

# Immunisation against respiratory diseases

## Introduction



### Key points

- Although pertussis vaccination coverage is high across Europe, vaccination rates for influenza, pneumococcal disease and tuberculosis vary wildly.
- Vaccinating groups other than the most vulnerable can have a protective 'herd effect' on society as a whole by reducing disease transmission within the population.
- New vaccines against *Streptococcus pneumoniae* offer the possibility of striking reductions in invasive disease.
- The only available vaccine against tuberculosis dates to the early 20th century. Although it is generally safe, its efficacy is limited and it does not provide complete protection.

Population protection by vaccination against infections has been one of the major achievements of public health and is of considerable importance in controlling respiratory disease. This chapter will discuss vaccines for the prevention of seasonal and pandemic influenza, pertussis, pneumococcal infection and tuberculosis (TB).

## Influenza

After the second world war, vaccination became the main strategy for preventing and controlling seasonal and pandemic influenza worldwide. European Respiratory Society (ERS) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines define influenza as an acute illness, usually with fever, with one or more of the following: headache, myalgia (muscle pain), cough or sore throat. Influenza is caused by influenza viruses. While most illnesses are brief and without consequence, regular seasonal epidemics of influenza include significant rates of severe illness and death, particularly among elderly people and those with underlying chronic medical conditions. Type A virus causes the most severe disease and is associated with epidemics and pandemics. Spontaneous mutations in the viral surface proteins, haemagglutinin and neuraminidase, are responsible for so-called 'antigenic drift'. If this results in changes in the viral

“

*Influenza vaccine should be given yearly to people at increased risk of complications due to influenza*

”

amino acid structure, pre-existing antibodies might be unable to bind to viral particles to a sufficient extent to prevent disease. This phenomenon is responsible for the annual influenza waves observed worldwide.

Avian influenza infections are much more severe than the common seasonal influenza, and are associated with severe illness and a mortality rate exceeding 50%. Occasionally, a new strain develops to which many humans have little or no immunity and a worldwide pandemic occurs, as was seen in 2009. This pandemic, caused by the influenza A (H1N1) virus, spread in two waves, a modest spring/summer wave and a more sustained wave in the autumn and early winter with moderate intensity. Almost all influenza cases in 2009 were caused by the pandemic virus. Surveillance of hospitalised acute respiratory cases was implemented in various forms by 10 European Union (EU) countries during the pandemic, with 9469 laboratory-confirmed cases reported and 569 deaths. Severe disease was more frequent, and the death rate was higher in individuals under 65 years of age and in those with underlying disease, even though in 25% of the severe cases there were no underlying conditions.

Seasonal influenza vaccine has proved effective in preventing laboratory-confirmed influenza among healthy adults (16–65 years of age) and children (6 years of age or older). The evidence of vaccine effectiveness is much more limited in relation to the prevention of complications such as pneumonia, hospitalisation and influenza-specific and overall mortality. However, vaccinating children might have a protective effect for nonrecipients of the vaccine of all ages living in the same community as it prevents transmission. Scientific evidence suggests there would be advantages to vaccinating older people and those with chronic disease.

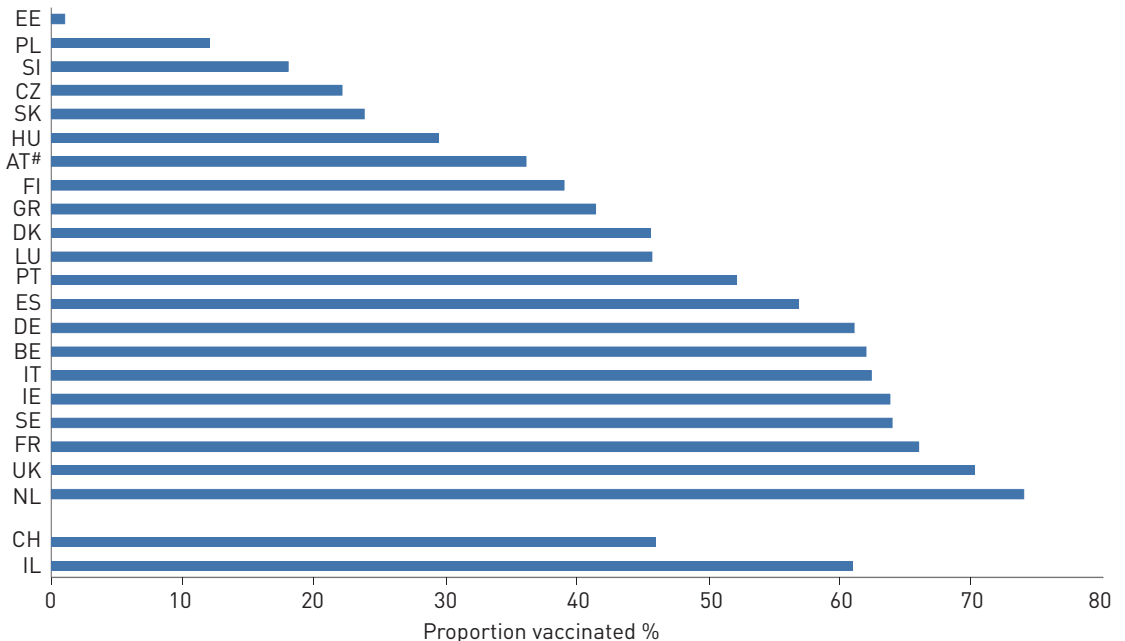
The ERS/ESCMID guidelines recommend that influenza vaccine should be given yearly to people at increased risk of complications due to influenza. Vaccination should be given to immunocompetent adults belonging to one or more of the following categories: over 65 years of age; resident in an institution (such as a nursing home); chronic cardiac disease; chronic lung disease; diabetes mellitus; chronic renal disease; haemoglobinopathies; and women who will be in the second or third trimester of pregnancy during the influenza season. In addition, the guidelines suggest yearly vaccination for healthcare personnel, especially in settings where elderly people or other high-risk groups are treated. Figure 1 shows the influenza

vaccination rates in Europe in people over 65 years of age in the 2008–2009 influenza seasons.

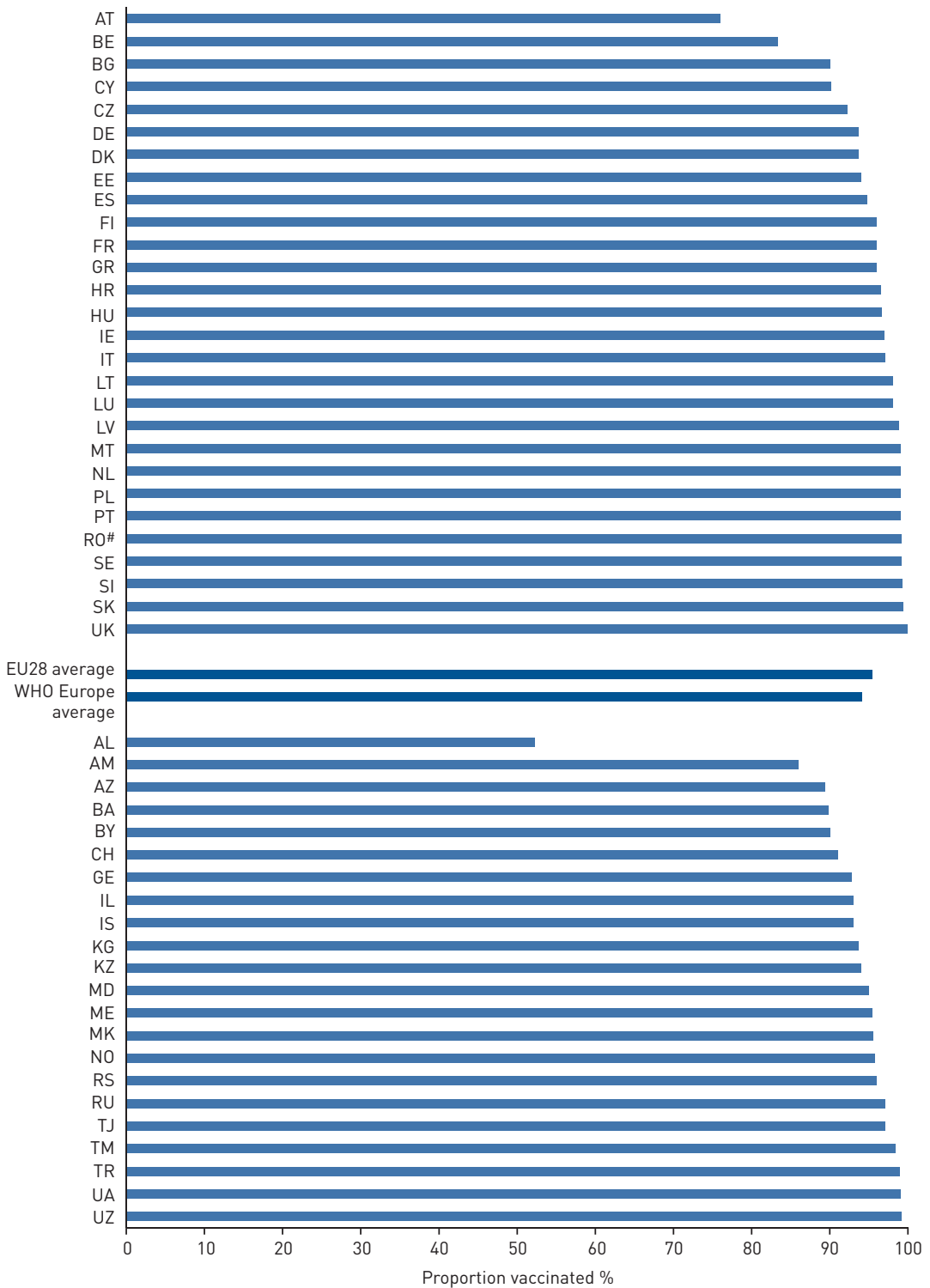
## Pertussis

*Bordetella pertussis* infection, known as pertussis or whooping cough, is one of the leading causes of vaccine-preventable deaths. Worldwide, an estimated 50 million cases of pertussis and 300 000 deaths occur every year, mainly in unvaccinated children younger than 12 months of age. *B. pertussis* infection in adults and adolescents usually causes mild or atypical symptoms. Pertussis should be considered in the differential diagnosis of illnesses with cough lasting more than 1–2 weeks. Pertussis may also cause infection in adults with comorbid conditions such as chronic obstructive pulmonary disease (COPD), and it is one of the less common causes of exacerbations of COPD. Pertussis shows a slight seasonality, with a usually modest increase in cases in the summer and autumn. The percentage of infants reaching their first birthday fully vaccinated against pertussis is shown in figure 2. Vaccination coverage is high throughout the EU28 countries.

