6).

MRI 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 (e.g. tamponade). However, some of metastases may 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.

Further reading

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 having similar diagnostic and therapeutic issues.

Epidemiology and pathogenesis

Malignant pleural mesothelioma (MPM), 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 years of age after occupational asbestos exposure (found in >80% of male cases but <40% of females), the main factor involved in MPM pathogenesis.

Pleural metastases and MPEs: Pleural tumour involvement may result from 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.

A 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 (~30% 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 depending on whether the patient has a cancer.

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 catheters represent an interesting alternative.
- Figures 1 and 2 summarise a proposal for MPE and MPM management.
Clinical and/or radiological diagnosis of unilateral pleural effusion: MPE?

Previous asbestos exposure?
Clinical and/or radiological suspicion of MPM

Proceed to Figure 2

Thoracentesis for diagnosis and drainage

Exudate

Light’s criteria

Transudate: seek and treat cause of transudate

Cytology: tumour cells?

NO

YES

If no argument for TB, infection, etc.

Chest CT mandatory if no contralateral mediastinal shift on chest X-ray ± bronchoscopy if main bronchus stenosis is suspected: trapped lung?

Previous diagnosis of malignancy (lung, breast, etc.)?

NO

YES

Is pleural histology needed for diagnostic clarity?
Otherwise start treatment

Contraindications
Thoracoscopy
Surgery at risk
Pleural symphysis

CT scan or US-guided transthoracic biopsies
Mini-thoracotomy for pleural biopsies

Histological proof of pleural metastases

Thoracoscopy

At the same time if large effusion and bulky tumour lesions of the pleura

Pleurodesis (talc poudrage, etc.) also is recurrent pleural effusion; alternatives: undwelled pleural catheter (in particular if trapped lung and/or frail patients), talc slurry, undwelled catheter, etc.

Treatment of the primary cancer
(chemotherapy and/or hormone therapy and BSC, etc.)

Figure 1. Proposed management for MPE. US: ultrasound; BSC: best supportive care.

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
Primary soft-tissue sarcoma of the chest wall is a rare disease (≤10% of the 8000 new cases per year of soft-tissue sarcomas in the USA). The most common sarcomas of the chest wall are chondrosarcoma, osteosarcoma, Ewing’s sarcoma/primitive neuroectodermal tumour, malignant fibrous histiocytoma and fibrosarcoma. Primary pleural and pulmonary sarcomas are rare.

**Prognosis**

The prognosis of patients with pleural metastases or MPM is poor (median survival <12 months). However, survival may vary according to the primary cancer (better outcome for breast cancer or lymphoma) and/or presence of favourable markers (EGFR mutation or ALK amplification in non-small cell lung cancer, etc.). Sarcomas have a variable prognosis, with a reported 5-year survival from 15% to 90%, depending mostly on the localisation, grade and differentiation the tumour, and the possibility of achieving 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, i.e. bronchus obstruction, carcinomatous lymphangitis or associated (pulmonary or 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 ipsilateral lung mimicking a large effusion, or MPM.

In MPM patients, chest radiography or, better, CT typically shows an unspecific, unilateral (95% of cases) pleural effusion with or without mediastinal shift. More rarely, pleural thickening or mass, without pleurisy, 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 but this is recommended for diagnosis and staging (after removal of pleural effusion if applicable). MRI is mostly useful to assess the tumour extent into the diaphragm and chest wall.

**18F-fluorodeoxyglucose positron emission tomography (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.

Although histological analysis is almost always required for accurate diagnosis, imaging is important for staging of chest wall sarcomas, and several of these tumours have distinctive radiological features, allowing the radiologist to narrow the differential diagnosis.

**Pathology and diagnostic procedures** In patients suspected of having MPE, a thoracocentesis is the first diagnostic step (American Thoracic Society/European Respiratory Society (ERS) guidelines). Pleural fluid analysis usually finds an exudate according to Light’s criteria but a transudate due to major hypoproteinaemia with cachexia or to malignant pericardial effusion does not eliminate the diagnosis of MPE. Assessment of the pleural level of adenosine deaminase can yield false-positive results in some cases of MPM or lymphoma but may be helpful in countries with medium-to-high prevalence of TB. The diagnostic sensitivity of pleural cytology in MPE may vary depending on the extension of the pleural lesions and the primary cancer, from 62% to 90% in case 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, the positive yield of blind biopsies is low (30–40%).
adding little to a negative cytology, except in countries with a high incidence of TB.

CT- or ultrasound-guided biopsies have a better diagnostic sensitivity than blind biopsies in series of MPEs (70–80% sensitivity), but lower than that of thoracoscopy. They are not recommended for MPM diagnosis except in patients for whom thoracoscopy (or mini-thoracotomy with pleural symphysis) is contraindicated or rejected by the patient. If MPM is not clearly suspected, closed needle biopsies may first be proposed in young patients with pleural lesions and exudative, cytology-negative pleural effusion from countries with a relatively high prevalence of TB.

Medical (pleuroscopy) or surgical (video-assisted thoracoscopic surgery) thoracoscopy with multiple pleural biopsies is the ‘gold standard’ for obtaining a 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 MPE. However, access to thoracoscopy may be limited in many places worldwide, as significant resources and expertise are required.

Immunohistochemistry is helpful in the search for the primary cancer for pleural metastases or to obtain an accurate diagnosis of mesothelioma, referring to the international classification of pleural tumours (World Health Organization, 2004). The 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 practice. Soluble mesothelin (or soluble mesothelin-related peptides (SMRPs)) levels were increased in the 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 tumour and node extent by current imaging procedures. Only a patient’s performance status and histological subtype are recognised as prognostic factors for the management of MPM in routine.

The 2010 ERS/European Society ofThoracic Surgeons (ESTS) guidelines on MPM management proposed a simple and sequential three-step pretreatment assessment (Scherpereel et al., 2010).

**Treatment**

Treatment includes palliative local therapies, mostly to improve the patient's symptoms, and treatment of the primary cancer depending on the nature of the malignancy, and the clinical status and the wishes of the patient.

**Treatment of primary cancer** MPM treatment, summarised by the 2010 ERS/ESTS guidelines, relies mostly on best supportive care (BSC) (oxygen, pain relief, nutrition, etc.) associated with chemotherapy.

There is limited evidence for the efficacy of radical surgery for mesothelioma, except parietal pleurectomy in very early and rare stage Ia disease. Debulking surgery (radical pleurectomy or pleurectomy/decortication (PD)) is now preferred to extrapleural pneumonectomy because of the lower morbidity/mortality and better outcome when combined with chemotherapy or radiotherapy. Both surgical procedures should be performed only in clinical trials, in specialised centres and as a part of
multimodal treatment. P/D can also be considered to achieve symptom control, especially in symptomatic patients with entrapped lung syndrome who cannot benefit from chemical pleurodesis.

Palliative radiotherapy aimed at pain relief may be considered in the 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 based on recent studies and does not permit any recommendation.

When a decision is made to treat patients with chemotherapy, subjects with a good performance status should be treated with first-line chemotherapy combining platinum and an antimetabolite (pemetrexed), or could be included in clinical trials. No drug has been validated in second-line chemotherapy, and patients with a good performance status should 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 relapse. For tumour assessment and follow-up of MPM, only chest CT is recommended. PET and biological markers (SMRP) are promising tools but still under investigation. The modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria are the preferred method of measuring response to treatment.

**Pleural metastases** Treatment of metastatic cancer relies on chemotherapy and/or hormone therapy, and BSC. The choice of cytotoxic drugs depends on the nature of the primary cancer. Mediastinal 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 preventing recurrent effusions. Sterile talc is the most effective agent available for pleurodesis and may be administered in the pleural space through a chest drain (‘talc slurry’) or, better, during thoracoscopy (‘talc poudrage’). 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 World Health Organization performance status (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 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 talc poudrage versus slurry 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 and chest pain) were observed with both methods, but no acute respiratory distress syndrome and death.

Alternatives to talc pleurodesis are repeated pleural punctures or better indwelling/tunnelled pleural catheters (TPCs). In fact, current guidelines consider TPCs an effective and ambulatory procedure for symptomatic, recurrent MPE. Their use as a first-line treatment is feasible; TPCs should be preferred for patients with trapped lung or those who are not considered good candidates for chemical pleurodesis because of short life expectancy, rather than a second talc pleurodesis, a pleuropertitoneal shunt with a high risk of complications, or parietal pleurectomy. Spontaneous pleurodesis may be obtained by TPC without mortality or major morbidity in nearly half of the cases when pleural drainage is performed via the catheter every...
other day, or even up to 70% in MPE patients fit for pleurodesis.

Further reading

Mediastinal tumours

Paul E. Van Schil, Patrick Lauwers and Jeroen M. Hendriks

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 the 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 CT, MRI 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 used. In the case of suspicion of lymphoma, germ

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.
- The mediastinum, which is defined as the anatomical compartment between both lungs, is a fascinating region due to its surprising complexity and variety.

Table 1. Primary tumours and cysts encountered in the mediastinum

<table>
<thead>
<tr>
<th>Superior mediastinum</th>
<th>Substernal goitre</th>
<th>Ectopic thyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior mediastinum</td>
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<tr>
<td>Anterior</td>
<td>Thymoma</td>
<td>Thymic cyst</td>
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<tr>
<td></td>
<td>Germ cell tumours</td>
<td>Pleuropericardial cysts</td>
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<tr>
<td>Middle</td>
<td>Lymphoma</td>
<td>Bronchogenic cyst</td>
</tr>
<tr>
<td>Posterior</td>
<td>Neurogenic tumours</td>
<td>Enterogenic cysts</td>
</tr>
</tbody>
</table>
cell tumour or thymoma, 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 transcapsular 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.

Further reading


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).
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 carbon dioxide tension 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
- 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 AASM Task Force 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 AHI, only weakly correlate with quantified measures of sleepiness, such as the Epworth Sleepiness Scale (ESS). This probably means that interindividual sensitivity, with some individuals coping better with sleep fragmentation than others, does compromise the relationship between the AHI and daytime sleepiness 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, thoracoabdominal movement, snoring, electroencephalography, electro-oculography, electromyography and oxygen saturation. Cardiorespiratory monitoring alone can be considered as highly sensitive (78–100%) and specific (67–100%). Sleepiness is often evaluated using the ESS, which assesses the global level of sleepiness and is independent of short-term variations in sleepiness. The ESS discriminates between normal and pathological sleepiness.

**Pathophysicsiology**

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 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 ($P_{crit}$) remains low relative to the pressure upstream to the collapsible segment ($P_u$). Closure of the upper airway occurs when $P_u$ falls below the surrounding tissue pressure ($P_{crit}$). In the model of the Starling resistor, maximal flow ($V_{max}$) becomes a function of the pressure gradient and the resistance in the segment upstream to the collapsible segment ($R_u$):

$$V_{max} = (P_u - P_{crit})/R_u$$

The collapse of the upper airway then finally occurs during expiration when, due to the absence of dilator muscle, $P_{crit}$ 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.

Central and obstructive events are closely linked. Sometimes a central event with an 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** 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 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** OSA is associated with several components of the metabolic syndrome, mainly insulin resistance and abnormal lipid metabolism. Sleep restriction causes insulin resistance by inducing a pro-inflammatory state (increased release of interleukin (IL)-6 and tumour necrosis factor (TNF)-α). Epidemiological studies have shown that sleep-related hypoxaemia is associated with glucose intolerance independent of age, sex, BMI and waist circumference. Metabolic syndrome can be triggered by both intermittent hypoxia and sleep fragmentation/deprivation. The mechanisms are shown in figure 2.

Metabolic syndrome can be due to the release of free fatty acids, angiotensin II and adipokines by adipose tissue, which may damage the pancreas, leading to insufficient insulin release and apparent insulin resistance.

Mean and nadir \( S_{\text{aO2}} \) during sleep is an independent predictor of metabolic syndrome in overweight children and adolescents.

**CPAP treatment**

*Therapy with nasal CPAP* nCPAP is perceived by most physicians as a very effective treatment for sleep apnoea and has been shown to be effective in controlled studies.

---

**TABLE 1. Risk factors for OSA: factors promoting upper airway collapse**

<table>
<thead>
<tr>
<th>Abnormal anatomy of the upper airway</th>
<th>Pharyngeal muscle factors</th>
<th>Pharyngeal compliance</th>
<th>Sensory function</th>
<th>Lung volume dependence of upper airway cross-sectional area</th>
<th>Ventilatory control system factors</th>
<th>Sex factors</th>
<th>Weight</th>
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<tbody>
<tr>
<td><strong>Skeletal factors</strong></td>
<td>Insufficient reflex activation of upper airway dilator muscles</td>
<td>Increased upper airway collapsibility</td>
<td>Impaired pharyngeal dilator reflexes</td>
<td>Increased below functional residual capacity</td>
<td>Unstable ventilatory control</td>
<td>Male influences</td>
<td>Obesity causing peripharyngeal fat accumulation</td>
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<tr>
<td>Maxillary and/or mandibular hypoplasia or retroposition</td>
<td>Impaired strength and endurance of pharyngeal dilators</td>
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<td>Impaired mechanoreceptor sensitivity</td>
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<td>Increased ventilatory responses and loop gains</td>
<td>Centripetal pattern of obesity</td>
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<td>Hyoid position (inferior displacement)</td>
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<td>Absence of progesterone</td>
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<td><strong>Soft tissue factors</strong></td>
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<td>Presence of testosterone</td>
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<td>Increased volume of soft tissues</td>
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<td>Adenotonsillar hypertrophy</td>
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<td>Macroglossia</td>
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<td>Thickened lateral pharyngeal walls</td>
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<td>Increased fat deposition</td>
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<td>Pharyngeal inflammation and/or oedema</td>
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<td>Increased vascular volume</td>
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<td>Increased muscle volume</td>
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Reproduced from Verbraecken et al. (2009) with permission from the publisher.
nCPAP results in better sleep quality with a lower arousal index, and less stage 1 and more stage 3 and 4 sleep in a placebo-controlled 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 with an oral placebo, especially in patients using nCPAP for \( > 3.5 \text{ hours} \) 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 \( P_u \) (equation 1). Appropriate titration of the CPAP restores flow. nCPAP can increase \( P_u \) much more than local interventions, such as uvulopalatopharyngoplasty. Therefore, it also explains why 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 OSAS, 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 \( P_{aO_2} \) 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 (CSA). nCPAP can increase carbon dioxide tension

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**Figure 1. Cardiovascular consequences of OSA.** PNA: parasympathetic nerve activity; \( P_{O_2} \): oxygen tension; \( P_{CO_2} \): carbon dioxide tension; SNA: sympathetic nerve activity; HR: heart rate; BP: blood pressure; LV: left ventricle. Reproduced and modified from Bradley et al. (2009) with permission from the publisher.
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 $P_{a\text{CO}_2}$ 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 and, thus, overcome the burden of OSA on the cardiovascular system, as shown in figure 1. 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 nonfatal cardiovascular events; this difference disappeared with nCPAP treatment.