Pertussis vaccination schedules vary between European countries, as do the indications for booster vaccination in



**Figure 1** – Influenza vaccinations: proportion of people aged ≥65 years vaccinated, 2008–2011. Data not available for other countries. #: Austrian data are for 2006. Data from the Organisation for Economic Cooperation and Development.



**Figure 2 – Pertussis vaccination: proportion of infants fully vaccinated by 1 year of age.** Data are for the latest available year (2005–2010). #: Romanian data are for 2004. Data from the World Health Organization European Health for All Database.

adolescents and adults. These differences in approach are, at least in part, related to the varying incidence of pertussis in adolescents and adults in Europe. Data from EUVAC-NET show an increase in the number of reported cases in the EU and in European Economic Area (EEA)/European Free Trade Association (EFTA) countries between 2006 and 2009, from 3.75 to 4.89 per 100 000; the most affected group was 5–14-year-olds with a confirmed case rate slightly above 17 per 100 000.

The main problem in epidemiological analysis of the disease is the heterogeneity of pertussis surveillance, particularly in terms of the surveillance systems, coverage, laboratory methods used and case definition applied.

### *Streptococcus pneumoniae*

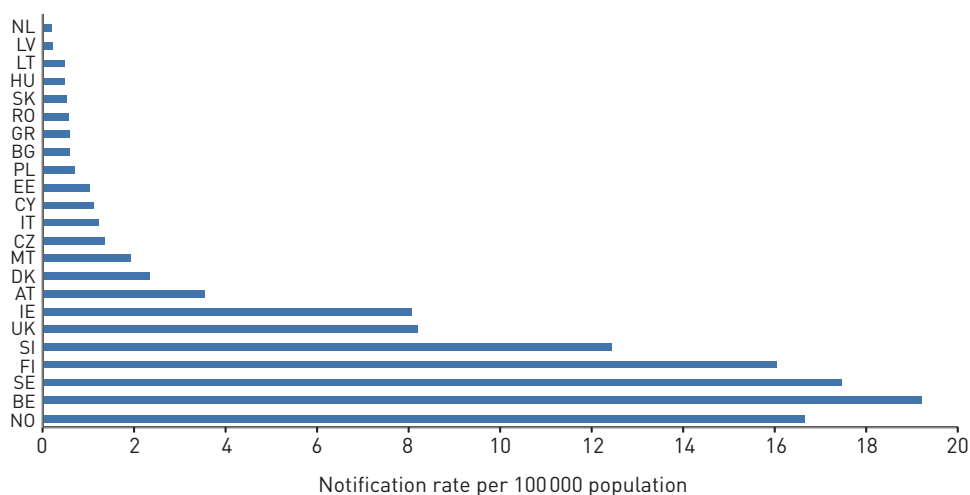
Despite good access to antibiotics, *Streptococcus pneumoniae* is still a significant cause of illness and death worldwide. *S. pneumoniae* causes several acute, invasive and noninvasive clinical infections; it is one of the leading causative agents in COPD exacerbations; and it is the most frequently detected pathogen responsible for community-acquired pneumonia (CAP). Pneumococcal pneumonia is accompanied by bacteraemia (bacteria in the blood) in 10–30% of cases.

*S. pneumoniae* is gaining resistance to the *in vitro* activity of several antimicrobial agents and, even if questions remain regarding the clinical impact of this phenomenon, increasing numbers of reports indicate that antibiotic resistance can lead to more treatment failures, if not higher mortality.

Reported incidence rates of invasive pneumococcal disease in European and US studies indicate an overall incidence of 11–23.2 per 100 000 people, rising to 16.2–59.7 per 100 000 in adults over 65 years of age. The studies in question were conducted between 1995 and 2003, before widespread use of pneumococcal conjugate vaccine in children, which has been associated with a 'herd immunity' effect, reducing the incidence of invasive pneumococcal disease in unvaccinated adults.

Figures reported by the European Centre for Disease Prevention and Control (ECDC) in EEA countries indicate a slight decrease in the rate of confirmed and notified cases of invasive pneumococcal disease between 2006 to 2009, from 5.92 per 100 000 to 4.32 per 100 000 (figure

“  
*Pertussis  
vaccination  
coverage  
is high  
throughout  
the EU*  
”



**Figure 3** – Rates of invasive pneumococcal disease, 2009. No data were reported for some countries. Data from the European Centre for Disease Control and Prevention and Control Annual Epidemiological Report 2011.

3). It should be noted, however, that there is a wide heterogeneity of the type of surveillance systems in place in different countries, as well as in their coverage and the case definition used, while in some countries there are no surveillance systems at all.

The development of effective pneumococcal vaccines was hampered by the poor immunogenicity of bacterial cell-surface polysaccharides. In the early 1980s, a vaccine containing purified capsular polysaccharides from 23 of the known pneumococcal serotypes (PPV-23) was marketed in the USA, and later in Europe. These 23 serotypes are involved in about 85–90% of invasive pneumococcal disease cases among adults. This polysaccharide vaccine stimulates short-lived B-cell immune responses by causing B-cells to differentiate into plasma cells, producing antibodies without producing memory B-cells. The immunological antibody response is age- and serotype-dependent, and is generally lower in elderly people than in younger adults. There is no memory response to a booster vaccination.

ERS/ESCMID guidelines indicate that the PPV-23 polysaccharide pneumococcal vaccine prevents invasive pneumococcal disease in older people and in other high-risk groups, and should be given to all adults at risk of pneumococcal disease including those over 65 years of age, those resident in institutions and those with dementia, seizure disorders, congestive heart failure, cerebrovascular disease, COPD, history of previous pneumonia, chronic liver disease, diabetes mellitus, functional or anatomical absence of the spleen or chronic cerebrospinal fluid leakage.

To enhance the immunogenicity of pneumococcal vaccines, conjugate vaccines have been developed. Polysaccharide antigens are chemically joined to a highly immunogenic protein carrier (such as tetanus or diphtheria toxoid). This process leads to the



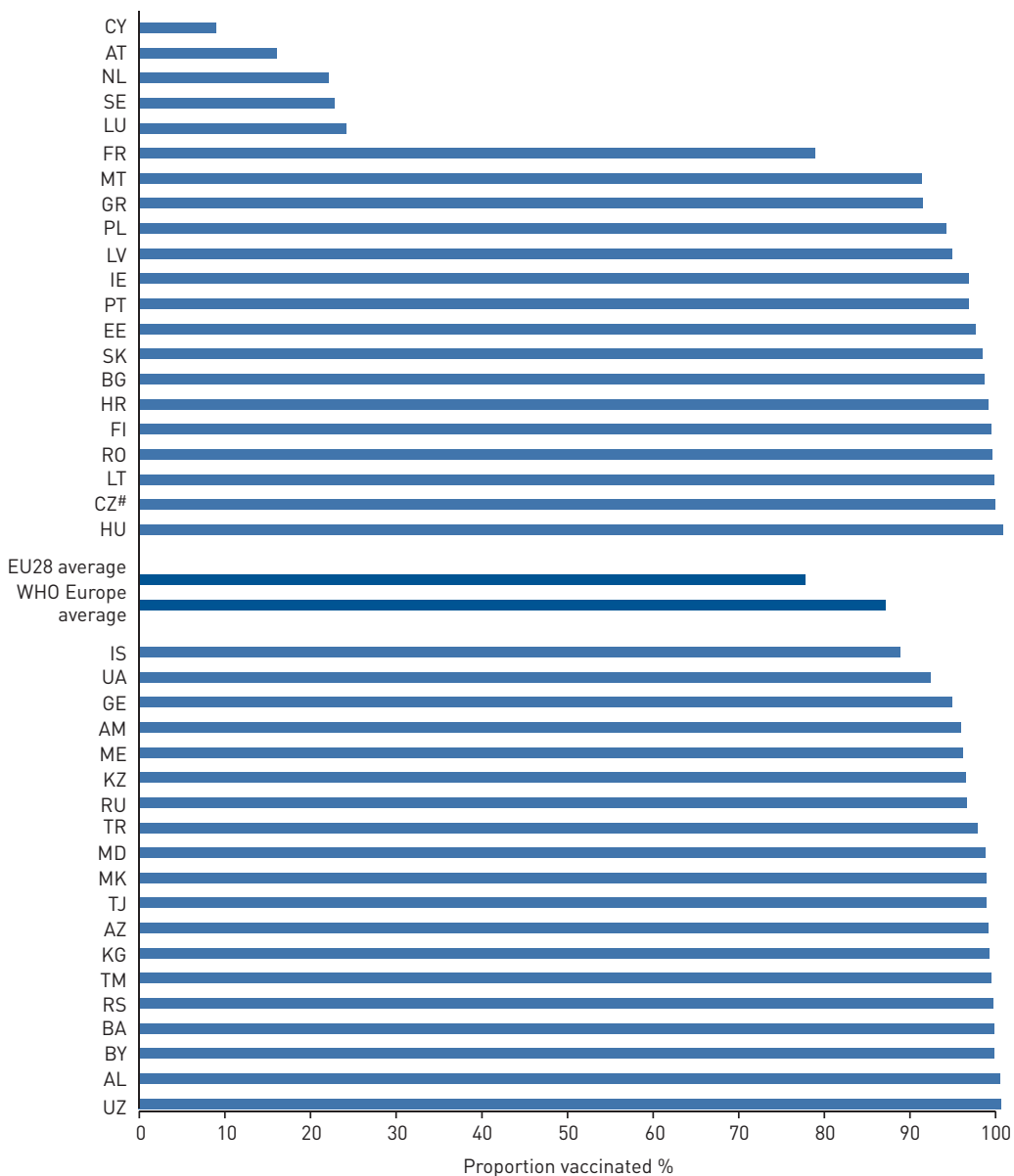
induction of both a B- and a T-cell-dependent response and a memory response to a booster dose of the vaccine.

In 2000, a pneumococcal conjugate vaccine containing capsular polysaccharides from seven pneumococcal serotypes (PCV-7), designed for children under 2 years of age, was approved in the USA. As a result of implementation of this vaccine, there was a striking decrease in invasive pneumococcal disease caused by the vaccine serotypes. Since children are the main reservoir of *S. pneumoniae* (about 60% of children are carriers), a reduction in the carrier rate in this population had beneficial effects on pneumococcal circulation, with a protective herd effect in adults. An additional observed benefit following the introduction of PCV-7 was a reduction in the rates of antimicrobial-resistant *S. pneumoniae* invasive pneumococcal disease. New conjugate vaccines are now being evaluated for children and adults: a 10-valent (PCV-10) version, which has been licensed in over 30 countries, and a 13-valent (PCV-13) vaccine. The increased serotype coverage of these vaccines, particularly PCV-13, may expand the clinical benefits of conjugate vaccines in adult populations at risk of pneumococcal disease. Vaccination strategies based on the use of more effective vaccines, in particular the PCV-13 vaccine, are expected to have a substantial public health impact on infectious disease and health service costs, reducing the burden of pneumococcal infection. However, there are concerns that, after introduction of the PCV-7 conjugate vaccine, serotypes covered by the vaccine could be replaced by serotypes not covered by it. Consequently, the introduction of the new conjugate vaccines in 2010 (PCV-10 and PCV-13) requires close monitoring.

## Tuberculosis

Vaccination against TB is also addressed in chapter 17.

In practice, the only available vaccine is the bacille Calmette-Guérin (BCG), which dates back to the early 20th century. Millions of doses of BCG have been used worldwide with a reported good safety profile and efficacy in preventing invasive TB in children. However, the protection induced against pulmonary TB, both in children and adults, is incomplete and the results of epidemiological studies on the duration of protection are inconsistent. In immunocompromised (HIV-infected) subjects, BCG vaccination seems to be associated with a higher risk of complications and even dissemination of BCG infection.



**Figure 4 –** Bacille Calmette-Guérin vaccination rates, by 1 year of age. Data are for the latest available year (2007–2010). #: Czech Republic data are for 2006. No data were reported for some countries. Data from the World Health Organization European Health for All Database.



“  
*BCG has a good safety profile and efficacy in preventing invasive TB in children*  
”

The rate of BCG vaccination in children in the EU is variable. Policies range from no use of BCG at all to vaccination of all children at birth, in infancy, at school entry and in later school years. Rates of infant vaccination in different EU and non-EU countries are presented in figure 4.

The World Health Organization (WHO) in Europe recommends that BCG vaccination should not be administered to HIV-positive children in areas with low TB incidence; in areas with high TB incidence, BCG vaccination should be restricted to HIV-positive children who do not have symptoms. WHO does not recommend BCG vaccination for adolescents and adults, including those with HIV infection, due to little or no evidence of protection from pulmonary TB.

New vaccines have been developed, including both therapeutic vaccines for immune therapy as an adjunct to chemotherapy, and potential preventive vaccines. Clinical trials are ongoing to test their efficacy.

### *Developments and research needs*

- There is a need for collection of better epidemiological data and surveillance across Europe.
- Active intervention should be used to enhance influenza and pneumococcal vaccination.
- There is a need for a better vaccine against TB.
- A uniform European policy for vaccination against TB in children, adolescents, adults, healthcare workers and immigrants is needed.

### *Further reading*



- Annual Epidemiological Report 2011. Reporting on 2009 surveillance data and 2010 epidemic intelligence data. Stockholm, European Centre for Disease Prevention and Control, 2011.
- Immunization of people living with HIV and people at risk of HIV infection: clinical protocol for the WHO European region. *In*: HIV/AIDS Treatment and Care: Clinical Protocols for the WHO European Region. Copenhagen, World Health Organization, 2007; pp. 438–464. [www.euro.who.int/\\_\\_data/assets/pdf\\_file/0004/78502/E90840\\_Chapter\\_12.pdf](http://www.euro.who.int/__data/assets/pdf_file/0004/78502/E90840_Chapter_12.pdf)
- International Union Against Tuberculosis and Lung Disease. Criteria for discontinuation of

vaccination programmes using bacille Calmette-Guérin (BCG) in countries with a low prevalence of tuberculosis. A statement of the International Union Against Tuberculosis and Lung Disease. *Tuber Lung Dis* 1994; 75: 179–180.

- Kaufmann SHE. Fact and fiction in tuberculosis vaccine research: 10 years later. *Lancet Infect Dis* 2011; 11: 633–640.
- Whitney CG, Farley MM, Hadler J, *et al*. Decline in invasive pneumococcal disease after the introduction of protein–polysaccharide conjugate vaccine. *N Engl J Med* 2003; 348: 1737–1746.
- Woodhead M, Blasi F, Ewig S, *et al*. Guidelines for the management of adult lower respiratory tract infections – full version. *Clin Microbiol Infect* 2011; 17: Suppl. 6, E1–E59.
- Zepp F, Heining U, Mertsola J, *et al*. Rationale for pertussis booster vaccination throughout life in Europe. *Lancet Infect Dis* 2011; 11: 557–570.

# Principles of respiratory investigation

## Introduction



### Key points

- A detailed clinical history should always be the first step in making a diagnosis.
- Physical examination provides crucial clues to guide more advanced diagnostic procedures.
- Microbiological, histological and cytological laboratory tests can diagnose or rule out a large number of diseases.
- Respiratory function testing enables assessment of severity and monitoring of treatment, as well as giving diagnostic information.
- A range of radiographic and other imaging techniques permit physicians to visualise problems within the chest, and can be used to guide more invasive investigations.

Respiratory diseases are of multiple origin, as detailed in the previous chapters of this book. Diagnosis and follow-up often requires various investigative procedures, which should be applied in an appropriate and cost-effective step-by-step evaluation.

### History

Taking a careful clinical history is always the first diagnostic step and is an essential approach to the patient. Specific respiratory symptoms include dyspnoea, abnormal breath sounds (such as wheezing or stridor), hoarseness, cough with or without sputum production, haemoptysis, snoring and chest pain. Each may be of different onset (acute or chronic) or severity, isolated or combined, and sometimes accompanied by general symptoms of disease such as fever, weight loss, oedema, night sweats, nocturia or daytime somnolence.

For some disease areas, additional specific questionnaires can be helpful; for example, in allergic or occupational diseases or suspected sleep apnoea.

Often, the clinical history provides – or at least suggests – the diagnosis prior to investigation.

“

*Taking a careful clinical history is always the first diagnostic step and is an essential approach to the patient*

”

## **Physical examination**

Physical examination classically follows a sequence: inspection, palpation (feeling with the hands), percussion and auscultation (listening with a stethoscope). Inspection may show important physical signs such as cyanosis, abnormal breathing patterns, finger clubbing, chest wall deformities, oedema, superior vena cava syndrome or Horner's syndrome. Palpation may detect, for instance, enlarged lymph nodes, subcutaneous emphysema or points of tenderness. Percussion may reveal areas of dullness (e.g. pleural effusion) or hyperresonance (e.g. pneumothorax) and auscultation may detect abnormal breath sounds, such as wheezes, crackles, or a pleural friction rub, signs that are characteristic of particular respiratory diseases.

The clinical history and physical examination provide the essential clues towards the possible underlying respiratory disease, guiding selection of the appropriate diagnostic investigations: laboratory tests, respiratory function tests, imaging techniques and/or biopsy procedures.

## **Laboratory methods**

Besides routine laboratory blood and urine tests, several specific blood and other tests for respiratory diseases are available (table 1). Investigations of sputum include bacteriological examination, cell differentiation, including eosinophils, and measurement of various inflammatory mediators. Exhaled gases or exhaled breath condensates, such as carbon monoxide and exhaled nitric oxide fraction, are used as markers of inflammatory and other diseases.

## **Microbiological tests**

Microbiological tests have an essential role in the investigation of infectious respiratory diseases caused by viruses, bacteria, fungi or parasites. They include examination of expectorated (or induced) sputum and of specimens acquired by invasive biopsy techniques

(discussed further later). The standard bacteriological techniques of microscopy and culture are often supplemented by molecular biological techniques (PCR) for detecting the DNA (or RNA) of the organism. Testing the susceptibility to antimicrobial agents is clinically very important.

Serological tests for confirming particular infections include identification of the relevant bacteriological or virological antigens and measurement of specific antibodies, in particular the demonstration of a rise in antibody titre. Urinary antigen detection may permit the rapid diagnosis of pneumococcal and Legionella infections.

Respiratory viruses may be cultured from different materials, most easily from nose or throat swabs. Serological tests in general provide only a retrospective assessment; specific immunoglobulin M may be of greater diagnostic value.

The laboratory diagnosis of pulmonary fungal infections is usually based on isolation of the organism from cultures, histological examination and serological tests, but also on direct microscopy after special staining (e.g. *Pneumocystis jirovecii*).

Parasitic lung infections may be detected by microscopy of certain materials (e.g. stool, blood), serological tests or histological tests.

Disease	Test
Pulmonary embolism	D-dimer
Inherited emphysema	$\alpha_1$ -antitrypsin
Cystic fibrosis	Specific genetic tests
Lung cancer	Tumour marker (e.g. CEA, CYFRA 21-1, NSE, SCC)
Malignant mesothelioma	Tumour marker (mesothelin, osteopontin, fibulin)
Pneumonia	Procalcitonin
(Latent) tuberculosis infection	Tuberculin skin test, interferon-gamma release assays
Unexplained breathlessness	NT-proBNP (increased in heart failure)
Sarcoidosis	Angiotensin-converting enzyme (ACE)
Extrinsic allergic alveolitis (hypersensitivity pneumonitis)	Specific precipitating antibodies
Asthma	Total and specific immunoglobulin E, skin testing with allergens
Eosinophilic diseases	Eosinophils
Connective tissue disorders	Immunological tests such as rheumatoid factor
Pleural effusion	Total protein, LDH, glucose, cholesterol and others in pleural fluid

**Table 1** – Specific laboratory tests for some respiratory diseases. NT-proBNP: N-terminal pro-brain natriuretic peptide; LDH: lactate dehydrogenase.

## *Histological and cytological examination*

Histology and cytology play a central role in the diagnosis of many malignant and benign respiratory diseases, including infections. Apart from expectorated sputum, which can be examined cytologically, the specimens are acquired using various biopsy techniques (discussed further later) and are sent for histological and/or cytological evaluation.