**nCPAP and metabolic/systemic effects of OSA** nCPAP may improve metabolic syndrome, although it is not always certain that nCPAP has an independent effect. nCPAP also lowers TNF-$\alpha$, IL-6 and C-reactive protein levels.

**Non-CPAP treatment**

**Mandibular advancement devices** (MADs) 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. Customised devices have a better retention,
tolerance and efficacy. MADs 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. In addition, 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. Overall, these oral appliances are recommended for patients with mild-to-moderate OSA and for those with more severe disease when they do not tolerate CPAP. Side-effects, such as pain in the teeth and jaws, are mostly mild. Short-term compliance seems to be very high while long-term compliance (after >2 years) is ~50%.

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 the tonsils are found to be enlarged. Maxillomandibular advancement osteotomy advances the maxilla and mandible to enlarge the retrolingual and retropalatal spaces. This technique is not yet often used but additional studies are needed to establish its place, presumably in the more severe OSA patients who do not tolerate nCPAP and where an adequate therapy is needed to improve daytime sleepiness and prevent cardiovascular and metabolic consequences. Adenotonsillectomy is the 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. Overall, the results of upper airway surgery are poor when patients are unselected. Therefore, one must try to identify the site of the upper airway collapse and correct the anatomical abnormalities at that site. Sleep endoscopy has been most widely used to identify the site of collapse, although pressure catheters with multiple sensors have also been used to identify the site of collapse; in addition, functional imaging of the upper airway maybe a promising tool.

Bariatric surgery Several techniques have been used to perform bariatric surgery including gastric banding, use of a gastric balloon, gastric sleeve resection and gastric bypass. Bariatric surgery is used in morbidly obese patients with a BMI ≥40 kg·m⁻². Almost half of patients improve after these interventions but, therefore, a substantial number of patients has still to continue with nCPAP.

Drug treatment Several drugs have been tried, such as protriptyline (a tricyclic antidepressant), paroxetine (a serotonin reuptake inhibitor) and mirtazapine (a serotonin receptor agonist). None of these has given convincing results. Acetazolamide, although quite efficient in the treatment of central apnoeas, has also no effect on obstructive apnoeas.

Further reading
Central sleep apnoea/hypopnoea refers to the cessation or reduction of ventilation lasting for $\geq 10$ s (in adults) due to a transient loss of neural output to the respiratory muscles. Many patients with central sleep apnoea (CSA) have mild hypocapnia or normocapnia but hypercapnia is less common, although hypoventilation may also accompany CSA. 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 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 CHF, pulmonary hypertension, ischaemic stroke, neuromuscular disease, obesity hypoventilation syndrome and narcotic use, or during initiation of CPAP therapy in certain patients with OSA. In healthy subjects, CSA may occur during hypoxia at altitude. Idiopathic CSA, by definition, is not associated with any comorbid condition.

Pathophysiological mechanisms underlying CSA include:

- respiratory control instability, due to an increased chemical drive, so that the prevailing $P_{aCO_2}$ approaches the apnoea threshold
- a prolonged circulation time
- altered respiratory mechanics

Subsequently, different forms of CSA will be discussed.

CSR/CSA syndrome in CHF patients

Left-heart failure that increases pulmonary venous pressure is regarded as a source of CSR, as pulmonary congestion stimulates stretch receptors that sensitize the peripheral chemoreceptors to carbon dioxide through vagal afferents. The increased ventilatory sensitivity to carbon dioxide drives the $P_{aCO_2}$, closer to the apnoea threshold, thereby promoting the susceptibility to central apnoea. Moreover, hypoxia that follows apnoea/hypopnoea enhances post-apnoeic hyperventilation. If chemical control prevails over cortical
influences on the respiratory controller, as typically occurs during sleep, patients develop an oscillatory breathing pattern that causes sympathetic overstimulation in patients who are already sympathetically stimulated through their heart failure.

Among patients with moderate to severe heart failure (left ventricular ejection fraction (LVEF) ≤55%) the prevalence of sleep apnoea (both obstructive and central) is very high irrespective of the clinical suspicion (fig. 1).

Criteria for CSR/CSA have not been uniformly accepted. According to the American Academy of Sleep Medicine, CSR should be scored if at least three successive cycles of cyclic crescendo–decrescendo changes in breathing amplitude are present for at least 10 consecutive minutes or when a central AHI >5 events·h⁻¹ arises. In the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP) trial, a large multicentre study that evaluated the effectiveness of CPAP therapy in patients with heart failure and CSA, inclusion criteria required ≥15 apnoeas/hypopnoeas per hour with >50% central events and a LVEF <40%. Obviously, the AHI threshold used to define the presence of CSR has a major impact on prevalence estimates (fig. 1).

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 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 daytime CSR during physical activity (fig. 2).

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 years)
- male sex
- hypocapnia
- atrial fibrillation
- CSR observed during the day

The diagnosis should be evaluated by polysomnography or a cardiorespiratory sleep study, as pulse oximetry cannot 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 alone is ineffective, NIV may also be required.

Nocturnal CPAP has been shown to improve nocturnal CSR/CSA, oxygen saturation, LVEF, sympathetic nervous system activity and 6-min walking distance. These effects are thought to be mediated by the increase in intrathoracic pressure induced by CPAP, which reduces both afterload and preload by decreasing transmural ventricular pressure and venous return so that cardiac function...
improves in patients with increased filling pressures. Additionally, CPAP stabilises CSR by raising the end-expiratory lung volume. Despite its positive effects on several outcomes described above, CPAP did not prolong survival without heart transplantation during a 2-year follow-up in a large trial (CANPAP). Yet, a post hoc analysis suggested a survival benefit in a subgroup of patients in whom CPAP sufficiently suppressed CSR/CSA. Adaptive servoventilation is a mode of bilevel positive airway pressure ventilation that continuously adjusts pressure support according to the breathing pattern of the patient in order to stabilise periodic breathing (fig. 3). 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 survival. Acetazolamide and theophylline both have reduced CSR/CSA in some studies but these drugs are currently not generally recommended because of limited data on their effectiveness and potential adverse effects. Supplemental nocturnal oxygen has provided inconsistent results with some studies showing a reduction in CSR/CSA,

Figure 2. CSR in a patient with CHF. Inductive plethysmographic signals from rib cage and abdominal sensors showing regular waxing and waning of ventilation with central hypopnoeas 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). Reproduced and modified from Brack et al. (2007) with permission from the publisher.
along with improvements in physical performance or quality of life while others failed to reproduce these benefits. 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, as 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 servoventilation has been successfully used to normalise the breathing pattern and improve sleep quality.

Idiopathic CSA syndrome

Idiopathic CSA syndrome (fig. 4) is, by definition, not associated with any underlying disease. CSA causes sleep fragmentation, which may be perceived as unrefreshing sleep and 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 acetzolamide, 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 servoventilation, although the relevance of the breathing disturbances requires further study. Patients with stroke and neuromuscular disease, such as postpolio syndrome, motor neuron disease or multiple system atrophy, or with idiopathic central hypoventilation may exhibit CSA with or without associated OSA and/or hypoventilation. Depending on the prevailing breathing disturbance, bilevel positive pressure ventilation, CPAP or adaptive servoventilation may improve breathing and alleviate symptoms.

High-altitude periodic breathing

In healthy subjects, hypobaric hypoxia at altitudes of >1600 m may induce periodic breathing with central apnoea/hypopnoea. Breathing instability is related to an

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**Figure 3.** Recordings of instantaneous lung volume by respiratory inductive plethysmography and mask pressure during adaptive servoventilation in a patient with severe heart failure. In this mode of pressure support ventilation, the inspiratory pressure support is increased during hypopnoic or apnoeic phases of CSR whereas pressure support is reduced to a minimal level during hyperpnoeic phases. PS: pressure support.

**Figure 4.** Idiopathic CSA in a 56-year-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 respiratory muscle activity.
enhanced chemosensitivity (high controller gain) causing a tendency for a ventilatory overshoot and hyperventilation with a reduced carbon dioxide reserve, i.e. the eupnoeic 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. 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 CHF, neuromuscular disorders, opioid use and high altitude, the prevalence of CSA is high. Treatment for CSA is not as well established as that for OSA, and it may include oxygen, acetazolamide and positive pressure ventilation, in particular adaptive servoventilation.

Further reading

Sleep-related hypoventilation syndromes, together with central and obstructive sleep apnoea syndromes, are a part of so-called sleep-related breathing disorders (table 1).

Pathophysiology

Nocturnal hypoventilation can be attributed to respiratory pump failure in relation with decreased ventilatory drive, which may be due to respiratory dysfunction secondary to polio sequelae, central hypoventilation, amyotrophic lateral sclerosis, Arnold–Chiari malformation, or the following: respiratory centres depression (hypnotics); alteration of respiratory nerve conduction (Guillain–Barre´ 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 carbon dioxide levels, as predicted by the alveolar air equation. If the lungs are abnormal (COPD, tuberculous sequelae, CF 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 ventilation by altering V′E and/or dead space volume/tidal volume (fig. 1).
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 deleterious effects in conditions for which these muscles are

<table>
<thead>
<tr>
<th>Table 1. Sleep-related breathing disorders</th>
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<tbody>
<tr>
<td>Presence of an extra-/intraspulmonary restrictive disorder</td>
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<tr>
<td>OHS</td>
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<tr>
<td>Neuromuscular diseases</td>
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<tr>
<td>Duchenne muscular dystrophy, Steinert myotony, polio sequelae, amyotrophic lateral sclerosis, high spinal injuries with tetraplegia and respiratory paralysis (less frequent: acid maltase deficiency and spinal muscular atrophy)</td>
</tr>
<tr>
<td>Chest wall diseases</td>
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<tr>
<td>Kyphoscoliosis and/or tuberculosis sequelae</td>
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<tr>
<td>Other conditions</td>
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<tr>
<td>Respiratory centers depressant drugs</td>
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<tr>
<td>Neurologic conditions</td>
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<tr>
<td>Arnold-Chiari malformations, brainstem tumors, space occupying lesions, vascular malformations, central nervous system infection, stroke and neurosurgical procedure which may be associated with central hypoventilation</td>
</tr>
<tr>
<td>Congenital central hypoventilation</td>
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<tr>
<td>Presence of an obstructive disorder</td>
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<tr>
<td>COPD, diffuse bronchiectasis and CF are the most frequent conditions</td>
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</table>

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 deleterious effects in conditions for which these muscles are

Figure 1. REM hypoventilation in a patient with OHS. Reproduced from Chouri Pontarollo et al. (2007).
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 measurement of arterial blood gases in the awake and asleep patient, *i.e.* $\text{SaO}_2$ and transcutaneous carbon dioxide tension. The results of this initial investigation are concluded by full night ventilatory polygraphy (respiratory signals only) or polysomnography (respiratory and neurological signals; electroencephalography (EEG), electrooculography (EOG), electromyography (EMG)). Chronic daytime hypercapnia is associated with and preceded by sleep-related hypoventilation.

Aetiology

Presence of an extra/intrapulmonary 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 (BMI $\geq 30 \text{ kg}\cdot\text{m}^{-2}$) and sleep-disordered breathing with daytime hypoxemia and hypercapnia (*PaCO}_2 $>45 \text{ 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 $\geq 50 \text{ kg}\cdot\text{m}^{-2}$.

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 mechanical NIV. Mechanisms of action include resting of the respiratory muscles, an increase in thoracic compliance and resetting of the respiratory centres. In OHS, nocturnal mechanical 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 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% of cases) (fig. 2). Data from a large cohort of OHS patients who had been treated with mechanical NIV showed a very significant decrease in the number of hospital stays for cardiac and/or respiratory illness for the 3 years following the initiation of mechanical 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. Recent studies discussed the necessity to begin with mechanical NIV as first-line treatment versus nasal CPAP (nCPAP) with supplemental oxygen; in patients with low levels of hypercapnia, a trial of night CPAP is useful to detect patients without severe nocturnal hypoxemia who could be proposed to nCPAP plus oxygen as a first line treatment. In patients who demonstrate a severe nocturnal hypercapnia, mechanical NIV is chosen; expiratory positive airway pressure (EPAP) is titrated to control hypopnoeas and apnoeas and inspiratory positive airway pressure (IPAP)
is added to control \( \text{PaCO}_2 \). If pressure pre-set NIV fails, target-volume ventilation or, in some cases, nasal volume pre-set ventilation may be used. In patients with OHS and predominant OSA, once hypercapnia has improved using mechanical NIV (which may take several weeks or months), mechanical NIV may be changed to nCPAP (fig. 3). Mechanical NIV has also largely improved the immediate vital prognosis of OHS and acute respiratory failure.

Medical management is mainly orientated towards weight loss. A reduction of 5–10% of body weight can result in a significant decrease in \( \text{PaCO}_2 \). Unfortunately, weight loss by diet alone is difficult to achieve and sustain; thus, bariatric surgery may be proposed in the youngest patients. After significant weight-reduction surgery, patients with OHS experience long-term improvement of arterial blood gases and dyspnoea, which may lead, after night ventilator polygraphy monitoring showing disappearance of sleep-disordered breathing, to discontinuation of the ventilator treatment.