Conventional histopathological techniques are often supplemented by immunohistochemistry using specific markers for the differentiation of several neoplasms, such as small cell neuroendocrine carcinoma and malignant lymphoma. In addition, results from molecular diagnostic tests may have important therapeutic ('targeted' treatment) as well as prognostic implications in certain types of nonsmall cell lung cancers (e.g. if mutations of the epidermal growth factor receptor (EGFR) are present).

Cytopathological examination is used mainly in the diagnosis of malignancies (e.g. malignant effusion). In bronchoalveolar lavage fluid, it may be helpful in the diagnosis of some interstitial lung diseases, such as extrinsic allergic alveolitis (hypersensitivity pneumonitis), eosinophilic pneumonia, alveolar proteinosis or asbestosis.

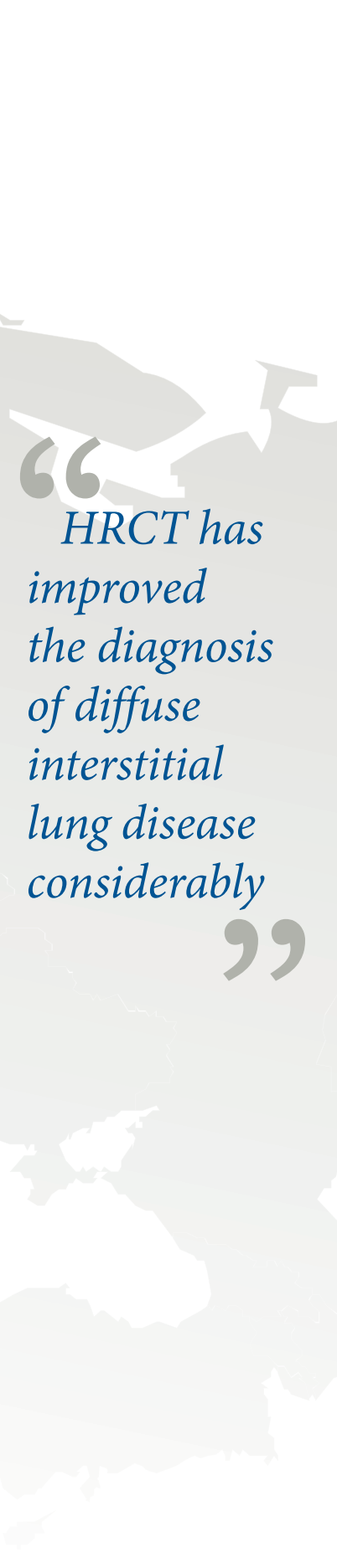
Ultimately, autopsy examination of the lung may provide important information regarding the underlying disease, but it is rarely performed nowadays.

## *Respiratory function tests*

The main clinical roles of respiratory function tests include diagnosis, assessment of severity, monitoring treatment and evaluation of prognosis.



**Figure 1** – a) Patient performing spirometry. b) Interpretation of spirometric curves. Reproduced from GARBE, 2010.



“HRCT has improved the diagnosis of diffuse interstitial lung disease considerably”

## ***Spirometry***

Spirometry (figure 1) is the most important function test – it measures vital capacity (VC) and forced expiratory volume in 1 second (FEV<sub>1</sub>). This permits differentiation between restrictive and obstructive respiratory diseases. If expired volume is measured by electrical integration of airflow (using a pneumotachograph), maximum flow–volume curves can also be registered. These tests are used to measure the effect of bronchodilating drugs on reversibility of obstruction as well as to determine responsiveness to bronchial provocation tests. Simple instruments for patient home use include peak flow meters, which measure the degree of obstruction.

## ***Lung capacity and airway resistance***

The total lung capacity can be determined using either gas dilution techniques or body plethysmography. The latter method also allows the measurement of airway resistance. The forced oscillation technique, which measures the resistance of the total respiratory system, has the advantage that the patient does not need to perform specific breathing manoeuvres.

## ***Diffusing capacity***

The diffusing capacity of the lung for carbon monoxide (also known as transfer factor), which is usually performed as a single-breath test, measures the overall gas-exchange function of the lung.

## ***Blood gas analysis***

Arterial blood gas (ABG) measurement to determine the arterial oxygen tension ( $P_{aO_2}$ ) and arterial carbon dioxide tension ( $P_{aCO_2}$ ) is one of the most useful diagnostic tests: blood can be sampled directly from an artery, or an estimate can be obtained from capillary blood from, for instance, a warmed earlobe. ABG measurement allows the diagnosis of hypoxaemia (decreased  $P_{aO_2}$ ) with or without hypercapnia (increased  $P_{aCO_2}$ ), a sensitive index of inefficient pulmonary gas exchange, which is also used for defining respiratory failure.  $P_{aO_2}$  measurement after breathing 100% oxygen is sometimes used to estimate the anatomical right-to-left shunt. Arterial oxygen saturation ( $S_{aO_2}$ ) represents the percentage of binding sites on the haemoglobin molecule occupied by oxygen and offers a noninvasive method of estimating arterial blood oxygenation; it is measured directly by an oximeter with a probe attached to either the finger or the earlobe.  $P_{aCO_2}$  can also be estimated noninvasively, using a transcutaneous electrode but such devices are not yet as widely used as oximeters. ABG measurement also allows evaluation of acid–base disorders.

## ***Cardiopulmonary exercise testing***

Cardiopulmonary exercise testing (CPET), with determination of minute ventilation, cardiac and respiratory frequency, oxygen uptake and carbon dioxide output, is an objective measure of exercise capacity (spiroergometry). Simpler tests use capillary oxygen partial pressure measurements during exercise on an ergometer or symptom-limited walking tests, such as the 6-min shuttle walk test, with measurement of SaO<sub>2</sub> using an oximeter.

## ***Respiratory muscle function measurement***

Respiratory muscle function is commonly assessed by measuring maximal pressures generated at the mouth during maximal inspiratory and expiratory efforts against an occluded airway.

## ***Control of ventilation***

Tests of ventilatory control include the hyperoxic rebreathing method and the hypoxia-withdrawal method. Simpler, but less specific, is the measurement of the mouth occlusion pressure.

## ***Diagnosis of sleep breathing disorders***

The diagnosis of sleep-related respiratory disorders requires special tests. The gold standard is polysomnography, but simpler tests are available for screening purposes ('respiratory polysomnography').

## ***Right heart catheterisation***

Right heart catheterisation is used in the differential diagnosis of pulmonary hypertension.

## ***Intensive care monitoring***

The management of respiratory failure in the intensive care unit requires, in addition to frequent checking of ABGs, the measurement of several special parameters (e.g. tidal volume, inspiratory and expiratory pressures); in mechanically ventilated patients, these are often measured automatically by the ventilator.

## ***Imaging techniques***

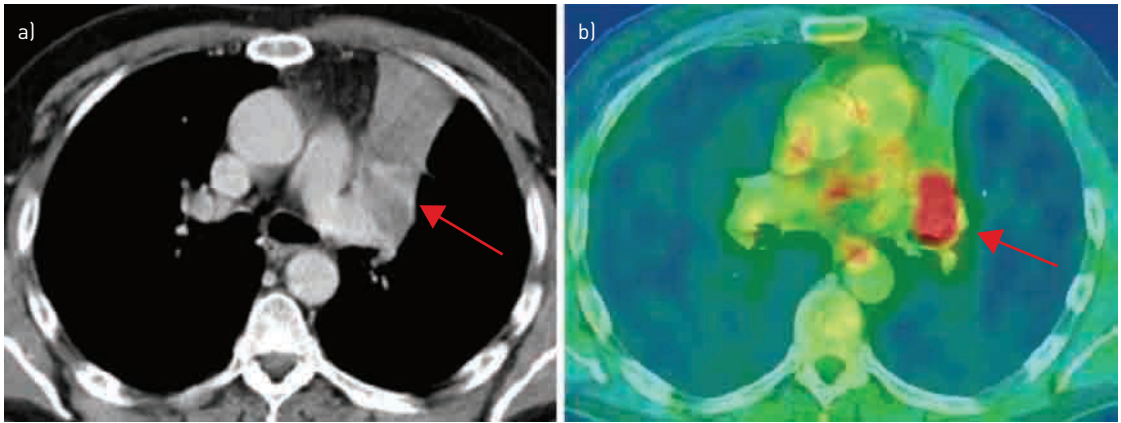
### ***Chest radiography***

Chest radiography (X-ray) is an essential part of the diagnostic (and monitoring) examination, and is the first step in the radiological evaluation of patients with suspected respiratory diseases. Modern digital radiography offers a high image quality and the potential for reduction of the radiation dose.

### ***Computed tomography***

Computed tomography (CT) of the chest is the second most important radiological modality in respiratory medicine, allowing much more detailed visualisation of thoracic structures than radiography. It is often performed with intravenous contrast





**Figure 2** – a) Axial computed tomographic (CT) image showing a central tumour (arrow) in the left lung with a post-stenotic atelectasis (collapse) of the left upper lobe. b) The integrated positron emission tomography/CT image shows a hot spot (red) located on the central tumour (arrow), allowing discrimination between tumour and post-stenotic atelectasis. Reproduced from DE WEVER *et al.*, 2011.

enhancement (in suspected pulmonary embolism cases, for example). CT is also helpful for guiding needle aspiration of peripheral lung lesions. High-resolution CT (HRCT) has improved the diagnosis of diffuse interstitial lung disease considerably. Low-dose CT is used in follow-up and serial early lung cancer detection. CT can be used for virtual bronchoscopy or angiography, but this has not become routine. CT is applied in combination with positron emission tomography (PET) mainly for staging lung cancer and other malignancies, and in the differential diagnosis between benign and malignant lung lesions (figure 2). CT/HRCT has almost wholly replaced bronchography for the diagnosis of bronchiectasis.

### ***Pulmonary and bronchial angiography***

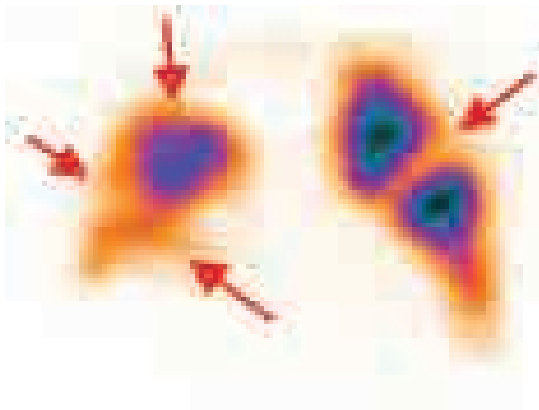
Pulmonary angiography and bronchial angiography (together with bronchial artery embolisation for the treatment of haemoptysis) are invasive techniques for imaging vessels and are only used if less invasive techniques (contrast CT/magnetic resonance imaging (MRI)) fail or need to be confirmed.

### ***Fluoroscopy***

Fluoroscopy (an X-ray technique by which respiratory movement is visualised directly) is used mainly for guidance of biopsy of peripheral lung lesions and for differential diagnosis of an elevated diaphragm.

### ***Magnetic resonance imaging***

MRI has the advantage that radiation is avoided. Its main indications are visualisation of the great vessels and the heart, but it is also useful with suspected tumour invasion of the mediastinum and the chest wall.



**Figure 3** – Perfusion scintigram showing multiple areas with absent perfusion (arrows) in a patient with pulmonary emboli. Reproduced from BAJC, 2012.

## Ultrasonography

Ultrasonography has become an important imaging technique. Its advantages are lack of radiation, low cost and mobility. It is mainly used in the investigation of pleural effusions (in which it also has a role in guiding thoracentesis) but also in pleural thickening, chest wall abnormalities, for the diagnosis of pneumothorax and for biopsies of lesions adjacent to the chest wall. A special application is endobronchial ultrasound (EBUS), which can be used for visualisation of mediastinal lymph nodes as well as pulmonary parenchymal lesions. Its most important use is the sampling of mediastinal lymph nodes in the setting of endoscopic lung cancer staging, where EBUS has largely replaced mediastinoscopy. Echocardiography allows noninvasive screening for pulmonary hypertension, although right heart catheterisation may be needed for the final diagnosis.

## Nuclear medicine techniques

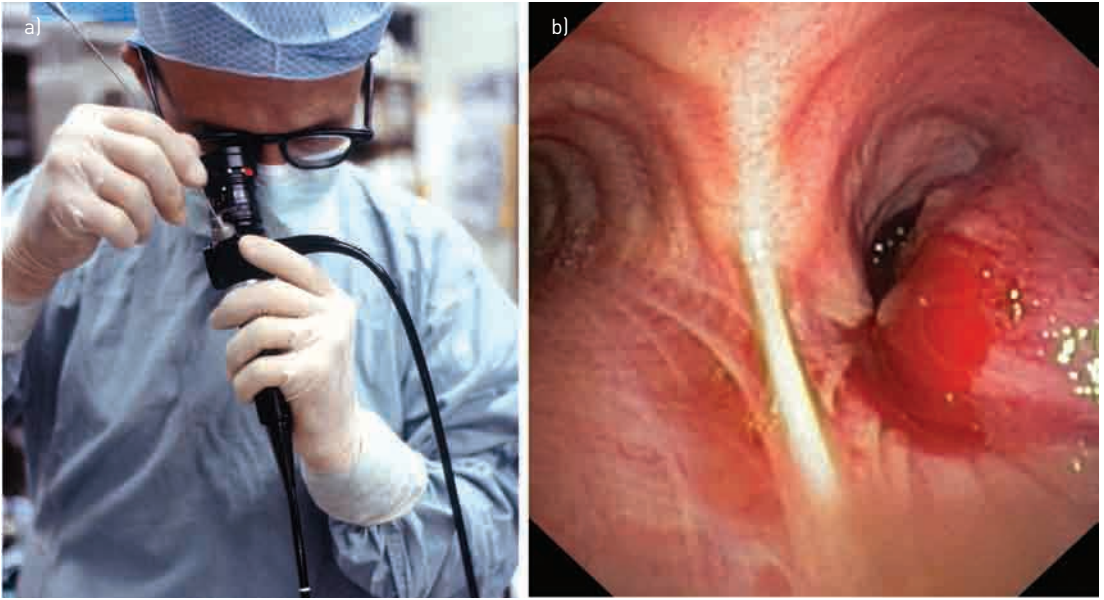
Nuclear medicine techniques include perfusion and ventilation scintigraphy, which are mainly indicated in the diagnosis of pulmonary embolism (figure 3) but also for regional lung function studies, *e.g.* for predicting post-operative lung function before lung surgery. Inhalation scintigraphy can be used to investigate mucociliary clearance.

## Invasive biopsy techniques

Endoscopy and biopsy techniques are essential tools in many respiratory diseases when simpler clinical and laboratory methods of investigation have failed to yield a diagnosis. The results of biopsies are heavily dependent upon the quality of the pathological and microbiological examinations.

## Bronchoscopy

The most important endoscopic method in respiratory medicine is bronchoscopy; for diagnostic purposes, this is almost exclusively performed with a flexible bronchoscope using video-assisted imaging, usually under local anaesthetic (figure 4). Bronchoscopy is associated with very few complications. The procedure not only allows inspection and sampling of the airways, but also facilitates transbronchial needle aspiration (TBNA)



**Figure 4 –** a) Transbronchial needle aspiration during flexible bronchoscopy. b) Flexible bronchoscopy showing a tumour that is almost completely obstructing the right main bronchus, indicating inoperability due to the location of the tumour. Reproduced from HERTH, 2011.

from the lymph nodes, sampling material from peripheral lesions with special catheters and brushes, or transbronchial lung biopsy (TBLB) by forceps, often under guidance of EBUS or fluoroscopy. A more elaborate technique to guide the bronchoscopist to small lesions is electromagnetic navigation.

### ***Bronchoalveolar lavage***

Bronchoalveolar lavage (BAL) involves the instillation of saline via a bronchoscope in order to collect specimens for cytological or microbiological investigation. It is used mainly in interstitial lung diseases or lower respiratory tract infections, as material can easily be obtained from the periphery of the lung.

### ***Autofluorescence and narrow-band imaging***

Autofluorescence or narrowband imaging may be helpful in the detection of precancerous lesions and early cancers located in the bronchial tree.

### ***Percutaneous needle biopsy***

Percutaneous (or transthoracic) needle biopsy is mainly performed to investigate peripheral lung lesions when bronchoscopy is negative. It is performed with the guidance of either fluoroscopy or, preferably, CT. When lesions are adjacent to the chest wall, ultrasound guidance can also be used.

## Thoracentesis and pleuroscopy (medical thoracoscopy)

Thoracentesis (pleural fluid aspiration or 'tap') is a frequently performed procedure in pleural effusions, preferably used under ultrasound guidance, at least when the effusion is small. Additional biopsy procedures, such as closed-needle biopsy of the pleura or pleuroscopy (medical thoracoscopy), may be necessary to confirm or exclude malignant or tuberculous causes of an effusion.

### Surgical methods

Surgical investigative methods include mediastinoscopy and the minimally invasive technique of video-assisted thoracic surgery (VATS). Mediastinoscopy is used for biopsy of mediastinal lymph nodes (if TBNA is negative). VATS has almost completely replaced the use of open surgery for diagnostic purposes in intrathoracic lesions (including interstitial lung disease), in which the aetiology remains uncertain after performance of the above less invasive procedures.

### Further reading



- Bajc M. Potential of hybrid V/P SPECT-low-dose CT in lung diagnostics. *Breathe* 2012; 9: 49–60.
- De Wever W, Coolen J, Verschakelen JA. Imaging techniques in lung cancer. *Breathe* 2011; 7: 338–346.
- Garbe B. Achieving quality spirometry in the office. *Breathe* 2010; 6: 211–219.
- Gibson GJ, Geddes DM, Costabel U, *et al.*, eds. *Respiratory Medicine*. 3rd Edn. Edinburgh, Saunders Elsevier Science, 2003.
- Herth FJF. Bronchoscopic techniques in diagnosis and staging of lung cancer. *Breathe* 2011; 7: 324–337.
- Loddenkemper R, Séverin T, Eiselé J-L, *et al.* HERMES: a European core syllabus in respiratory medicine. *Breathe* 2006; 3: 59–69.
- Mason RJ, Broaddus VC, Martin T, *et al.* eds. *Murray and Nadel's Textbook of Respiratory Medicine*. 5th Edn. Philadelphia, Saunders Elsevier, 2010.
- Palange P, Simonds AK, eds. *ERS Handbook of Respiratory Medicine*. 1st Edn. Sheffield, European Respiratory Society, 2010.

# Principles of respiratory therapy

## Introduction



### Key points

- Bronchodilators relax airway smooth muscle and are widely used in adults and children. The most frequently used are  $\beta$ -sympathomimetic agonists.
- Oral or intravenous steroids are the main treatment of acute asthma and also hasten recovery in acute COPD exacerbations. However, side-effects are seen with long-term treatment.
- Antibiotic treatment should be tailored to the specific infecting organism(s). This is particularly important in tuberculosis due to the increasing frequency of drug-resistant strains.
- The main methods of mechanical ventilatory support are: intermittent positive pressure ventilation, noninvasive ventilation and continuous positive airway pressure.
- Surgery is the treatment of choice for nonsmall cell lung cancer; surgical treatment is also used for selected patients with nonmalignant disease, including removal of benign tumours, lung volume reduction and pleural disease.

The broad spectrum of respiratory disease implies that the range of therapeutic options is similarly wide. Where appropriate, preventive measures should also be applied – smoking cessation, immunisation and improvements in air quality should be particularly encouraged.

Some forms of treatment are common to several diseases; this applies to both pharmacological agents (antibiotics for various infections, bronchodilators for narrowed airways) and nonpharmacological treatments (oxygen, physiotherapy, mechanical ventilatory support).

## Pharmacological therapy



### Aids to smoking cessation

Smokers should be strongly encouraged to stop; smoking cessation advice and support, together with various pharmaceutical products are available for those who wish to do so. Nicotine replacement allows some individuals to ease the effects of tobacco withdrawal. Nicotine can be administered in various forms, including lozenges, gum, transcutaneous patches and by inhalation. Pharmaceutical agents with demonstrable benefits in selected individuals include bupropion, originally an antidepressant, and varenicline, a selective nicotine receptor agonist.