If obesity is absent or not predominant, the most frequent conditions are: neuromuscular diseases with Duchenne muscular dystrophy; Steinert 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), and chest wall diseases with kyphoscoliosis and/or TB sequelae.

These diseases 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 and tracheostomy.

Other conditions of sleep-related hypoventilation There are less frequent conditions including neurological conditions such as Arnold–Chiari malformations, brainstem tumours, space occupying lesions, vascular malformations, central nervous system infection, stroke, or neurosurgical procedure which may be associated with central hypoventilation.

Congenital central hypoventilation syndrome is a rare disorder of ventilatory control that typically presents in newborns and mainly results from a polyalanine repeat expansion mutation in the \( \text{PHOX2B} \) gene. It results in the failure of automatic central

**Figure 2. A ventilator polygraphy from a patient with severe OHS (J.L. Pepin, personal communication, with permission).**
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 mechanical NIV. Electrostimulation of the phrenic nerves and/or the diaphragm is currently being tested as a new therapeutic option.

Some rare conditions of proven sleep-related hypoventilation for which all the previous aetiologies have been ruled out are considered as idiopathic; it is always important to review the medications of such patient in order to detect intake of respiratory centres depressors (morphine, antitussive drugs, hypnotic and sedatives compounds) which are often used by elderly people.

**Presence of an obstructive disorder**

COPD, diffuse bronchiectasis and CF are the most frequent conditions. During sleep there is a worsening of awake hypoxaemia and hypercapnia, especially during REM sleep. Mechanical 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 and is frequently a good responder to mechanical NIV.

**Further reading**

Almost all patients with primary antibody deficiencies suffer from upper and lower respiratory tract bacterial infections. Severe and recurrent infections with encapsulated bacteria, asthma, and bronchiectasis represent the most important morbidity and mortality factors. The pathogens commonly isolated from the sputum are *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Streptococcus pyogenes*, with *Pseudomonas aeruginosa* and *Moraxella catarrhalis* occurring less frequently (table 1).

Pneumonia is a common acute infection in primary antibody deficiency (PAD). Studies of PAD patients have revealed that at least two-thirds of patients have one or more episodes of pneumonia prior to diagnosis. Patients are prone to pneumonia-associated complications that require hospitalisation. Respiratory infections lead over time to permanent lung damage.

Chronic lung disease (CLD) represents the principal morbidity factor. As already demonstrated in patients with CF, 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, 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, data indicate the role of a very low IgA level as a major independent risk factor for all the main primary immunodeficiency (PID)-associated clinical conditions (pneumonia, CLD, and acute and chronic sinusitis), underlining the well-known role of IgA in immune defence against a variety of potentially pathogenic organisms when they are encountered in the respiratory and 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 demonstrated in common variable immunodeficiency (CVID) patients with bronchiectasis: patients with decreased frequencies of memory B-cells have low levels of IgG/ IgM, and high rates of autoimmune disease and bronchiectasis. Thus, assessment of memory B-cells could be considered a prognostic factor in CVID patients.

In patients with cellular and combined immunodeficiencies and in patients with PID who have undergone a haematopoietic stem cell transplant, respiratory viral infections are major causes of morbidity and mortality. Any virus may be detected and all worsen the clinical outcome. Herpes viruses, paramyxoviruses and adenoviruses are common significant pathogens in these patients. Aggressive antiviral treatments may reduce viral replication and lung damage. Fungal infections can result in significant morbidity and potentially fatal outcomes if misdiagnosed or not correctly treated.

Noninfectious associated respiratory diseases might also occur in PID patients and should be taken into consideration in the differential diagnosis: nonspecific interstitial pneumonia, granulomatous lymphocytic interstitial pneumonia, cryptogenic organising pneumonia and lymphocyte interstitial pneumonia.

Medical imaging, especially HRCT, plays a crucial role in the initial detection and characterisation of changes, and in monitoring the response to therapy. The spectrum of abnormalities seen in thoracic imaging includes noninfectious airway disorders, infections, CLD, chronic inflammatory conditions, and benign and malignant neoplasm. Bronchial wall thickening and bronchiectasis are the most common pulmonary changes observed in patients with primary humoral immunodeficiencies: their presence is indicative of a poor prognosis and is suggestive of the evolution of the disease process to an irreversible stage (e.g. lung fibrosis). Small airway involvement leads to ventilation abnormalities and chronic

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<td>Salmonella typhi</td>
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<td></td>
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<tr>
<td>Pneumoniae aeruginosa</td>
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<tr>
<td>Nocardia asteroides</td>
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<tr>
<td>Salmonella typhi</td>
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<tr>
<td>Mycobacteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fungi</td>
<td>Candida</td>
<td>Aspergillus</td>
</tr>
<tr>
<td>No</td>
<td>Pneumocystis jiroveci</td>
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obstructive disease, which are found in 33–43% of patients with PAD and are almost always irreversible. In addition, air trapping, emphysema, bullae, ground-glass nodules and parenchymal abnormalities are common.

Granulomatous-lymphocytic interstitial lung disease (GLILD) is a ‘sarcoid-like’ inflammatory process with nodular lymphocytic infiltrates, bronchus-associated lymphoid tissue (BALT) hyperplasia and peribronchiolar lymphocytic infiltrates, perivascular granuloma, and lymphocytic interstitial pneumonia. It is present in as many as 8% of patients with PAD. The presence of sarcoid-like granulomatosis is indicative of a dismal prognosis, with terminal respiratory insufficiency developing in ~24% of cases. By HRCT, interstitial nonspecific pneumonia findings include ground-glass opacities (in one-third of cases, these are the only abnormalities), lobe volume loss, a reticular pattern, traction bronchiectasis, and areas of fibrosis predominantly at the basal level with a subpleural, peribronchovascular distribution.

Lung alterations in patient with PID might be evaluated also by MRI, a radiation-free alternative to CT. Lung function tests are also useful: they show ventilatory disturbance, an obstructive pattern or pattern mix.

**Treatment**

In PID where the defect is an inability to produce an effective antibody response to pathogens, IgG can be replaced. However, despite IgG replacement, the percentage of patients with CLD and bronchiectasis increases over time (>50% in adults and 30–40% in children). The overall probability of developing CLD reaches ~80% after 17 years of follow-up. In fact, substitutive therapy with IgG reduces the risk of acute respiratory infections, particularly of pneumonia, but has a low efficacy in the reduction of chronic lung complications, infective exacerbations and asthma promoted by vicious circle infection–inflammation (protease release from polymorphonucleates, epithelial damage, epithelial cuboidalisation, mucus accumulation predisposing to recurrent infections and chronic inflammatory phenomena favouring remodelling).

Treatment strategies for progressive GLILD in CVID include corticosteroids, methotrexate, azathioprine, leflunomide or mofetil mycophenolate. Biological therapies have been used in single patients or in small trials. Aside from immunoglobulin replacement, a strategy to reduce lung

<table>
<thead>
<tr>
<th>Symptoms and signs</th>
<th>Respiratory clinical diagnosis</th>
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<tbody>
<tr>
<td>Recurrent chest infection</td>
<td>Bronchiectasis</td>
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<tr>
<td>Productive cough</td>
<td>Recurrent chest infection/pneumonia</td>
</tr>
<tr>
<td>Wheeze</td>
<td>Asthma</td>
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<tr>
<td>Weight loss</td>
<td>Granulomatous lung disease</td>
</tr>
<tr>
<td>Rhinosinusitis</td>
<td>Emphysema</td>
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<tr>
<td>Otitis media</td>
<td>Previous TB</td>
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<tr>
<td>Progressive dyspnoea</td>
<td>Cavitating lung lesion</td>
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<tr>
<td>Hypoxaemia</td>
<td>Rhinosinusitis</td>
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<tr>
<td>TLCO alteration</td>
<td></td>
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<tr>
<td>Polycythaemia</td>
<td></td>
</tr>
<tr>
<td>Cyanosis</td>
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</table>
damage should be approached. Prophylactic antibiotics, macrolides as anti-inflammatory agents, inhaled corticosteroids, bronchodilators, mucolytic agents, or mechanical or rehabilitative respiratory methods need to be considered.

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 (table 2).

Further reading

- Associazione Italiana Ematologia Oncologia Pediatrica. www.aeiop.org
Most HIV-infected people experience at least one significant episode of respiratory disease during their lifetime. Although the widespread use of effective combination antiretroviral therapy (CART) has led to a 50–90% fall in the incidence of many HIV-associated opportunistic infections and some malignancies, the associated reduction in short-term mortality means that people with HIV infection are now living longer, and so are developing (often at an increased frequency) noninfectious pulmonary conditions usually present in older age. Thus, HIV patients with respiratory symptoms require careful, systematic investigation to exclude a wide variety of illnesses and pathogens.

This chapter will focus upon common causes of HIV-related respiratory disease (table 1). For an individual, the scope and scale of the problem depends on a number of factors including their risk of exposure to pathogens (e.g. through geography or lifestyle, such as injecting drug use; their ability to obtain and consistently use CART successfully; the use of specific preventive therapies such as co-trimoxazole; and co-factors such as cigarette smoking). Unfortunately, there are still a large number of people who present with severe respiratory disease and undiagnosed HIV infection. This is avoidable and should be regarded as a failure of societal medical care.

In the following sections we use 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 cells·μL⁻¹). In HIV-infected subjects with preserved immunity, typical community-acquired
infections occur but at a greater frequency than in the general population. With advancing HIV-induced immunosuppression (CD4 counts <200 cells \( \cdot \mu L^{-1} \)), the risk of opportunistic infections and malignancy rapidly increases.

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 jiroveci* pneumonia or bacterial infection.

Compared with HIV-negative populations, bacterial pneumonia is six to 10 times more frequent in HIV-infected subjects not using CART. Injecting drug users are particularly vulnerable (with a risk approximately double that of other HIV-infected people). The presentation of HIV-associated community-acquired bacterial pneumonia is similar to that in HIV-negative subjects. However, the chest radiograph may be atypical, and mimic *P. jiroveci* 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 are probably no more frequent.

Bacteraemia is reported to be up to 100 times more common in HIV-infected patients with bacterial pneumonia, irrespective of blood CD4 count. These data come from studies performed prior to CART. Even so, it highlights the importance of undertaking a full set of investigations (including blood cultures) in HIV-infected individuals presenting with community-acquired pneumonia.

Complications of bacterial infection 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 years). Conjugate vaccines appear to offer better protection than polysaccharide vaccines. Humoral responses and clinical efficacy are probably impaired in those with CD4 counts <200 cells \( \cdot \mu L^{-1} \), although

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**Table 1. Common causes of HIV-associated respiratory disease**

<table>
<thead>
<tr>
<th>Infectious conditions</th>
<th>Non-infectious conditions</th>
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<tbody>
<tr>
<td><strong>Upper respiratory tract infection</strong></td>
<td>Nonmalignant conditions</td>
</tr>
<tr>
<td>Acute sinusitis</td>
<td>COPD</td>
</tr>
<tr>
<td>Chronic sinusitis</td>
<td>HIV-associated pneumonitis <em>e.g.</em> NSIP and LIP</td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>Pulmonary arterial hypertension</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>Pneumothorax</td>
</tr>
<tr>
<td><strong>Bacterial pneumonia</strong></td>
<td>HIV therapy causing respiratory symptoms <em>e.g.</em> IRD</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td></td>
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<tr>
<td><strong>Viral infection</strong></td>
<td></td>
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<tr>
<td>Influenza A</td>
<td></td>
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<tr>
<td><strong>TB</strong></td>
<td></td>
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<tr>
<td><em>Pneumocystis pneumonia</em></td>
<td></td>
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<tr>
<td><em>Histoplasma capsulatum</em></td>
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<tr>
<td><em>Cryptococcus neoformans</em></td>
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<tr>
<td><strong>Fungal infection</strong></td>
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<tr>
<td><strong>NSIP</strong>: nonspecific interstitial pneumonitis</td>
<td></td>
</tr>
<tr>
<td><strong>LIP</strong>: lymphocytic interstitial pneumonitis</td>
<td></td>
</tr>
<tr>
<td><strong>IRD</strong>: immune reconstitution disease</td>
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</tbody>
</table>

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vaccination can be successfully re-administered to subjects on CART who have not developed protective immunity from prior vaccination when not using CART.

**Viral infection** The recent influenza A H1N1 pandemic has served as a reminder that opportunistic viral infections, such as Cytomegalovirus pneumonitis, are, for many HIV-infected individuals, much less of an issue than common viral pathogens. H1N1 appears to have a similar presentation and outcome when associated with HIV co-infection. CART probably offers little specific protection and annual influenza immunisation is recommended.

**Fungal infection** P. jiroveci, formerly P. carinii, is the cause of Pneumocystis pneumonia (PCP). It remains a common problem in individuals unaware of their HIV serostatus and also among HIV-infected patients intolerant of, or nonadherent with, 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% of cases). The most common abnormality is bilateral perihilar, interstitial infiltrates, which may progress to diffuse alveolar shadowing over a period of days. Atypical radiographic appearances include upper zone infiltrates resembling TB, hilar/mediastinal lymphadenopathy, intrapulmonary nodules and lobar consolidation (present in up to 20% of cases).

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 the need for mechanical ventilation are associated with a worse outcome.

PCP can be stratified clinically as mild (\(P_{A\:O_2}\) >11.0 kPa, \(S_{A\:O_2}\) >96% breathing air at rest), moderate (\(P_{A\:O_2}\) 8.0–11.0 kPa, \(S_{A\:O_2}\) 91–96%) or severe (\(P_{A\:O_2}\) <8.0 kPa, \(S_{A\:O_2}\) <91%). This categorisation is helpful, as oral therapy may be given to those with mild disease. The 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 (e.g. intense gastro-intestinal upset, rash, bone marrow suppression, or renal or liver dysfunction) is common, while <10% who tolerate therapy do not respond to treatment (defined by deterioration ≥5 days after initiation).

In patients with drug toxicity or poor response to co-trimoxazole, alternative therapy in mild/moderate disease includes clindamycin (450–600 mg four times daily 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 twice daily). In severe disease, alternative therapy is clindamycin with primaquine or i.v. pentamidine (4 mg·kg⁻¹ daily).