“*Long-term oxygen at home has been shown to improve the life-expectancy of patients with severe hypoxaemia*”


## Bronchodilators

Bronchodilators vary in both their mode and duration of action and they can be administered by various routes. The commonly used inhaled bronchodilators are listed in table 1. All are aimed essentially at relaxing the smooth muscle of the airway wall and they are very widely used, both in adults and children, either as sole or adjunctive treatment for asthma and chronic obstructive pulmonary disease (COPD), and for other conditions characterised by diffuse airway narrowing, e.g. bronchiectasis.

Among the most frequently used bronchodilators are the  $\beta$ -sympathomimetic agonists, which mimic the action of the sympathetic nervous system by selectively stimulating the  $\beta_2$  receptors on bronchial smooth muscle. They are most commonly administered *via* inhalation, traditionally from a metered-dose inhaler (MDI). However, careful attention to inhaler technique is important, as many individuals experience difficulty in coordinating the manoeuvres necessary for effective inhalation with the traditional ‘press and breathe’ inhaler. Detailed guidance on the available inhaler devices and their use has recently been published by a task force set up jointly by the European Respiratory Society (ERS) and the International Society for Aerosols in Medicine (ISAM). Devices used to overcome problems with inhaler technique include inhalation *via* a ‘spacer’ (figure 1a) and breath-activated inhalers (figure 1b). Alternatively, the drug can be inhaled as a very fine dry powder (dry powder inhaler (DPI)) (figure 1c) or as a soft mist (soft mist inhaler (SMI)) (figure 1d). Sometimes (during an acute asthma attack, for example) larger doses are inhaled as a nebulised solution driven by a flow of air or oxygen (usually available only in hospital) or by a portable, electrically powered compressor (figure 1e).

Short-acting  $\beta_2$ -agonists are a mainstay of treatment for symptomatic relief and for acute exacerbations of asthma and COPD, while longer-acting agents are used on a regular basis to produce background bronchodilatation in patients with chronic airway obstruction, usually in conjunction with an inhaled steroid (table 1).

Anti-muscarinic drugs inhibit the action of the parasympathetic nervous system and produce bronchodilatation by reducing the tone of the airway smooth muscle; as with



$\beta_2$ -agonists (together with which they are often used), both short- and long-acting versions are available. Administration is by inhalation, which avoids the side-effects of widespread parasympathetic inhibition.

The methylxanthine bronchodilator drug theophylline is a nonspecific inhibitor of the enzyme phosphodiesterase (PDE). It is administered orally; its more soluble derivative, aminophylline, is given intravenously and has been a traditional method of treating acute asthma attacks. Theophylline is, however, less favoured nowadays as side-effects are frequent and blood level monitoring is desirable for control of the appropriate dose. More recently developed, specific PDE inhibitors include the PDE<sub>4</sub> inhibitors (*e.g.* roflumilast) which have bronchodilator and anti-inflammatory effects in COPD and the PDE<sub>5</sub> inhibitors (*e.g.* sildenafil) used in the treatment of pulmonary hypertension.

### ***Corticosteroids***

Corticosteroids, such as prednisolone (given orally) or methyl prednisolone (given parenterally), are powerful anti-inflammatory agents used in a wide range of medical conditions. In respiratory practice, steroids are used most commonly by inhalation in the long-term treatment of asthma and COPD. Oral or intravenous steroids are the mainstay of treatment of acute asthma; in most cases, regular treatment for 5–10 days suffices and a similar approach has been shown to hasten recovery in acute exacerbations of COPD.

When introduced in the 1970s, inhaled steroids revolutionised the long-term treatment of asthma, as they allowed better control of the condition without the side-effects of oral steroids, which had been widely used previously. Though less effective than in asthma, regular inhaled corticosteroid treatment has also been shown to benefit patients with severe COPD, by reducing the frequency of exacerbations. An inhaled steroid is usually administered twice daily from an MDI or DPI and, increasingly, a steroid is combined with a long-acting  $\beta_2$ -agonist in the same inhaler (table 1).

Oral steroids are also used for the longer-term treatment of some types of interstitial lung disease, particularly sarcoidosis, hypersensitivity pneumonitis and some of the interstitial pneumonias. Long-term oral steroid treatment is, however, accompanied by frequent side-effects, against which the benefit of suppressing troublesome symptoms (usually breathlessness) has to be balanced.

Category	Duration of action	Generic name	Proprietary name (manufacturer)
$\beta_2$ -agonist	Short	Salbutamol	Ventolin (GSK), Airomir (Graceway Pharmaceuticals)
		Terbutaline	Bricanyl (AstraZeneca)
	Long	Salmeterol	Serevent (GSK)
		Formoterol	Oxis (AstraZeneca), Foradil (Schering Plough and Novartis), Atimos (Chiesi)
Antimuscarinic	Short	Indacaterol	Onbrez (Novartis)
		Ipratropium	Atrovent (Boehringer Ingelheim)
		Tiotropium	Spiriva (Boehringer Ingelheim and Pfizer)
Corticosteroid	Long	Beclomethasone	Becotide (GSK), Qvar (Teva), Clenil (Chiesi)
		Budesonide	Pulmicort (AstraZeneca)
		Fluticasone	Flixotide (GSK)
		Mometasone	Asmanex (Merck, Sharpe and Dohme)
		Ciclesonide	Alvesco (Takeda)
Compound preparations	Long	Salmeterol+fluticasone	Seretide (GSK)
		Formoterol+budesonide	Symbicort (AstraZeneca)

**Table 1** – Commonly used inhaled therapy for asthma and chronic obstructive pulmonary disease.

## Antibiotics

For respiratory infections, antibiotics can be given either as a short course (5–10 days for acute infective exacerbations of COPD, for example) or on a longer-term basis, particularly for chronic bronchial infection (in cystic fibrosis (CF) or non-CF bronchiectasis, for instance).

Ideally, antibiotic treatment is tailored to the specific infecting organism(s), but often, especially in COPD, this may not be apparent or may come to light only after a couple of days when culture results become available; consequently, a broad-spectrum antibiotic is usually prescribed in order to cover the most likely pathogens. Most infective exacerbations of COPD are due initially to viral infection, which is not generally susceptible to conventional antibiotics; however, this is often superseded by bacterial infection, at which stage the sputum becomes purulent and an antibiotic is indicated.

In nonimmunocompromised patients, less severe community-acquired pneumonia usually responds to a broad-spectrum antibiotic, *e.g.* one of the  $\beta$ -lactam (penicillin) family. However, combinations of antibiotics are used when pneumonia is more severe



“  
Many  
individuals  
find it difficult  
to coordinate  
the manoeuvres  
necessary for  
inhalation with  
the traditional  
'press and  
breathe'  
inhaler  
”

and specifically targeted treatment is desirable when the infecting agent is likely to be less susceptible to the commonly used broad-spectrum agents, for instance *Mycoplasma pneumoniae*, *Staphylococcus aureus* or *Legionella pneumophila* (Legionnaires' disease).

With chronic bronchial infection, as in CF or bronchiectasis, longer-term antibiotic treatment may be indicated, particularly to control pathogens such as *Pseudomonas aeruginosa*; some, such as tobramycin, can be given effectively as an aerosol by nebulisation.

The treatment of tuberculosis (TB) and related mycobacterial infections requires specific antibiotics, which are given in combination for a prolonged period (at least 6 months for TB and up to 24 months for non-tuberculous mycobacteria). The most frequently used combination for TB comprises isoniazid plus rifampicin for 6 months, supplemented by pyrazinamide and ethambutol for the first 2 months. Identifying the drug sensitivity of the infecting organism is particularly important due to the increasing frequency of drug-resistant strains.

## Other drugs

### Diuretics

Diuretics are frequently used in patients with chronic fluid retention ('cor pulmonale') due to severe pulmonary hypertension, either primary or secondary to advanced COPD.

### Anticoagulation and thrombolytic agents

Anticoagulation is the usual primary treatment in acute pulmonary embolism, with thrombolytic agents used if embolism is sufficiently extensive to compromise cardiac output.

### Vasodilators

Specific vasodilator and other drugs are increasingly used to improve the pulmonary circulation in patients with primary pulmonary hypertension.

### Mucolytic drugs

Mucolytic drugs, such as carbocysteine and dornase alpha (DNAse) reduce the viscosity ('stickiness') of sputum and aid expectoration, e.g. in CF, where they may reduce the frequency of acute exacerbations. Mucolytic drugs may also reduce the frequency of exacerbations in COPD.

### Cytotoxic drugs

Cytotoxic drugs are used in the treatment of lung cancer and mesothelioma. Although not likely to be curative,



**Figure 1** – Various inhalers: a) metered-dose inhaler (MDI) plus spacer; b) breath-actuated MDI; c) dry powder inhaler (DPI) 'Accuhaler/Diskus'; d) soft mist inhaler (SMI) 'Respimat'; e) nebuliser.

some agents, usually in combination, prolong average life-expectancy in small cell lung cancer and they are increasingly used as palliative treatment of nonsmall cell lung cancer.

Some cytotoxic drugs are also useful in the treatment of certain types of interstitial diseases and pulmonary vasculitis; for example, cyclophosphamide in granulomatosis with polyangiitis (Wegener's).

**Tumour growth modifiers**

Biological therapy with drugs such as those that inhibit the enzyme tyrosine kinase is effective against cancers that express certain genes (e.g. the epidermal growth factor receptor); this type of 'tailored' approach to certain lung cancers offers hope for greater therapeutic success in future.

## Comorbidity

Many patients with respiratory disease also require medication for comorbid disease: for instance, in cases of coexisting ischaemic heart disease and COPD, which are common comorbidities due to their shared smoking aetiology.