Patients with an admission \(P_{A\:O_2}\) ≤9.3 kPa should also receive adjunctive gluco-corticoids within 72 h of starting specific anti-PCP treatment. A frequently used regimen is prednisolone, 40 mg twice daily 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. Patients should be monitored carefully for steroid-related adverse events, including hypertension, hyperglycaemia, and local and systemic viral reactivation.

Co-trimoxazole, dapsone and primaquine should be avoided in patients with glucose-6-phosphate
dehydrogenase deficiency, and testing for the enzyme deficiency is recommended as standard practice.

Patients are at increased risk of PCP as their blood CD4 count decreases.

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

The indication for secondary prophylaxis is:
- all patients who have had a previous episode of PCP

Indications for discontinuing secondary prophylaxis are:
- patients on CART with a 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 below 200 cells·μL−1 and/or the HIV RNA load increases, prophylaxis should be re-instituted)
- based on the rates of recurrent PCP noted within observational cohorts, some clinicians will discontinue treatment if the HIV load is undetectable and blood CD4 is >100 cells·μL−1

It is recommended that, if possible, all patients with an episode of PCP start CART within 2 weeks of completing their anti-*Pneumocystis* treatment.

**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. Worldwide, almost 15% of new TB cases occur in HIV-infected subjects. TB accounts for ~25% of all HIV-related deaths. TB is also covered in other chapters, so here the focus is on issues of particular relevance in HIV infection.

More than two-thirds of patients with TB and HIV co-infection present with

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**Table 2. Recommended PCP prophylaxis regimens**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First choice</strong></td>
<td></td>
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</tr>
<tr>
<td>Co-trimoxazole (sulphamethoxazole + trimethoprim 5:1)</td>
<td>960 mg once daily#</td>
<td>Protects against certain bacterial infections and reactivation of toxoplasmosis</td>
</tr>
<tr>
<td></td>
<td>480 mg once daily</td>
<td>Adverse effects include nausea (40%), rash (up to 20%), bone marrow suppression (20%)</td>
</tr>
<tr>
<td></td>
<td>960 mg thrice weekly</td>
<td></td>
</tr>
<tr>
<td><strong>Second choice</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aerosolised pentamidine</td>
<td>300 mg once per month via jet nebuliser</td>
<td>Use once per fortnight if CD4 count &lt;50 cells·μL−1</td>
</tr>
<tr>
<td>Dapsone</td>
<td>100 mg once daily</td>
<td>Plus oral pyrimethamine 25 mg once per week against reactivation of toxoplasmosis</td>
</tr>
<tr>
<td><strong>Third choice</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atovaquone</td>
<td>Suspension 750 mg twice daily</td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>1250 mg once per week</td>
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</tr>
</tbody>
</table>

# the use of lower doses of co-trimoxazole may be associated with fewer adverse events.
pulmonary disease. When blood CD4 counts are normal or only slightly reduced (e.g. >350 cells μL⁻¹), clinical features are similar to adult post-primary disease. Chest radiography often shows upper lobe infiltrates and cavitory changes. Sputum and BAL fluid are often smear positive.

In advanced HIV disease, and/or 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 specific for TB and include diffuse or miliary-type shadowing, mediastinal/hilar lymphadenopathy and pleural effusions; cavitation is uncommon. Sputum or BAL fluid is often smear negative though 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 as many body sites or fluids as clinically practical. For example, the yield from early-morning urine cultures is reasonable.

If smears or unspeciated mycobacterial cultures are positive, treatment should initially include a four-drug anti-TB regimen with a rifamycin (either rifampicin or rifabutin) plus isoniazid, pyrazinamide and ethambutol, until mycobacterial identification and drug sensitivities are known. TB diagnosis using rapid nucleic acid amplification tests are increasingly sensitive in HIV-infected individuals, although, generally, this remains less than in HIV-negative TB patients. The molecular probes 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) and mutations associated with resistance to other anti-TB drugs, depending on the test kit used.

Rapid molecular diagnostic assays, such as the Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA), are increasingly simple to use in a field setting. They enable often scarce resources to be allocated effectively; for example, if a patient is shown to have rifampicin resistance using the probe, then an early decision can be made to treat for multidrug-resistant TB in the first instance and appropriate samples set up for mycobacterial culture and sensitivity testing, which may not be a part of local, routine care.

Point-of-care rapid antigen assays using relatively easily obtained body fluids (e.g. the mycobacterial cell wall antigen lipoarabinomannan tested in urine) may be of more value in HIV-infected than -uninfected individuals with suspected active TB. However, despite good specificity, their sensitivity appears generally low other than in patients with TB and advanced HIV infection (presumably due to such individuals having a greater mycobacterial load).

The wider use of rapid mycobacterial detection systems has led to the discovery that ‘subclinical’ TB is common in HIV-infected subjects from TB endemic areas. Here, patients are generally well but have viable bacilli isolated from, for example, sputum and, hence, require treatment for TB. This has been reported in up to 20% of patients being screened for active TB prior to starting CART. In lower TB prevalence areas, it is less common and probably occurs in, at most, 5% of such individuals.

Short- and long-term 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 is often present in patients with low blood CD4 counts) receive daily and not higher-dose (twice- or thrice-weekly) intermittent therapy. Compared with non-HIV-infected individuals, there is possibly a 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. Generally, the lower the blood CD4 count, the more
pressing is the clinical need to start CART (e.g. if blood CD4 <200 cells·μL⁻¹, then commence within 2–4 weeks of start of anti-TB treatment).

Issues with early use of CART in TB patients include:

- high pill burden
- overlapping toxicities, e.g. neuropathy
- drug–drug interactions, e.g. CART and rifamycins
- poor adherence to complex regimens
- increased risk of immune reconstitution disease (IRD) (see later, and of particular relevance when starting CART within days of anti-TB treatment in cerebral TB)

Multidrug- and extensively drug-resistant TB have 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 preventive 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 can be affected by the immune dysregulation present in HIV co-infected subjects.

Malignant conditions

**Kaposi sarcoma** Kaposi sarcoma is the most common 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 uncommon.

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 most common 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 considerably better if patients treated with chemotherapy also receive CART.

**Bronchial carcinoma** Lung cancer appears to be around twice as common in HIV-infected compared with HIV-negative smokers. It is now more frequently diagnosed than in the pre-CART era and probably reflects the protection CART offers from other conditions that otherwise would have occurred. The clinical presentation is often late and, despite specific treatment, plus the use of CART if not already prescribed, the prognosis is, therefore, generally poor.

Nonmalignant, noninfectious conditions

**Chronic obstructive pulmonary disease** HIV-infected smokers are at increased risk (approximately 20–30%) of developing COPD. Although this does not approach the relative risk associated with many respiratory infections, in a similar manner to lung cancer, the onset of symptoms appears to be at a younger age. Some studies suggest that such individuals have a greater degree of
breathlessness and functional disability compared with HIV-negative COPD patients with equivalent lung function.

The large number of HIV-positive ageing smokers together with the synergistic effects of smoking, recurrent bacterial and opportunistic infections, injecting drug use, and possibly the direct effect of HIV in the lung (plus also the inflammatory response generated by use of CART), argue strongly for scaling up smoking cessation services. This is important as in many developed-world settings, smoking rates in HIV-infected populations are higher than national averages. Smoking cessation 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 immunocompetent individuals, although CART is associated with improved haemodynamics and survival.

**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** The clear beneficial impact of antiretroviral therapy on long-term morbidity and mortality means that CART is now a global standard of care for most HIV-infected people. The changes in immunity that occur when it is first started can be intense. In up to 30% subjects who have documented or subclinical co-infection, the immune response may be overexuberant and manifest as a clinical deterioration in health status. This has been given several names including immune reconstitution inflammatory syndrome and IRD. It has been reported to occur with a number of conditions, but particularly mycobacterial disease and chronic fungal and viral infections.

The underlying mechanism is not completely understood, and its clinical features represent both innate and acquired host responses to exogenous antigen. The ‘paradoxical’ type of IRD is similar to that seen in non-HIV-infected patients being treated for TB but is generally more intense. Here, subjects with known TB improving on treatment start CART and within a median of 2–3 weeks develop new clinical manifestations, e.g. peripheral lymphadenopathy, pleural or pericardial effusions or cerebral disease. There is no specific diagnostic test and so drug resistance, patient nonadherence to treatment and other disease processes must be actively excluded. It is more likely in people with low baseline CD4 counts (<100 cells·μL⁻¹), faster suppression of HIV viral load and shorter time between starting anti-TB therapy and CART. IRD can be severe, though is rarely fatal. When this does happen it is generally due to the pressure effects associated with a rapid increase in size of the inflammatory lesions. Hence, care must be taken with IRD associated with cerebral, pericardial and, sometimes, mediastinal disease. 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 a median of 3–6 weeks after starting CART. Treatment is generally directed at the underlying mycobacterial infection. In TB-endemic areas,
such as sub-Saharan Africa and South-East Asia, screening subjects for subclinical TB prior to CART initiation is important. Studies have indicated that up to one in five of individuals who are minimally symptomatic will have sputum culture-positive TB and, hence, require treatment. The use of rapid molecular and mycobacterial diagnostic tests (described earlier in this chapter) are a useful and effective means of excluding TB in people who need to start CART.

The antiretroviral 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. It should not be given again.

Further reading

Graft versus host disease

Federica Pulvirenti, Cinzia Milito, Maria Anna Digiulio and Isabella Quinti

Pathogenesis

Graft versus host disease (GVHD) is the principal complication of allogeneic haematopoietic stem cell transplantation (HSCT): it limits HSCT success and is fatal to ~15% of transplant recipients. The number of patients at high risk for GVHD is increasing, as more HSCTs are performed from unrelated donors, mainly in older patients. GVHD results from immunological attack on target recipient organs or tissues (such as the skin, liver and gut) by donor allogeneic T-cells that are transferred along with the allograft. The development and severity of GVHD in transplant recipients depends on many factors, such as recipient age, toxicity of the conditioning regimen, haematopoietic graft source and GVHD prophylaxis approaches.

GVHD is divided into acute and chronic forms. Acute GVHD and chronic GVHD involve distinct pathological processes: acute GVHD has strong inflammatory components, whereas chronic GVHD displays more autoimmune and fibrotic features.

Chronic GVHD is defined as occurring after the first 100 days post-HSCT and has a characteristic clinical presentation, which resembles autoimmune vascular diseases and is distinct from that observed in acute GVHD. Chronic GVHD occurs in 30–65% of allogeneic HSCT recipients, can be highly debilitating in its extensive form and has a 5-year mortality rate of 30–50%, mainly due to immune dysregulation and opportunistic infections.

Acute GVHD was thought to be a process driven mainly by T-helper(Th)1- and Th17-type immune responses, whereas chronic GVHD was thought to be predominately mediated by Th2-type responses. Vascular endothelial damage and increased secretion of pro-inflammatory cytokines are involved in the pathogenesis of lung disorders.

Key points

- Graft versus host disease (GVHD) is the principal complication of allogeneic HSCT.
- 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 pneumonia, bronchiolitis obliterans syndrome, organising pneumonia, alveolar haemorrhage, capillaritis, post-transplant lymphoproliferative disorders.
- CMV infection is the most frequent viral complication in patients undergoing HSCT and acute GVHD significantly affects active CMV infection recurrence.
- GVHD has beneficial effect of on the incidence of leukaemia relapse and increase the overall survival of patients with leukaemia: this phenomenon is known as the graft-versus-tumour effect.
- New insights from basic immunology, preclinical models and clinical studies have led to novel approaches for prevention and treatment.

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pro-inflammatory cytokines are involved in systemic disorders post-HSCT, 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.

The pivotal role of T-cells in acute GVHD is supported by the complete abrogation of GVHD following T-cell depletion from the graft, an approach that remains the most effective in preventing acute GVHD.

Tissue damage caused by the cytotoxic T-cells leads to the recruitment of other effector cells (including natural killer (NK) cells and neutrophils), which further increase tissue injury and result in a self-perpetuating state of GVHD that is difficult to control once it is fully initiated.

Current data implicate the innate immune response as being responsible for initiating or amplifying acute GVHD. Molecules such as bacterial lipopoly-saccharide (LPS), released from the injured gut during the conditioning regimen, activate innate immune receptors, including Toll-like receptors (TLRs), and cause a cytokine storm, which favours the development of acute GVHD. Commensal microflora may modulate innate response and reduce the severity of GVHD by stimulating other TLRs (TLR): to re-address the gut flora to make it less GVHD favourable might be a way to ameliorate GVHD, as suggested by the decreased severity of GVHD and improved survival of animals following the administration of probiotic bacteria.

Great progresses have been recently achieved in discerning the role of antigen presenting cells (APCs) in GVHD: MHC class II-bearing host haematopoietic APCs were previously thought to be essential for the induction of CD4\(^+\) T-cell-dependent acute GVHD. Recent studies have shown that host haematopoietic professional APCs in lymphoid organs may have only a limited capacity to induce GVHD, and host dendritic cells (DCs) may not be required. Parenchymal tissue cells can acquire APCs functions and they have been shown to promote a marked expansion of allo-reactive donor T-cell populations in the gastrointestinal tract. In the absence of functional host haematopoietic APCCs, the presentation of minor histocompatibility antigens by donor haematopoietic APCs or host non-haematopoietic APCs is sufficient for GVHD induction.

**The graft versus tumour effect**

Obstacles to the improvement of HSCT treatment 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.

The long-known beneficial effect of GVHD on the incidence of leukaemia relapse and the overall survival of patients with leukaemia is known as the graft versus tumour (GVT) effect.

The role of T-cells in both GVHD and the GVT effect was supported by the finding that T-cell depletion from the graft eliminates GVHD but at the expense of an increased leukaemia relapse rate. The major GVT effectors are cytotoxic T-cells that recognize allogeneic histocompatibility antigens and unique tumour antigens. In addition, NK cells and NK T-cells can directly recognize MHC class-I molecules and stress-induced peptides and mount anti-tumour responses.