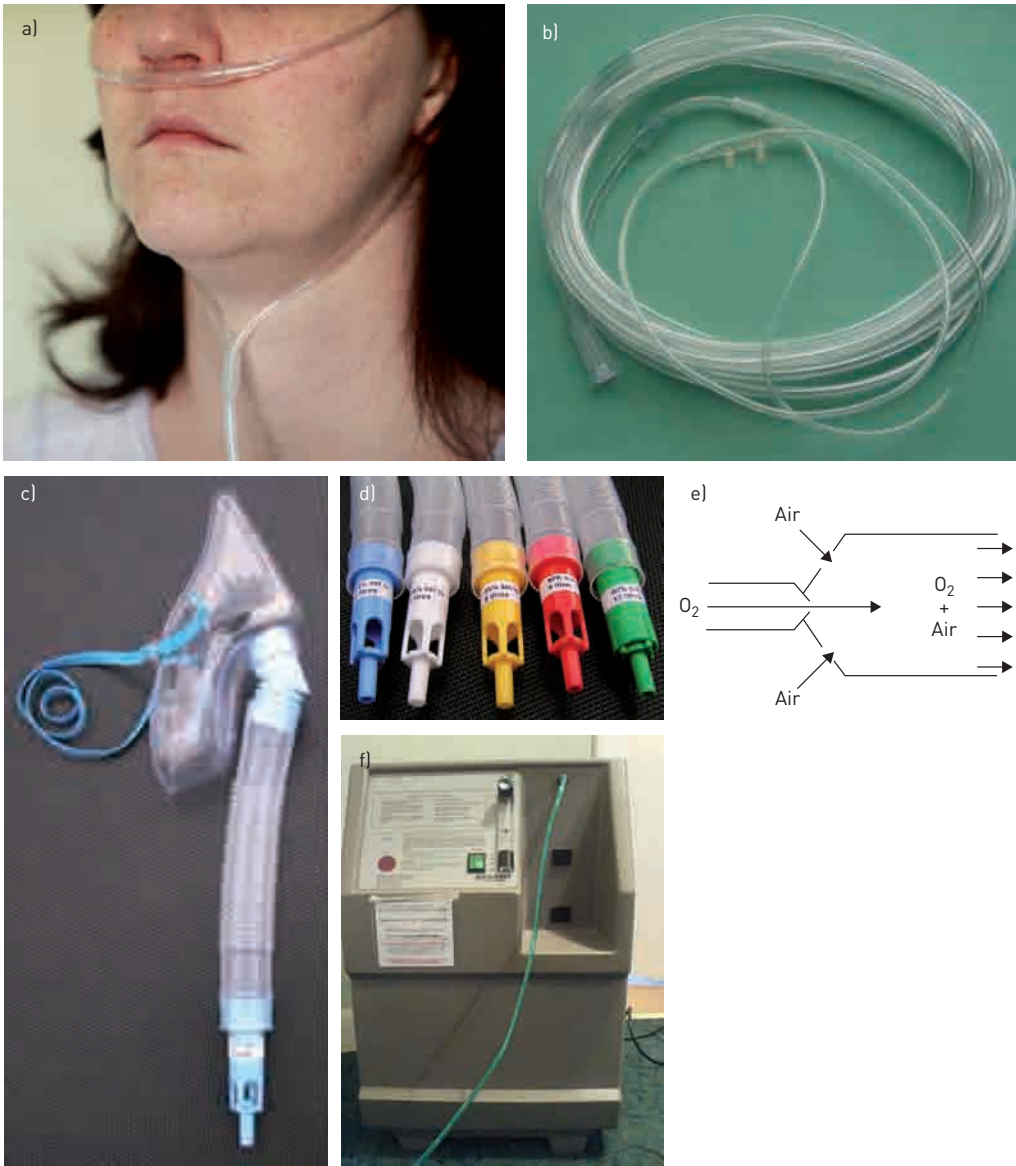
## Nonpharmacological therapy

### Oxygen

Oxygen is widely used in patients with advanced respiratory disease, both in hospital and, on a long-term basis, in the patient's home. Indications include both the relief of symptoms and prolongation of survival. In general, oxygen is only likely to be beneficial when the level of oxygen in the arterial blood (arterial oxygen tension ( $P_{aO_2}$ )) is low; it is not a general panacea for breathlessness, as this often results from factors other than shortage of oxygen. Therefore, accurate assessment is essential before oxygen is prescribed; this includes confirmation of hypoxaemia when the patient is breathing air and demonstration of improvement when breathing oxygen.

Several different methods for administering oxygen are available (figure 2). The optimal method for an individual patient depends on the nature and severity of the underlying condition, as well as the situation in which oxygen is to be used. In very ill patients in hospital with severe hypoxaemia (e.g. in acute respiratory distress syndrome, extensive pneumonia or severe acute asthma), high-flow oxygen, *via* a face mask or in conjunction with assisted ventilation, may be required. However, in patients with exacerbations of severe COPD, uncontrolled high-flow oxygen can result in progressive retention of carbon dioxide (hypercapnia) and respiratory acidosis, which itself may be life-threatening. In this situation, therefore, it is necessary to restrict the concentration or flow of oxygen being breathed. Low-flow oxygen can be delivered comfortably *via* small nasal cannulae (figure 2a and b), but this does not give precise control of the inspired oxygen concentration. The latter can be controlled by use of a mask that operates on the Venturi principle, where the concentration of oxygen breathed by the patient is relatively independent of the oxygen flow rate. Such masks allow only a small increase of inspired oxygen concentration – for example to 24% or 28%, compared to the 21% present in room air – but in COPD this is usually sufficient to relieve life-threatening hypoxaemia, while at the same time minimising the risk of serious hypercapnia.

Long-term oxygen at home has been shown to improve the life-expectancy of patients with severe hypoxaemia resulting



**Figure 2** – Common modes of oxygen administration. a and b) Nasal cannulae ('prongs'), which allow control of oxygen flow rate but not inspired concentration. c–e) Venturi masks, which allow precise control of inspired oxygen concentration: the flow of oxygen through a nozzle entrains air *via* holes around the nozzle; increasing the oxygen flow entrains more air so that, within certain limits, the percentage oxygen the patient breathes remains constant. A larger orifice in the nozzle gives a higher oxygen concentration, here colour-coded from 24% to 60% [compared with 21% in room air]. f) An oxygen concentrator suitable for home use. Figure 2a credit: istockphoto/Beano5.

from advanced COPD. To achieve this, oxygen treatment needs to be given for as long as possible each day (minimum: average 15 out of 24 hours). It is delivered most conveniently by an oxygen concentrator (which, as the name implies, concentrates the oxygen from room air) or by using a large tank of liquid oxygen, from which a small cylinder can be refilled as required. Patients who show worsening oxygenation ('desaturation') during exercise may benefit from breathing oxygen during exertion; this can be supplied by a refillable small liquid oxygen tank or by a portable concentrator.

However, even severely hypoxaemic patients may not show desaturation during exercise and so prescription of ambulatory oxygen should be preceded by specialist assessment and the demonstration of both desaturation when breathing room air and improved performance when breathing oxygen.

### *Physiotherapy*

Physiotherapy is particularly helpful as an aid to clearing bronchial secretions, for example in acute exacerbations of COPD and in patients with chronic production of infected sputum, as in CF and bronchiectasis. Various techniques are used, including postural drainage and forced expiration; often, these are taught to patients who continue to use them regularly at home. Other important aspects of physiotherapy, including exercise and muscle training, are employed as part of pulmonary rehabilitation (see chapter 29).

### *Ventilatory support*

#### **Intermittent positive pressure ventilation**

The traditional method of mechanically assisting the ventilation of seriously ill patients in hospital is by intermittent positive pressure ventilation (IPPV), in which the patient's airway is connected to a ventilator that blows air (usually with supplementary oxygen) into the lungs, with the ventilator set to deliver a specified volume or pressure. The air is delivered into the trachea *via* an endotracheal tube, or if ventilation needs to continue for a prolonged period, via a tracheostomy tube. Modern ventilators are highly sophisticated and allow a range of modes and patterns of ventilation, including total ventilation, in which the machine does all the work, and various 'assist' modes, in which the ventilator detects and then supplements each inspiratory effort.

#### **Noninvasive ventilation**

Over the past 20 years, noninvasive ventilation (NIV) has increasingly been used. It offers several advantages: in particular, the need for sedation is avoided; the patient retains the ability to cough and communicate; and the risk of further infection associated with intubation of the airway is minimised. Ventilation is achieved by delivering air (with or without supplementary oxygen) *via* a tight-fitting face mask applied to the nose, or nose and mouth (the range of patient 'interfaces' is the same as is used for delivering continuous positive airway pressure (CPAP) for treating obstructive sleep apnoea syndrome (OSAS) – see below). In most respiratory departments, NIV is now first-line management for

“  
NIV is  
first-line  
management  
for patients  
requiring  
ventilatory  
assistance  
for acute  
exacerbations  
of COPD  
”

patients requiring ventilatory assistance for acute exacerbations of COPD. It is also increasingly used for long-term nocturnal domiciliary ventilation in certain groups of patients with chronic hypercapnia. It is particularly suitable and effective for chronic respiratory failure due to severe respiratory muscle weakness (e.g. various muscular dystrophies or motor neurone disease/amyotrophic lateral sclerosis) or severe deformity of the chest wall (e.g. scoliosis). Long-term domiciliary NIV is also used in some patients with severe COPD, but its indications in this condition require further investigation.

### **Continuous positive airway pressure**

CPAP is a simpler form of ventilatory support, which is used with one of two aims. CPAP delivered by a conventional ventilator is used in the management of very ill patients with severe hypoxaemia, as applying a continuous inflating pressure to the airway (in addition to the fluctuating pressure required to ventilate the lungs) increases lung volume, which is beneficial in improving oxygenation.

In its alternative, and now much more common, application, CPAP is used as the treatment of choice in most patients with symptomatic obstructive sleep apnoea syndrome (OSAS) in order to overcome the narrowing or obstruction of the upper airway (pharynx), which is the prime mechanism of OSAS. In this situation, applying a positive pressure at the nose or mouth (or both) during sleep stabilises the upper airway; maintaining airway patency in this way prevents the recurrent apnoeas and the accompanying hypoxaemia and sleep disturbance which they cause. The pressure delivered is adjusted either manually or automatically to the level necessary to maintain the patency and stability of the airway and the patient is encouraged to use this treatment every night, usually indefinitely. Although some individuals experience discomfort or intolerance, the majority find that the improvement in daytime alertness, which is often dramatic, more than compensates for this. A variety of patient interfaces is available by which the pressure is delivered, *via* the nose or mouth or sometimes both (figure 3 – see also chapter 23).