Current strategies to improve GVT effects are based on selectively targeting tumour-specific killing and inhibiting immune escape mechanisms commonly used by tumours. These immune escape mechanisms include the loss of tumour-specific molecules on presented peptides, the downregulation or loss of MHC class-I or co-stimulatory molecules expression by tumour cells, the induction of functional defects in T-cells or NK cells, the production
of soluble inhibitors of NK cell function, the expression of death receptor ligands such as CD95 ligand by tumour cells, and tumour cell resistance to apoptosis.

**Treatment**

Systemic corticosteroid therapy, despite its major shortcomings, remains the standard primary therapy for GVHD. Patients with steroid-refractory acute GVHD have a dismal outcome, with long-term mortality rates that can reach 90%.

New and improved therapies are therefore desperately needed, particularly in cases of steroid-refractory chronic GVHD. Most of the current therapeutic approaches that are routinely used for GVHD (like corticosteroid and the calcineurin inhibitors) are broad-spectrum approaches that target T-cells and are therefore likely to have a negative impact on GVT responses as well as immune reconstitution.

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.

Because of donor CD4⁺ and donor CD8⁺ T-cells have a crucial role in the pathogenesis of GVHD, the most effective approaches for GVHD prevention and therapy focus on the depletion, tolerisation or functional incapacitation of donor T-cells. Recently the role of TH17 cells has been highlighted. The TH17 cells are a T-lymphocyte helper subset characterised by the production of interleukin (IL)-17A, IL-17F, IL-21 and IL-2; they have been shown to have a direct role in GVHD pathogenesis and they may yet prove to be a viable target for neutralisation in patients with GVHD in the gut. The TH17-type cytokine, IL-21, is another potential neutralisation target, given its role in promoting the activation, differentiation, maturation or expansion of NK cell, B-cell, T-cell and APC populations.

Inhibition of IL-21 receptor signaling in vivo reduced acute GVHD activity in the gut, and this effect was associated with decreased TH1 cell and increased regulatory T-cell (Treg) numbers in the gut mucosa. An alternative approach to manipulating the TH17 cell response is to target the cytokines that are involved in the induction of TH17 cells, such as IL-6. Together with transforming growth factor (TGF)-β, IL-6 promotes the differentiation of naive T-cells into TH17 cells. Infusion of an IL-6 receptor-specific monoclonal anti-body in a model of acute GVHD led to increased Treg numbers and a reduction in GVHD-induced pathological damage, particularly in the gut. The neutralisation of IL-6 may result in a direct anti-tumour response, particularly in multiple myeloma.

Because of the key role for pro-inflammatory cytokines in acute GVHD, inhibition of cytokine-induced signal transduction is an appealing approach for GVHD treatment. Janus kinases (JAKs) are cyto-plasmic protein tyrosine kinases that initiate cytokine-triggered signaling events by activating the cyto-plasmic latent forms of STAT proteins. In preclinical models, a small-molecule inhibitor of JAK3 has shown great promise in reducing lethality from GVHD without impeding GVT effects. Small-molecule inhibitors of JAK2 or JAK3 may therefore prove to be useful in inducing donor cell tolerance towards the host.

Other tyrosine kinase inhibitors, such as imatinib, which is commonly used to treat chronic myeloid leukaemia, have been shown to have marked anti-GVHD effects, especially in patients with chronic GVHD. Although the exact mechanism of action of imatinib in GVHD seems to be independent of its capacity to inhibit the platelet-derived growth factor receptor (PDGFR), imatinib represents an attractive agent for suppressing chronic GVHD and preserving GVT responses.

Proteasome inhibitors, such as bortezomib, prevent or treat GVHD in mice because they have inhibitory effects on cytokine signaling and nuclear factor (NF)-κB activation. Bortezomib, even at very low doses, can specifically deplete alloreactive T-cells, allow T-Reg cell survival and attenuate IL-6-mediated T-cell differentiation; it can also inhibit APCs by targeting TLR4-mediated activation. Bortezomib and possibly other
proteasome inhibitors are attractive therapeutic agents and worth testing in various clinical HSCT settings.

Modulating the trafficking patterns of alloreactive T-cells could be an efficacious mean of ameliorating GVHD. Inhibition of T-cell homing to inflamed tissues can be accomplished by interrupting one of four key stages of T-cell migration: 1) tethering and rolling on the endothelium; 2) chemokine ligand–receptor interactions; 3) adhesion to the endothelium; and 4) migration in response to sphingosine-1-phosphate.

Other approaches include NK cell infusion and the in vivo activation of NK cells to promote the deletion of alloreactive T-cells; infusion of mesenchymal stem cells (MSCs), transfer of donor-derived Treg populations, infusion of myeloid-derived suppressor cell (MDSC) populations expanded ex vivo using granulocyte colony-stimulating factor (G-CSF) and granulocyte–macrophage colony-stimulating factor (GM-CSF), sirolimus, anti-tumour necrosis factor and anti-lymphocyte function-associated (anti-LFA)-3 antibodies, extracorporeal photopheresis.

Non-infectious pulmonary-associated complications

Common pulmonary complications occur in 25–50% of HSCT recipients and are responsible for 50% of transplant related deaths (table 1). Acute and subacute patterns of lung injury have been recognised. Idiopathic pneumonia syndrome occurs within the first 120 days after HSCT 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-HSCT. Although long-term disease-free survival after HSCT could exceed 60%, pulmonary infiltrates, due to either inflammatory or infectious pneumonitis, occur in 40–60% of HSCT recipients causing the 80% of transplant-related deaths. In children undergoing HSCT, the incidence of pulmonary complications varies from 10% to 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

<table>
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<th>Frequency</th>
<th>Mortality</th>
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<td>100</td>
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<tr>
<td>Post-transplant lymphoproliferative disorders</td>
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Data are presented as %. CMV: cytomegalovirus; PCP: Pneumocystis jiroveci pneumonia. Adapted from Wang et al. (2004)
factor is a 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 HSCT patients are observed in 1–56% of patients. CMV infection is the most frequent viral complication in patients undergoing HSCT. 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 HSCT recipients has changed the natural history of the disease. As 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 and no longer isolated to the transplant pulmonologists.

Further reading

Amyloidosis is a group of diseases caused by accumulation of protein as insoluble fibrillar deposits within the extracellular space. These progressively disrupt the structure and function of affected tissues. Amyloidosis may be either acquired or inherited and ≥ 26 different proteins can form amyloid fibrils in vivo in humans. The ultrastructural morphology and histochemical properties of all amyloid fibrils, regardless of the precursor protein type, are remarkably similar. Diffraction studies of amyloid fibrils have demonstrated a shared common core structure consisting of antiparallel β-strands lying perpendicular to the long axis of the fibril. This extremely abnormal, highly ordered conformation underlies the distinctive physicochemical properties of amyloid fibrils: they are relatively stable and are resistant to proteolysis, and they all bind molecules of the dye Congo red in a spatially organised manner, which results in the pathognomonic apple-green birefringence when viewed under cross-polarised light. Amyloid deposits also always contain the normal plasma glycoprotein, serum amyloid P component (SAP) as a nonfibrillar constituent. The universal presence of SAP in amyloid deposits reflects its specific binding to an, as yet, uncharacterised ligand common to all amyloid fibrils, which forms the basis for diagnostic scintigraphic imaging of amyloid with radiolabelled SAP.

Untreated amyloidosis progresses relentlessly and systemic forms of the disease are generally fatal, 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 may give rise to systemic amyloidosis
- systemic amyloidosis may present with respiratory symptoms
- localised pulmonary and respiratory tract amyloid deposits may present either symptomatically or as an incidental finding on imaging

**Key points**

- Amyloidosis is a protein deposition disease.
- Diagnosis is by biopsy and Congo red staining.
- Systemic amyloidosis is a life threatening condition that usually affects several organs.
- Localised amyloidosis can present with obstructive symptoms, haemoptysis or as an incidental finding on imaging.
- Treatment depends on the type and distribution of amyloid deposits.

**Systemic amyloidosis complicating respiratory diseases**

*AA amyloidosis* is a potential complication of any sustained inflammatory condition, which usually presents as proteinuric renal impairment. 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...
longstanding bronchiectasis, which underlies 5% of cases. Previously, tuberculosis was common, and other associations include lung neoplasia (Castleman’s tumours, lymphoma and adenocarcinoma; accounting for 3% of AA amyloidosis cases), CF, sarcoidosis 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 is the commonest type, accounting for 60% of cases, and may occur in association with any B-cell dyscrasia, as the amyloid fibrils are 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 on post mortem examination, symptoms are rare and dyspnoea generally reflects amyloid cardiomyopathy. Chest radiographs are usually normal but can demonstrate diffuse reticulonodular infiltration. 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. Serious pulmonary side-effects from treatment are rare but fever and asthma-like symptoms and progression to respiratory failure with pulmonary infiltrates have been reported following treatment with the proteasome inhibitor bortezomib. There have also been descriptions of lung toxicity following the use of thalidomide and lenalidomide with toxic granulomatous interstitial pulmonary disease, which may be steroid responsive.

Amyloidosis localised to the respiratory tract

This results either from local production of fibril precursors or from properties inherent to a particular microenvironment, which favour fibril formation of a widely distributed precursor protein. The majority of deposits are AL-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

Amyloidosis 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 years.

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.
Pulmonary amyloidosis associated with Sjögren’s syndrome

This chronic, organ-specific autoimmune disease predominantly affects females and carries a 44-fold increase in lymphoproliferative disorders. Pulmonary AL amyloidosis is a rare but well recognised complication, resulting in cough and dyspnoea.

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 long-standing 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.

Further reading

Pulmonary alveolar proteinosis (PAP) is a rare syndrome occurring worldwide with an estimated prevalence of 0.1 cases 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.

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 by mutations in the GM-CSF receptor $\alpha$ or $\beta$ chains. Passive transfer of PAP features in monkeys inoculated with human GMAb strongly supports the concept that GMAb are the causative factor of autoimmune PAP.

- **Secondary PAP** occurs as a consequence of the presence of several underlying diseases associated with PAP, such as haematological disorders (mostly myelodysplastic syndrome), immunodeficiency, 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 genes encoding surfactant protein (SP)-B and SP-C genes, as well as in the ABCA3 (ATP-binding cassette subfamily A member 3) gene.

According to a recently published meta-analysis and large cohort report, $>90\%$ of immune PAP patients are middle-aged adults, complaining of 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 increased exertional alveolar–arterial oxygen tension gradient. The classic chest radiographic presentation is a diffuse bilateral infiltrate with a distribution that is sometimes similar to that of pulmonary oedema (fig. 1a). More typical is the HRCT presentation defined as...
‘crazy paving’ (thickening of interlobular and intralobular septa and ground-glass opacities, with a 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 crazy paving pattern on HRCT
2) macroscopic appearance of milky fluid and cytology of bronchoalveolar lavage (BAL) fluid
3) elevated serum level of GMAb (whose sensitivity and specificity for diagnosing PAP is ~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 of care for 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.

Further reading


Langerhans’ cells are bone marrow-derived dendritic cells, the physiological function of which is to process and present antigens to lymphocytes. Langerhans’ cell histiocytosis (LCH) is a rare systemic disorder characterised by aberrant accumulation of Langerhans’ cells in various organs, usually in the form of granulomas. LCH is part of a spectrum of other histiocytic disorders that includes include LCH, non-Langerhans’ histiocytosis such as Erdheim–Chester disease and Rosai–Dorfman disease, and malignant histiocytic disorders. LCH in adults may especially involve the lung, bones, skin and pituitary gland. The presentation in childhood is different, with acute disseminated disease and a poor prognosis, and, in older children and adolescents, with multifocal involvement including the bone. However, single-system involvement of LCH is possible. Pulmonary LCH is characterised by polyclonal accumulation of Langerhans’ cells and other inflammatory cells in the small airways, resulting in nodular inflammatory lesions that may evolve into extensive cavitating destruction of the lung parenchyma and respiratory insufficiency.

**Epidemiology**

Pulmonary LCH in adults is a rare disease with an estimated prevalence of less than one case in 200 000. It occurs almost exclusively in smokers, with no sex predominance, between the ages of 20 and 40 years, and is more common in the white population.

**Pathologic features**

Pulmonary LCH is characterised by granulomatous bronchiocentric organisation of Langerhans’ cells associated with inflammatory cells including eosinophils. Langerhans’ cells do not differ from their normal counterpart in tissues, exhibiting convoluted irregular nuclei with characteristic Birbeck granules visible by electron microscopy. These cells stain positive with anti-CD1a and anti-CD207 (langerin) antibodies. Some features of alveolar macrophage pneumonitis (desquamative interstitial pneumonia) or respiratory bronchiolitis with interstitial lung disease are often associated with LCH. Progression of the bronchiocentric 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 in patients who are smokers) and gradually progressive dyspnoea on exercise. Spontaneous pneumothorax is the first manifestation leading to diagnosis in about...
10–20% of patients. A number of patients have almost no reported symptoms and the disease is discovered incidentally on routine chest X-ray or CT. 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 possible chest pain), hypothalamic–pituitary involvement resulting in diabetes insipidus (polyuria and polydipsia) and skin lesions.

**Imaging**

The chest X-ray is usually abnormal, with micronodular and reticular opacities, typically sparing the lower lobes. In advanced disease, nodules are absent and the chest X-ray may suggest emphysema.

HRCT of the chest usually shows characteristic features in early disease with disseminated infracentimetric nodules, which may show cavitation and may spontaneously disappear. The cavitated nodules may evolve to thick- then thin-walled cysts (fig. 1). The cysts may then enlarge and become confluent, with HRCT features resembling emphysema.

The differential diagnosis includes other multiple cystic lung diseases on imaging, especially Birt–Hogg–Dubé syndrome and spontaneous familial pneumothorax related to FLCN mutations, lymphangioleiomyomatosis, Sjögren’s syndrome, and nonamyloid immunoglobulin deposition disease. Pleural effusion and mediastinal lymphadenopathy are 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, TLco is usually decreased, including in patients with relatively few lesions on imaging. About one-third of patients develop airflow obstruction with hyperinflation, which may progress to severe obstructive respiratory insufficiency.

**Diagnosis**

The gold standard for diagnosis of LCH is lung biopsy showing the characteristic features described above. Surgical biopsy is often obtained during pleurodesis for recurrent 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. 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 do not contribute to the diagnosis of LCH.

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 deteriorated or deteriorating lung function who are considered for treatment. In patients with diffuse cystic lesions on HRCT with irreversible lung function impairment, lung biopsy is of limited benefit, especially as it may not show characteristic granulomatous lesions.

![Image of HRCT of the chest demonstrating numerous thin-walled cysts in a patient with LCH.](image-url)
Evolution

About half of the patients improve spontaneously or with corticosteroid treatment (which has, however, not been rigorously evaluated). Poor outcome with respiratory failure may occur, especially in older patients with systemic involvement and deteriorating lung function tests. Pulmonary hypertension often severe is common in advanced disease. Lung cancer may develop resulting from smoking habits.

Treatment of pulmonary LCH

Given the possibility of spontaneous recovery in a number of patients and the absence of controlled therapeutic trials, there is currently no evidence of efficacy of any treatment.

The strong association between pulmonary LCH and tobacco smoking suggests a causal relationship, and numerous observations have reported improvement of the disease following smoking cessation. However, worsening or relapse despite smoking cessation has also been described. In any case, smoking cessation is an essential component of management in pulmonary LCH, at least to prevent further development of COPD and/or lung cancer.

Although without evidence of efficacy, corticosteroid treatment is often used in patients with symptomatic disease and worsening lung function, starting with prednisone 0.5–1 mg·kg⁻¹ then tapering over 6–12 months. Whether improvement, when occurring, results from treatment efficacy or from spontaneous improvement cannot be established.

Cytotoxic agents (especially vinblastine) have been occasionally used with no conclusive efficacy. 2-chloro-deoxyadenosine (cladribine) has consistently been shown to be efficient in isolated cases. However, cladribine may induce profound myelo- and immunosuppression, and should be administered only in expert 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 them present with moderate-to-severe pulmonary hypertension. Post-transplant survival is rather good, with 10-year survival >50%. However, pulmonary LCH may recur in about one-fifth of patients.

Further reading

Lymphangioleiomyomatosis

Vincent Cottin, Romain Lazor and Jean-François Cordier

Epidemiology and genetics

Lymphangioleiomyomatosis (LAM) is a rare (so-called orphan) lung disease affecting about 3.4–7.8 per million adult females (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 in affected cells (LAM cells).

Lung 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 stain with antibodies against smooth muscle actin, desmin and HMB-45 (detecting characteristic pre-melanocyte proteins). As LAM cells have been shown to invade the lymphatic vessels and spread to selected distant sites such as the lung and kidney, LAM is increasingly considered a low-grade metastatic tumour. The source and physiological counterpart of LAM cells are currently unknown. LAM cell clusters have recently been found in the uterus of 90% patients with LAM, suggesting that these cells could originate from this organ.

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 maybe bilateral). Chylous effusion (chylothorax and chylous ascites) may be present.

Lung function tests are characterised by airflow obstruction and impaired gas transfer with a decrease in TLCO. Exercise performance and maximal oxygen uptake are impaired. Hypoxaemia is present in advanced disease.

Imaging

Chest X-ray shows reticular opacities, cysts, pleural effusion or pneumothorax.

HRCT of the chest plays a major role in diagnosis. It shows characteristic multiple round, thin-walled cysts evenly distributed.

Key points

- LAM is a rare disease occurring in women of child-bearing age, characterised by dyspnoea on exertion, relapsing pneumothorax and numerous thin-walled cysts on chest imaging.
- Diagnostic criteria have been proposed recently.
- The disease may slowly progress to respiratory insufficiency.
- No effective therapy is available.
throughout the lung parenchyma; these cysts may progressively become confluent (fig. 1).

Cysts may be associated with small nodules in TSC (corresponding to multifocal micronodular pneumocyte hyperplasia), pleural effusion and pneumothorax. The axial lymphatics of the thorax and 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 (AMLs) of the kidney are benign tumours composed of blood vessels, smooth muscle and adipose tissue that are easily identified by HRCT. AMLs are found in 50% of patients with sporadic LAM and 80% of patients with TSC, in whom they are more often bilateral and larger. AMLs may slowly enlarge with time and become prone to bleeding, especially when >4 cm or rich in microaneurysms (percutaneous embolisation or, rarely, nephron-sparing nephrectomy is therefore indicated). Regular screening for AML is recommended in patients with LAM.

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. However, the combination 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 associated with mutations of the folliculin gene (FLCN), especially Birt–Hogg–Dubé syndrome and familial primary spontaneous pneumothorax, Langerhans’ cell histiocytosis, cysts associated with lymphoid interstitial pneumonia, nonamyloid immunoglobulin deposition disease, etc. A diagnostic work-up for alternative causes of multiple-cystic lung disease is mandatory in patients with probable and especially possible LAM. Levels of vascular endothelial growth factor (VEGF)-D, a major angiogenic growth factor produced by tumour cells that promotes formation of lymphatic vessels and spread of tumour cells to lymph nodes, are increased in the serum of patients with LAM, as compared with other cystic lung diseases and healthy controls. Serum VEGF-D level contributes to the noninvasive diagnosis of LAM if elevated (high positive predictive value if >800 pg·mL⁻¹) but does not rule out the disease if normal.

Evolution and prognosis

Disease progression is variable, with some patients remaining relatively stable for a long time but others deteriorate rapidly with ensuing respiratory insufficiency. Median annual FEV₁ decline is around 100 mL·year⁻¹. Repeated measurement of FEV₁ and TLCO is used to assess disease progression with arterial oxygen measurement in advanced disease. Pulmonary hypertension, usually mild, may develop.

The 10-year 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 progesterone to prevent the development of LAM. However, hormonal interventions have not demonstrated significant advantages. Nevertheless, oestrogens (the contraceptive pill or hormone replacement) should be avoided.
The mTOR inhibitor and immunosuppressive agent sirolimus has recently been shown to stabilise lung function in patients with LAM compared with placebo. However, significant side-effects occurred (mouth ulcers, diarrhoea, nausea, increased blood cholesterol levels, skin rash and swelling of the extremities) and disease progression resumed when sirolimus was stopped. Sirolimus and everolimus also appeared effective on chylous effusion in small observational studies, and in AML not amenable to embolisation therapy. As mTOR inhibitors are not currently approved for LAM, their compassionate use should be restricted to expert centres.

There is a greater risk of pneumothorax and chylous effusion during pregnancy. Whether or not to become pregnant is the patients’ decision; however, pregnancy may be discouraged in patients with severe disease.

Influenza and pneumococcal vaccination should be offered to patients with LAM.

Inhaled bronchodilators should be prescribed to patients with airflow obstruction and continued if a response is observed.

In patients with end-stage LAM, lung 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 the most severe cases with poor prognosis. Recurrence of LAM on transplant is possible but does not affect survival.

Further reading


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 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.

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 assessment. Interestingly, there is wide variance in tasks undertaken by physiotherapists across countries; for example, in some, assisting in delivery of pharmacotherapy, oxygen therapy and NIV is the role of the respiratory physiotherapist, while in others, these roles may be provided by other healthcare professionals.

Airway clearance

To help the patient better manage their secretions, a range of airway clearance techniques are available, including:

- independent techniques
- mechanical or other devices
- postural drainage
- nebulised substances (e.g. hypertonic saline)
- techniques for cough enhancement or support

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 physiotherapy intervention. Physiotherapists can also help in the delivery and correct application of oxygen therapy, including ambulatory oxygen, as well as in offering improvement of poor ventilatory function, including in the sedated and paralysed patient.

Key points

Physiotherapy is indicated in most respiratory conditions, both for groups and individuals, for:

- self-management advice and education on lifestyle modifications,
- 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.
Enhancing ventilation and gas exchange

Strategies to enhance ventilation and gas exchange include:

- Positioning
- Breathing techniques
- Manual hyperinflation
- Intermittent positive pressure breathing (IPPB)
- CPAP
- 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 to that of nonrespiratory populations, this is especially warranted during coughing and forced expiratory manoeuvres.

Disease-specific physiotherapy

**Chronic obstructive pulmonary disease**

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
- breathing techniques 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 programs 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 oxygen
- 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 the 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 oxygen therapy should be delivered as per 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, with an emphasis on nasal breathing and either a smaller tidal volume or lower respiratory rate, or both, to reduce \( V_E \), combined with relaxation (technique as for asthma), is an effective strategy to reduce symptoms once the diagnosis is confirmed.

**CF and non-CF bronchiectasis** Physiotherapy is integral to the management of patients with bronchiectasis from any cause, including CF, with airway clearance and exercise being 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 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, oxygen and NIV or IPPB). These supportive therapies and postural drainage 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.

- 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 interstitial lung diseases. Studies on the effectiveness of engaging in exercise training are emerging and patients with interstitial lung diseases can gain benefit from pulmonary rehabilitation providing they are referred early in the disease process. Patients at a later stage of disease may benefit from wheeled walking aids, ambulatory oxygen, breathlessness management and energy conservation strategies.

**Community-acquired pneumonia** Traditional airway clearance techniques are rarely indicated.

For patients admitted to hospital with uncomplicated community-acquired pneumonia (CAP):

- Regular use of positive expiratory pressure may reduce length of stay
- Medical condition permitting, early mobilisation is indicated
- Patients should be encouraged to sit out of bed for \( \geq 20 \) min on the first day, increasing the time and general mobility each subsequent day

CPAP may be helpful for patients in type I respiratory failure who remain hypoxaemic despite optimum medical therapy and oxygen, and NIV may be an option for selected patients in type II respiratory failure, especially those with underlying COPD.

**Chest wall disorders** Pulmonary rehabilitation 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 oxygen or NIV should be assessed before undertaking exercise. Respiratory muscle training may have a role. Work has yet to establish whether breathing or thoracic mobility exercises are helpful in this client group.

**Neuromuscular disease and spinal cord injury** Respiratory problems are the most common 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 oxygen saturation, vital capacity (VC) and peak cough flow can indicate impending problems with either ventilation or cough effectiveness
- The use of respiratory aids when these measures fall may prevent or reduce complications

Oxygen therapy should be administered with great care in patients with neuromuscular disease because of the risk of increasing ventilation/perfusion mismatch and increasing hypercapnia. In those at risk of developing hypercapnia, NIV should be considered. These are done together with the treating physician.

Traditional physiotherapy techniques are not useful in this group of patients. Strategies to enhance maximal insufflation capacity (MIC) are indicated and include:

- resuscitation bags
- NIV
- mechanical insufflation
- breath stacking via the above or
glossopharyngeal (frog) breathing

The presence of severe bulbar dysfunction or paralysis renders breath stacking ineffective. MIC enhancement, used regularly, is also a means of maintaining range of movement in 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 spinal cord injury (SCI).

In patients with SCI, exercise should be encouraged; respiratory muscle training and functional electrical stimulation may enhance muscle strength or VC. 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 in critically ill patients as in other patients; physiotherapists provide rehabilitation for the prevention and treatment of the common complications associated with prolonged bed rest, immobility and recumbence, including deconditioning, weakness and dyspnoea. Physiotherapy is also used to target specific respiratory problems, such as retained airway secretions, atelectasis and weaning failure.

Further reading

Pulmonary rehabilitation

Thierry Troosters, Hans Van Remoortel, Daniel Langer, Marc Decramer and Rik Gosselink

Definition

Pulmonary rehabilitation is now a recognised therapy for patients with respiratory diseases. Its effectiveness is supported by countless randomised controlled trials. In 2012, the European Respiratory Society (ERS) and American Thoracic Society (ATS) defined pulmonary rehabilitation as ‘a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies which include, but are not limited to, exercise training, education and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors’. This is definition – although long – identifies the core components of a rehabilitation programme (Spruit et al., 2013). The definition per se is perhaps not as clear as it could be on the expected outcomes of rehabilitation programmes. The full rehabilitation statement of the ATS and ERS, however, does provide that insight. In an initial phase, a rehabilitation programme aims to map out and restore the nonrespiratory consequences of respiratory diseases (i.e. muscle weakness, depressive symptoms, poor coping with the disease, impaired engagement in physical activities, nutritional deficits, etc.). Subsequently or in parallel, the rehabilitation programme calls for the self-management of patients to engage in a healthy lifestyle in terms of physical activity, nutrition, smoking and coping. The rehabilitation team becomes the patient’s coach. In the first phase, exercise training is a crucial part of the rehabilitation programme; later on, the focus can gradually shift towards more lifelong behavioural change. Whereas the science of the former has reached a very high standard, with a clear evidence base, the latter is less well studied but is probably of equal importance and it is expected that progress can be made in the years ahead. Here, we will review the different aspects of this definition:

- the evidence base and anticipated effects;
- the selection of patients;
- the individualisation of the programme; and
- the mechanisms through which the programme works (reversing the systemic, extrapulmonary consequences).

Importantly, pulmonary rehabilitation may be an integrated part of other care plans for COPD patients, such as self-management programmes, lung transplantation programmes, NIV or smoking cessation programmes.

Key points

- Pulmonary rehabilitation is an evidence-based treatment that improves health-related quality of life and symptoms in COPD.
- 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.
The evidence base for pulmonary rehabilitation

Several reviews have summarised the evidence for pulmonary rehabilitation (Lacasse et al., 2006; Troosters et al., 2005) and practice guidelines are available (Ries et al., 2007). Therefore, a comprehensive review of all evidence for the effectiveness of pulmonary rehabilitation is beyond the scope of this short review.

Briefly, in patients with COPD, pulmonary rehabilitation improves health-related quality of life and symptoms unequivocally and clinically significantly. The effect of pulmonary rehabilitation on health-related quality of life is similar or even larger than that obtained by pharmacotherapy in COPD. 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, to date, are less studied.

Psychological improvements A significant proportion of patients referred for pulmonary rehabilitation suffer from psychiatric morbidity. Anxiety and depression are the most common problems. Recently, depression was identified as a negative prognostic factor in patients with COPD, particularly in patients who suffered from exacerbations. A recent meta-analysis showed the potential small benefit of multidisciplinary pulmonary rehabilitation on mood (Coventry et al., 2007). In patients referred to our rehabilitation programme, depressive symptoms were present in 42% of patients and symptoms compatible with anxiety in 38% of patients (Trappenburg et al., 2005). Clearly, one has to take into account that effects on these variables are only to be expected if patients do have symptoms of depression and/or anxiety. Hence, the relatively small effect size reported in the meta-analysis may be induced by the dilution of the depressed patients in the larger patient pool.

Another, even less studied psychological effect of rehabilitation is the enhanced self efficacy of patients. Self efficacy is the confidence patients have in their ability to carry out a specific task or manage a specific condition (e.g. breathlessness). The confidence patients have that they can manage dyspnoea improves after pulmonary rehabilitation and one of the seminal studies in pulmonary rehabilitation also showed an improvement of their self efficacy for walking. It is still unclear to what extent this increased self efficacy contributes to an effective change in behaviour after pulmonary rehabilitation.

Physical activity The amount of activity patients carry out in their daily life is an important outcome for rehabilitation. The ‘systemic consequences’ of COPD, such as cardiovascular morbidity, muscle weakness and osteoporosis, originate, to a large extent, directly or indirectly from living an inactive lifestyle. When pulmonary rehabilitation aims to achieve a sustained effect, an inactive life style after rehabilitation should be avoided. Currently, it is unclear what effect pulmonary rehabilitation programmes have on physical activity levels. Open studies have reported conflicting results and randomised controlled trials have only studied limited patient numbers in specific situations. Changing physical activity behaviour is challenging and, in general, results are somewhat disappointing. While endurance capacity virtually doubles, physical activity levels increase by about 20% (Troosters et al., 2010a). Our group showed that walking time in daily life only modestly changed 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 the increased exercise capacity. Probst et al. (2011) showed that more increased exercise tolerance (by providing higher intensity exercise programmes) did not lead to further enhanced physical activity levels. Indeed, physical activity levels are a complex integration of the exercise capacity of patients and their willingness to use that acquired capacity in a more physically active lifestyle. In recent years, appealing new
strategies have been developed that may potentially help to increase the effects of classical rehabilitation on physical activities. First, providing patients real-time feedback on their physical activity levels using pedometers may, along with setting achievable goals, enhance daily activity levels within or without the context of pulmonary rehabilitation. Second, walking at home has been stimulated effectively using group activities, such as Nordic walking, or using modern interfaces, such as mobile phone technology that used walking paced to the rhythm of music adapted to the abilities of the patient. Even more recently, internet-based programmes have become available that may support rehabilitation programmes, but need to be further validated in this context. Future research should focus on further strategies that may help to lead to a sustainable behaviour change.

Utilisation of healthcare resources: An important spin-off of pulmonary rehabilitation may be a decrease in the utilisation of healthcare resources. The most important source of utilisation of healthcare resources is hospital admissions. In one of the first large randomised controlled trials on pulmonary rehabilitation, there was a trend for a lower number of hospital days and a more recent trial showed a significant reduction in the number of hospital days (Griffiths et al., 2000). In a study from Spain, a similar nonsignificant trend was observed (Guell et al., 2000). Comparable findings were obtained in relatively long open studies comparing utilisation of healthcare resources before and after taking part in pulmonary rehabilitation. When trials focus on more fragile patients, such as those recently admitted to hospital and at risk for re-admission.

A comprehensive intervention: programme content

As indicated above, programmes need to be individualised, aim to improve the systemic consequences (physiological and psychological) of the underlying respiratory disease, and guide the patients and their families towards a long-term change in physical activity and self-management behaviour. Several options are possible in terms of the content (the disciplines contributing), location, duration and frequency of the programme. These are summarised in table 1. Studies that compared different modalities of rehabilitation head-to-head are scarce and no unequivocal preference has been reported. Several studies compared hospital-based outpatient rehabilitation to rehabilitation at home and found no differences between them in short-term outcomes. One study compared, in a randomised controlled design, hospital-based outpatient rehabilitation to community-based outpatient rehabilitation and found a trend for a somewhat smaller increase in the exercise tolerance of patients after hospital-based rehabilitation. Effects on health-related quality of life revealed similar nonsignificant trends (Elliott et al., 2004). 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 enduring effects.

The exercise training component is essential, and the programme needs to be individualised in terms of exercise modalities, specificity of the training, the 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 the maximum capacity of the patients. Recently, programmes eliciting more significant skeletal muscle fatigue were related to better training effects in terms of functional exercise tolerance and reduction of symptoms (Burtin et al., 2012). In order to combine an effective training programme with patient comfort, clinicians have the choice of several exercise training modalities. These include endurance training, interval training and resistance training. The duration of an exercise training programme is generally believed to be minimally 8 weeks and a minimum of three sessions is needed, although, admittedly, solid evidence as to the optimal duration remains missing (Spruit et al., 2013). One of
these sessions can be conducted outside the formally supervised setting, by the patients, provided that the session is comparable in terms of duration and intensity to the supervised sessions.

Maintaining the effects of pulmonary rehabilitation

There has been a lot of debate as to whether the effects of a rehabilitation programme can be maintained or not. From earlier studies, it can be seen that it is indeed difficult to claim enduring effects of short term (6–8 weeks) pulmonary rehabilitation programmes. Older long-term studies (using up to 6 months of rehabilitation) did find more long-term effects.

Our current understanding of the development of systemic consequences of COPD may help to design successful longer term strategies to maintain the effects of pulmonary rehabilitation.

1. All 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 than before, it is likely that the effects of rehabilitation on enhanced exercise capacity and skeletal muscle force will be short lived. Efforts should be made to change physical activity behaviour during rehabilitation. We showed that longer programmes were more successful in achieving this goal than short-term programmes (Pitta et al., 2008). However, changes in the programme content, such as providing patients with direct feedback on their physical activity levels or using structured behavioural interventions, may prove to yield results more rapidly.

2. Exercise at home should be facilitated. This can be achieved 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, the exercises should be regularly supervised.

3. Specific attention should probably be paid to patients who suffer from exacerbations, as these events acutely reduce muscle force and functional exercise capacity. Prevention of such events can be achieved in patients at risk by implementing self-management strategies and a case manager. Although it seems intuitively useful, there is currently little evidence for a short ‘booster’ programme after a

<table>
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<tr>
<th>Table 1. Choices to be made when prescribing pulmonary rehabilitation</th>
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<td><strong>Aspects to be individualised</strong></td>
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<td>Content</td>
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<td>Exercise training component</td>
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hospital admission to maintain the benefits of rehabilitation. If these repeated programmes are pre-planned, they seem to contribute little to the overall long-term success of programmes.

Table 2 provides an overview of the different strategies used in the peer-reviewed literature to maintain the benefits of a rehabilitation programme. Many of these studies were relatively small and, as follow-up becomes longer, the drop-out rate is substantial. Altogether, it seems important to achieve an enduring change in physical activity behaviour and patients should continue to carry out planned exercises at high intensity to maintain the physiological benefits of rehabilitation. From table 2, it is clear that interventions that are not regular or are less structured were not successful in maintaining the benefits of rehabilitation. Further evidence suggests that exercise maintenance is important to maintain the benefits of rehabilitation. That study, however, did not find differences between supervised and unsupervised exercise maintenance programmes. Patients were free to choose their preferred form of exercise maintenance strategy, which may have led to selection bias. More research is needed to identify optimal maintenance strategies after pulmonary rehabilitation.

Further evidence suggests that exercise maintenance is important to maintain the benefits of rehabilitation. Such programmes are not exclusion criteria for pulmonary rehabilitation. On the contrary, oftentimes, pulmonary rehabilitation is strongly recommended for these patients. Figure 1 gives an overview of the selection process for patients with COPD and the design of the programme.

**Extrapulmonary consequences of COPD** In the context of exercise training, 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. Roughly 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. In patients with less severe, newly detected Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II COPD, van Wetering et al. (2008) suggested quadriceps weakness occurred in 28% of the patients. In these patients, quadriceps force was related to exercise capacity, as was shown previously in more severe patients. In milder patients (FEV₁ >80% predicted), muscle weakness was actually a predictor of physical activity levels (Shrikrishna et al., 2012). Reversal of skeletal muscle dysfunction is an important goal of the exercise training component of a rehabilitation programme and, hence, patients suffering from skeletal muscle weakness are particularly good candidates for exercise training. Skeletal muscle strength can be improved particularly effectively by including resistance training.
exercises in the sessions. When successful muscle force does increase and muscle oxidative capacity is enhanced.

More research is needed on pharmacological interventions that may assist pulmonary rehabilitation in order to restore muscle function more effectively. The short-term benefits 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 are the result of 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 guide the exercise training programme in terms of its intensity, training modalities and safety. Functional exercise capacity is best assessed using field tests such as the 6-min walk test. For this test, reference values exist, and benchmark improvements for programme quality (Lacasse et al., 2006), 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 the body composition. Both obesity, as a consequence of an inactive lifestyle, and cachexia, as observed in other chronic inflammatory disorders, are important to pick up on and treat in pulmonary rehabilitation programmes. Obese patients may experience less dyspnoea for a given oxygen consumption compared to nonobese

<table>
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<th>Table 2: Different maintenance strategies after outpatient (OP) or inpatient (IP) rehabilitation in randomised controlled trials</th>
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<td><strong>Initial programme</strong></td>
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| Moullec et al. (2008) | IP 4 weeks | 2 sessions per week of structured exercise (community gymnasium), group interaction, education sessions versus usual care | Within group: better preserved performance
Between groups: no significant differences |
| Berry et al. (2003) | OP 12 weeks | 15 months continuation of the OP programme | Longer programme more effective |
| Ries et al. (2003) | OP 8 weeks | Weekly telephone calls and monthly supervised reinforcement sessions | Overall, no major difference between programmes |
| Brooks et al. (2002) | IP or OP 6–8 weeks | Attend monthly 2-h group sessions and phone call between visits | Overall, no major difference between programmes |
| Steele et al. (2008) | OP 8 weeks | Weeks 1–4: establishing a home- and community-based exercise programme with emphasis on walking; weeks 5–12: implementing a regular programme of exercise; weekly phone calls and 1 home visit over 3 months | Limited effect for the duration of the intervention; no long-term benefits at 12 weeks |
| Du Moulin et al. (2009) | OP 3 weeks | Individualised training plan, based on their last 6MWT and monthly phone call | Enhanced 6MWD and health-related QoL until end of follow-up at 6 months |

Maintenance strategies were compared with a control group receiving usual care in all studies. 6MWT: 6-min walk test; 6MWD: 6-min walk distance; QoL: quality of life.
patients due to a favourable mechanical effect of obesity on the operating lung volumes. Nevertheless, obesity (defined as a BMI $\geq 30$ kg·m$^{-2}$) will limit the functional abilities of patients with limited ventilatory capacity, as it increases the ventilatory need during exercise against gravity. Cachexia, an involuntary loss of fat-free mass, leads inevitably to skeletal muscle weakness. It is a complex problem and its origin is not yet fully understood. Energy imbalance, disuse atrophy, hormonal imbalance, chronic hypoxia, accelerated ageing and systemic inflammation have been discussed as potential factors contributing to cachexia. 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 dual-energy X-ray absorptiometry (DEXA) or bioelectrical impedance measurements.

**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 activities of daily living using specific questionnaires.

**Physical activity** The participation of patients in daily activities is not easily assessed. The methodology to assess physical activity was reviewed by Pitta et al. (2005). Several questionnaires have been used but, increasingly, activity monitors find their way to the clinical arena and validation studies of several monitors are available (Haskell et al., 2007). In the future, it is likely that benchmark values for physical activity will become available for patients with COPD. As indicated earlier, patients not meeting current guidelines on healthy physical activity (30 min of moderately intense
exercise, 5 days per week) can be considered candidates for pulmonary rehabilitation where the focus lies on improving the physical activity lifestyle of the patient.

**Severe exacerbations** Patients with COPD who have been hospitalised with an acute exacerbation are particularly good candidates for enrolment in pulmonary rehabilitation programmes. Recent narrative (Burtin *et al.*, 2011) and systematic (Reid *et al.*, 2012) reviews exist on the topic. Patients suffering from exacerbations have acutely lost muscle force, functional exercise tolerance and health-related quality of life as the result of an exacerbation. Physical activity levels are also dramatically low during the hospital admission and at least up to 1 month afterwards. That observation prompted investigators to look at the effects of muscle activation during the hospitalisation phase by means of resistance training (Troosters *et al.*, 2010b) or neuromuscular electrical stimulation. In addition, it is well known that patients who had a hospital admission for COPD are very likely to face new hospital admissions in the year following the previous admission, imposing a high burden of healthcare cost. The risk of re-admission is particularly high in patients who remain inactive after a hospitalisation. In these patients, the rehabilitation programme may need significant modification. The emphasis should be on acquiring appropriate self-management skills to prevent subsequent admissions, and the exercise training programme may need to be adapted to more severe ventilatory and/or skeletal muscle limitation, using resistance training or interval training at high intensities. Patients who have experienced an exacerbation are generally excluded from clinical studies. A recent meta-analysis of a handful of studies, however, showed that patients who suffered from exacerbations are very good candidates for pulmonary rehabilitation (Puhan *et al.*, 2011). Clearly, these patients may impose a higher burden on the rehabilitation team and drop-out from the programme is a particularly important problem.

**Conclusion**

Pulmonary rehabilitation is an evidence-based intervention for patients with COPD. It is individually tailored to the needs of patients, both in terms of the programme structure and its components. The aim of the rehabilitation programme is to lead to an endurable 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 long-term benefits for patients with COPD. Further knowledge on the processes underlying an enduring 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.

**Further reading**


Background and definition

Originally, in end-stage diseases, the term ‘palliation’ was used synonymously with end-of-life support. Today, palliative care is extended to all patients at any stage of chronic disease and their relatives. Palliative care is defined as prevention and relief of symptoms, aiming for improved quality of life with respect to the needs of the patient and their family. It includes all methods to control symptoms like dyspnoea, pain, psychological and spiritual distress, as well as support in the process of dying and bereavement care (table 1).

Implementation

Palliative care is feasible for all progressive chronic diseases or life-threatening diseases where all curative therapies have been applied to maintain quality of life.

For patients who are able to make decisions, it is important to discuss their preferences together with their families at an appropriate time in their disease. Setting up goals of care and empowering the patient and their families to accept or exclude any form of therapy needs sensitive discussion of all symptoms that may cause suffering and disability. The palliative support should start in parallel with the curative approach.

The provision of competent caregivers is part of the implementation of palliative care.

The methods of palliative care include the following.

- Medication: opioids and other pain medication, and anxiolytic, antidepressant and sedative drugs
- Psychological counselling, spiritual support
- Dyspnoea management: NIV, oxygen therapy, endoscopic volume reduction
- Withdrawal or withholding of mechanical ventilation
- Bereavement care for the family

Pain relief

In chronic or progressive pain, morphine in combination with other pain relievers is effective in the control of pain. In some patients, the risk of sedation or depression of central ventilatory drive has to be discussed and agreed on. In far-advanced disease stages, sedation can be a treatment goal, as end-of-life support.

Dyspnoea management

Chronic severe dyspnoea is very frequent in COPD and other respiratory diseases. Medication, besides bronchodilators, does not directly address dyspnoea, but treats anxiety and depression. Pulmonary rehabilitation, endoscopic volume reduction and stenting are used in selected cases.

Key point

Palliative care is a multidisciplinary approach and needs teams of specialists with experience and training in palliative care.
cases. Oxygen therapy and NIV are not primarily used for dyspnoea reduction, but some patients feel relieved by the reduction of the work of breathing. It is feasible to have a trial period and select responders. Caregivers have to be trained well for home therapy.

Psychosocial support The burden of symptoms and the fear of dying lead to symptoms of depression and/or anxiety. Frequently used antidepressant drugs are serotonin re-uptake inhibitors and tricyclic antidepressants, whereas tranquilisers are often used as anxiolytic drugs. Effects have to be observed and discussed with the patient. In every case, psychological counselling and coaching must accompany any drug therapy. The aims of these are for the patient to cope with symptoms and accept the dying process at the end of life. Psychological support is also helpful in the creation of advance directives for end-of-life decisions. Spiritual coaching depends on the spiritual background of the patient, and may be helpful for the patient and the family.

Withdrawal or withholding of ventilatory support This is an important goal for life-threatening diseases and is often discussed in the intensive care unit. If an advance directive is available, life support may be withheld or withdrawn, as palliative care does not aim to prolong life. These measures are often difficult to accept for the family, who need enough time for bereavement, especially children.

Bereavement therapy It is important to have clear treatment goals from the beginning, and support the family and the patient in the process of dying before and after death if needed.

Further reading

Measuring the occurrence and causation of respiratory diseases

Riccardo Pistelli and Isabella Annesi-Maesano

When reduced to the simplest terms, all medical research may be defined as the study of relationships (differences or associations) between 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 given 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 below 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 FEV1 to identify subjects affected by different levels of severity of 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 between 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 readers of this book by

Key points

- Occurrence of a health outcome is estimated by prevalence (i.e. the proportion of subjects affected by the health outcome in the considered population) and/or incidence (i.e. the proportion of new cases of the health outcome in the considered population).
- The effect of exposure to a risk factor on the health outcome and the associated risk (i.e. the probability that the health outcome will occur following the exposure) is quantified through two measures: the ratio of the measures of disease frequency according to the presence or absence of the exposure to the factor, and the difference between these two measures.
- 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; causation must meet several criteria introduced by Austin Bradford Hill.
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 of disease in order to control health problems is of outstanding clinical relevance. One of the main goals of any epidemiological study is to measure, for instance, the occurrence or frequency of health outcomes, a disease (asthma, COPD, lung cancer, etc.) or the intake of a medication. Epidemiological studies allow also estimation of the occurrence of exposure (smoking, air pollution, 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 years old have a >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 a new health condition or outcome within a specified period of time, expressed as a proportion or rate. The risk, or incidence proportion (also known as the 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 formula

\[
\text{Risk} = \frac{a}{N} \quad (1)
\]

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 noncommunicable 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

<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, sex, 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>
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 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 formula

\[
\text{Incidence rate} = \frac{a}{t} \tag{2}
\]

in which \(a\) is the number of incident cases in the cohort, as in equation 1, and \(t\) is the total time interval experienced by the subjects followed. \(t\) is calculated by summing the time for which each subject has been at risk of developing the outcome. For events that may recur during the follow-up period, \(t\) 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 \(t\) 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 as a number in the range 0–1; however, the incidence rate may assume any value from 0 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 formula

\[
\text{Risk} = \text{incidence rate} \times t \tag{3}
\]

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** is the proportion of subjects affected by a disease (or symptom or dysfunction) or, more generally, presenting a 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 formula
\[
P = \frac{I \times D}{1 - P}
\]

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

\[
P = ID
\]

In this case, the prevalence proportion may be considered to approximate to 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 open. 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 disease.

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 design, according to the research question. Epidemiological study design is divided into:

- experimental studies, which include clinical or prevention trials (field trials and community trials)
- observational studies, which include 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, 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 ISAAC (International Study of Asthma and Allergies in Childhood). 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 relationship 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 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. Ecological studies also exist, in which the unit of analysis is a population rather than an individual. For instance, an ecological 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 ecological studies to be able to determine a link between health data and a source of environmental exposure. These ecological studies allow the development of hypotheses that provide limited information.

<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 in 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>
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, and 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 × 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 dichotomous variables is shown in figure 1 where, for instance, the highest number (a) is observed for individuals who were exposed to the factor and presented the health outcome, and the lowest (b) for individuals who were exposed to the factor but did not present the health outcome. In addition, the number of unexposed individuals who did not present the health outcome (d) is more elevated than the number of unexposed individuals presenting the health outcome (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 3. Contingency table presenting the association data from the case of exposure and disease that are dichotomous variables

<table>
<thead>
<tr>
<th></th>
<th>Health outcome</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Exposure</strong></td>
<td></td>
<td></td>
</tr>
<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**: number of individuals in the studied sample exposed to the potential risk factor who have experienced the health outcome;
- **b**: number of individuals exposed who have not experienced the health outcome;
- **c**: number of individuals unexposed who have experienced the health outcome;
- **d**: number of individuals unexposed who have not experienced the outcome;
- **N**: total number of individuals included in the study.

### Figure 1. Distribution of the individuals according to the presence or the absence of a health outcome and exposure to a factor.

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

\[
RR = \frac{\frac{a}{a+b}}{\frac{c}{c+d}}
\]

(6)

A relative risk of 1 means there is no difference in risk between the two groups, a relative risk >1 means the health event is more likely to occur in the exposed group than in the unexposed group and a relative risk <1 means that the health event is less likely to occur in the unexposed group than in the exposed group. To be statistically significantly >1, the RR has to belong to a confidence interval >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 significantly <1, the RR has to belong to a confidence interval <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 and is generally estimated as the ratio between the odds in exposed and nonexposed individuals:

\[
OR = \frac{\left(\frac{a}{a+b}\right)}{\left(\frac{c}{c+d}\right)} = \frac{ad}{bc}
\]

(7)

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%
An odds ratio 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 is a mathematical relationship between the odds ratio and the relative risk:

$$\text{RR} = \frac{1 - \frac{a}{a+b} \times \text{OR}}{1 - \frac{c}{c+d}}$$ (8)

As a consequence, when a disease is rare, $a$ and $c$ are small, and the odds ratio provides a valid estimate of the relative risk.

**Table 5. Parameters estimating differences between risks**

<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</td>
<td>$\text{AR} = \frac{a}{a+b} - \frac{c}{c+d}$</td>
</tr>
<tr>
<td></td>
<td>It is given by the difference in cumulative incidences or incidence densities of the disease in the exposed ($I_E$) and the unexposed individuals ($I_0$)</td>
<td>$\text{AR} = (I_E - I_0)$</td>
</tr>
<tr>
<td>Preventive fraction (PF)</td>
<td>The attributable risk in the case that the exposure is preventive, so that $a/(a+b) &gt; c/(c+d)$</td>
<td>$\text{PF} = \frac{c}{c+d} - \frac{a}{a+b}$</td>
</tr>
<tr>
<td>Attributable risk percentage or etiological fraction (AR%)</td>
<td>The attributable risk divided by the rate of disease among the exposed</td>
<td>$\text{AR%} = \left(\frac{\text{AR}}{\text{RR}}\right) \times 100$</td>
</tr>
<tr>
<td>Population attributable risk (PAR)</td>
<td>The incidence of a disease in a population that is attributable to the exposure</td>
<td>$\text{PAR} = \frac{a+c}{a+b+c+d} - \frac{c}{a+c}$</td>
</tr>
<tr>
<td></td>
<td>Given by the difference between the rate of the disease in the entire population ($I_{TOT}$) and $I_0$</td>
<td>$\text{PAR} = (I_{TOT} - I_0)$</td>
</tr>
<tr>
<td></td>
<td>or by multiplying the product of the attributable risk by the proportion of exposed individuals in the population ($P_E$)</td>
<td>$\text{PAR} = \text{AR} \times P_E$</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>Combined $\text{PAR}^* = 1 - (1 - \text{PAR}_1)(1 - \text{PAR}_2)...$</td>
</tr>
</tbody>
</table>

$a$: number of individuals in the studied sample exposed to the potential risk factor who have experienced the health outcome; $b$: number of individuals exposed who have not experienced the health outcome; $c$: number of individuals unexposed who have experienced the health outcome; $d$: number of individuals unexposed who have not experienced the outcome; $^*$: when there is no multiplicative interaction (no departure from multiplicative scale), combined PAR can be manually calculated by this formula.
Several types of difference exist between the measures of health outcome frequency according to the presence or the absence of 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). Notably, 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, and 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’. 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 bias:

- recall bias
- selection bias
- information bias
- 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 have no 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, until 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, which 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 matching individuals according to it.
Bias has a net direction and magnitude so averaging over a large number of observations does not eliminate its effect. In fact, bias can be large enough to invalidate any conclusion. Increasing the sample size will not eliminate all bias. 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, bacille Calmette–Guérin (BCG) immunisation is an effect modifier for the consequences of exposure to Mycobacterium tuberculosis 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 this example, the modification effect of BCG immunisation could be estimated by computing the odds ratio between tobacco smoking and TB according to the presence or absence of BCG immunisation. The effect of a modifier can be taken into account through matching individuals according to different levels of the modifier (stratification).

### Table 6. Criteria for assessing evidence of causation

<table>
<thead>
<tr>
<th></th>
<th>Strength</th>
<th>Consistency</th>
<th>Specificity</th>
<th>Temporality</th>
<th>Biological gradient</th>
<th>Plausibility</th>
<th>Coherence</th>
<th>Experiment</th>
<th>Analogy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The larger the association, the more likely that it is causal</td>
<td>Consistent findings observed by different persons in different places with different samples strengthen the likelihood of an effect</td>
<td>The more specific an association between a factor and an effect, the greater the probability of a causal relationship</td>
<td>The effect has to occur after the cause</td>
<td>Greater exposure should generally lead to greater incidence of the outcome</td>
<td>A plausible mechanism between cause and effect is helpful although, very often, knowledge of the mechanism is limited</td>
<td>Coherence between epidemiological and laboratory findings increases the likelihood of an effect of the exposure on the health outcome</td>
<td>‘Occasionally it is possible to appeal to experimental...evidence.’</td>
<td>The effect of similar factors may be considered</td>
</tr>
<tr>
<td>2</td>
<td>However, a small association does not mean that there is not a causal effect</td>
<td></td>
<td>Causation is likely in case of a very specific population at a specific site and disease with no other likely explanation.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</table>

Information from Hill (1965).
Sensitivity and specificity

Sensitivity is the probability that the criterion used to define the case will produce a true positive result when used in a population (compared to a reference or ‘gold standard’). Specificity is the probability that the criterion will produce a true negative result when used (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

\[
\text{Sensitivity} = \frac{TP}{TP + FN} \quad (9)
\]

\[
\text{Specificity} = \frac{TN}{TN + FP} \quad (10)
\]

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. An example of an application for sensitivity and specificity calculation is in the validation of biomarkers.

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 sample; 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.

Further reading


Suggested free software


Appendix 1: 95% confidence intervals for the relative risk and the odds ratio

Given the $2 \times 2$ contingency table relating exposure to health outcome, a common way to calculate the 95% confidence interval is as follows.

In the case of the relative risk (approximate estimate):

Upper limit = $e^{\ln RR + 1.96 \times \sqrt{\ln RR}}$ \quad (11)

Lower limit = $e^{\ln RR - 1.96 \times \sqrt{\ln RR}}$ \quad (12)

where $\sqrt{\ln RR}$ represents the square root of the natural log of the risk ratio, defined as

\[
\ln RR = \ln \left( \frac{a}{a+b} \right) \quad (13)
\]

which is asymptotically normal with variance

\[
\ln RR = \frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} - \frac{1}{c+d} \quad (14)
\]

When there are zeros, a common convention is to add $1/2$ to each cell.

In the case of the odds ratio:
Upper limit
\[ \text{InOR} = \text{InOR} + 1.96 \times \text{SE(lnOR)} \]  (15)

Lower limit
\[ \text{InOR} = \text{InOR} - 1.96 \times \text{SE(lnOR)} \]  (16)

which become
**Upper limit OR** = \( e^{\text{upper limit InOR}} \)  (17)
**Lower limit OR** = \( e^{\text{lower limit InOR}} \)  (18)

where \( \text{SE(lnOR)} \) is the standard error of the natural log of the odds ratio, which is the variance of lnOR, calculated as \( \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d} \).

**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 exposure in the case where 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><strong>Correlation</strong></td>
<td>A single number that describes the degree of relationship between two continuous variables</td>
</tr>
<tr>
<td><strong>Linear regression</strong></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><strong>ANOVA</strong></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><strong>Logistic regression model</strong></td>
<td>Approach to predicting 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>
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The European Respiratory Society (ERS) Handbook of Respiratory Medicine, now in its second edition, is a concise, compact and easy-to-read guide to each of the key areas in respiratory medicine. Its 18 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.

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