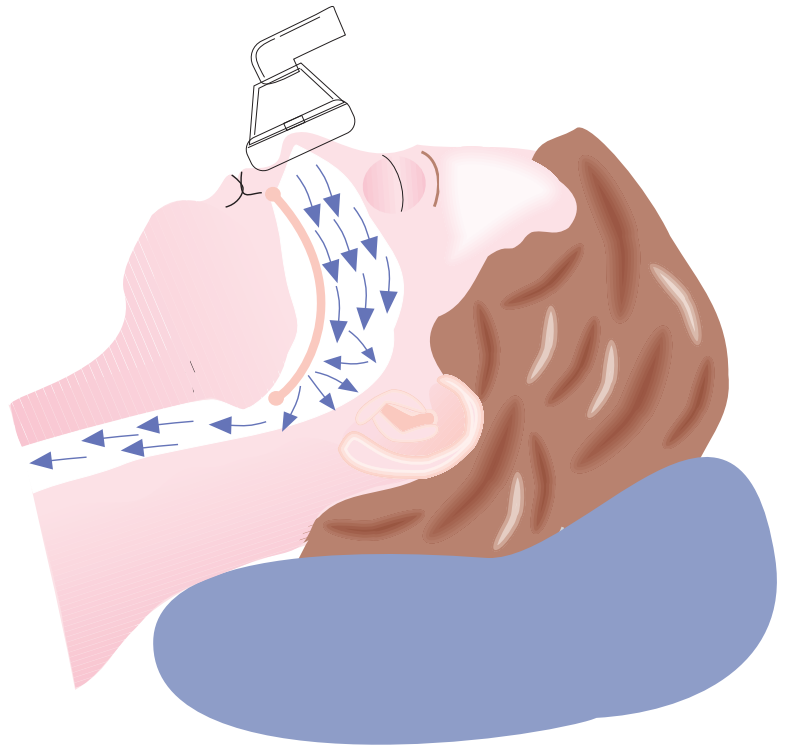
## ***Radiotherapy***

In a minority of patients with nonsmall cell bronchial carcinoma, radical radiotherapy is used with the aim of achieving a cure. This approach is only appropriate for patients with small peripheral tumours, with no evidence of spread, and in whom surgical resection is not an option. The direction of the radiation beam can be focused more precisely by use of stereotactic methods of three-dimensional imaging.

More commonly, radiotherapy is used, sometimes in combination with chemotherapy, in both small and nonsmall cell bronchial carcinoma, with the aim of achieving a partial or, occasionally, complete response, and also as palliative treatment to improve symptoms, particularly haemoptysis or pain due to bone invasion or metastasis.

## ***Thoracic surgery***

Surgical treatment is used for both malignant and nonmalignant respiratory disease. It is the treatment of choice for primary nonsmall cell bronchial carcinoma, and



**Figure 3** – Principle of continuous positive airway pressure (CPAP) for treating obstructive sleep apnoea syndrome: a modest pressure (e.g. 5–15 cm water) applied continuously at the nose and/or mouth during sleep supports the floppy pharyngeal airway (arrows), preventing it narrowing and closing during sleep.

gives the best prospect of cure when the tumour appears technically resectable, there is no evidence of metastasis and the patient is fit for the procedure. Depending on the extent and position of the cancer, resection may involve removal of a whole lung (pneumonectomy), one or more lobes (lobectomy) or, less commonly, a lung segment (segmentectomy).

Surgical treatment options for other respiratory conditions include: removal of benign tumours or of giant bullae; lung volume reduction surgery for selected patients with severe hyperinflation of the lungs due to emphysema; resection of lung abscess, severe localised bronchiectasis or lung affected by drug-resistant TB; and pleural surgery for empyema, persistent pneumothorax or extensive pleural thickening. The ultimate form of surgical treatment is lung transplantation, which is performed for a variety of end-stage lung diseases, most commonly nowadays for advanced CF.

Further information can be found in chapter 32.

## Other forms of treatment

### *Bronchoscopic procedures*

Therapeutic bronchoscopy *via* a rigid bronchoscope has several indications. It is used for control of bronchial haemorrhage (usually from a tumour), for removal of large mucous plugs or foreign bodies from the airway, and for palliative local tumour resection, dilatation of central airway narrowing and the insertion of stents to maintain patency in patients with obstruction of a central airway (due to malignant or nonmalignant conditions). Localised radiotherapy can be administered bronchoscopically where appropriate (brachytherapy). More experimental bronchoscopic techniques include photodynamic therapy (in which laser treatment is applied bronchoscopically after intravenous administration of a photosensitising agent), gene therapy (*e.g.* for CF) and the insertion of one-way valves in lobar and segmental airways, with the aim of deflating emphysematous lobes or lung segments.

### *Pleural procedures*

Pleural aspiration or intubation is a standard treatment for symptomatic pneumothorax, but in many cases of spontaneous pneumothorax, especially in young, otherwise fit individuals, no treatment is needed as the pneumothorax will resolve spontaneously over a few days. Aspiration, or intubation with underwater drainage, may be required for spontaneous or iatrogenic pneumothorax if this is very large (particularly if under tension) or if respiratory function is so poor that even a small collection of air in the pleural space increases breathlessness.

With a pleural effusion, drainage of fluid may be both diagnostic (see chapter 27) and therapeutic; simple needle aspiration may improve breathlessness but with a large volume of fluid, drainage may necessitate intercostal intubation for a few days. Introduction of a sclerosing agent prior to removing the intercostal drain can help to control accumulation of pleural fluid in patients with recurrent effusions. For long-term management of persistent pleural air, fluid or infected material, a semipermanent one-way valve may be used, attached, if necessary, to a drainage bag.

### *Therapeutic embolisation*

Bronchial artery embolisation is increasingly used to control severe or recurrent haemoptysis, due, for example, to lung cancer or bronchiectasis. Under radiological guidance, a catheter is introduced from the aorta into the relevant bronchial artery (or arteries) and an occluding device (gel foam or small metal coil) is injected. Less commonly, embolisation of the blood vessel supplying a pulmonary arteriovenous malformation may be treated similarly. In patients with recurrent haemoptysis due to widespread bronchiectasis or multiple arteriovenous malformations, the procedure may need to be repeated several times.





### Asthma

- British Thoracic Society/Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. [www.sign.ac.uk/guidelines/fulltext/101/index.html](http://www.sign.ac.uk/guidelines/fulltext/101/index.html)
- Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Updated 2012. [www.ginasthma.org/uploads/users/files/GINA\\_Report\\_2012Feb13.pdf](http://www.ginasthma.org/uploads/users/files/GINA_Report_2012Feb13.pdf)

### Bronchiectasis

- Pasteur MC, Bilton D, Hill AT, *et al.* Guideline for non-CF bronchiectasis. *Thorax* 2010; 65: Suppl. 1, i1–i58.

### COPD

- Global Initiative for Chronic Obstructive Lung Disease. Global strategy for diagnosis, management and prevention of COPD. Updated 2013. [www.goldcopd.org/uploads/users/files/GOLD\\_Report\\_2013\\_Feb20.pdf](http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013_Feb20.pdf)
- Roberts CM, Brown JL, Reinhardt AK, *et al.* Non-invasive ventilation in chronic obstructive pulmonary disease: management of acute type 2 respiratory failure. *Clin Med* 2008; 8: 517–521.

### Cystic fibrosis

- Flume PA, O'Sullivan BP, Robinson KA, *et al.* Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med* 2007; 176: 957–969.

### Inhaled therapy

- Laub BL, Janssens HM, de Jongh FHC, *et al.* What the pulmonary specialist should know about the new inhalation therapies. *Eur Respir J* 2011; 37: 1308–1417.

### Interstitial lung disease

- Raghu G, Collard HR, Egan JJ, *et al.* An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011; 183: 788–824.
- Wells AU, Hirani N. Interstitial Lung Disease guidelines: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax* 2008; 63: Suppl. 5, v1–v58.

### Lung cancer

- Alberts WM, American College of Chest Physicians. Diagnosis and management of lung cancer: ACCP guidelines. *Chest* 2007; 132: Suppl. 3, 1s–19s.
- National Institute of Health and Clinical Excellence (NICE). Lung cancer: the diagnosis and treatment. Clinical Guidance 121; 2011. [guidance.nice.org.uk/CG121](http://guidance.nice.org.uk/CG121)

## Obstructive sleep apnoea syndrome

- Scottish Intercollegiate Guidelines Network (SIGN). Management of obstructive sleep apnoea/hypopnoea syndrome in adults. Guideline no. 73. 2003. [www.sign.ac.uk/guideline/fulltext/73](http://www.sign.ac.uk/guideline/fulltext/73)

## Oxygen treatment

- O'Driscoll BR, Howard LS, Davison AG. BTS guideline for emergency oxygen use in adult patients. *Thorax* 2008; 63: Suppl. 6, vi1–vi68.

## Pleural disease

- Maskell N, British Thoracic Society Pleural Disease Guideline Group. British Thoracic Society pleural disease guidelines. *Thorax* 2010; 65: 667–669.

## Pneumonia

- Woodhead M, Blasi F, Ewig S, *et al.* Guidelines for the management of adult lower respiratory tract infections. *Clin Microbiol Infect* 2011; 17: Suppl. 6, 1–24.

## Pulmonary hypertension

- Galie N, Hoeper MM, Humbert M, *et al.* Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2009; 34: 1219–1263.

## Tuberculosis

- National Institute for Health and Clinical Excellence (NICE). Clinical diagnosis and management of tuberculosis and measures for its prevention and control. Clinical Guidance 117; 2011. [www.guidance.nice.org.uk/CG117](http://www.guidance.nice.org.uk/CG117)

# Pulmonary rehabilitation

## Background



### Key points

- There is a sound evidence base showing the effects of pulmonary rehabilitation on chronic obstructive pulmonary disease symptoms and health-related quality of life.
- Pulmonary rehabilitation may be carried out on an in- or outpatient basis, or in the patient's home – the outcome depends on the content of the programme and the quality of the team delivering it, rather than on the setting.
- Pulmonary rehabilitation is effective in patients with COPD after acute exacerbations as well as in the stable state.

Effective management of chronic pulmonary diseases aims to: 1) prevent progression; 2) relieve symptoms; 3) improve exercise tolerance; 4) improve health status; 5) prevent complications; 6) prevent exacerbations; and 7) reduce mortality. Pulmonary rehabilitation is a central aspect of the treatment of chronic obstructive pulmonary disease (COPD) and other chronic respiratory diseases, for which treatment other than smoking cessation and long-term oxygen therapy largely aims at improving symptoms. Pulmonary rehabilitation is a relatively recent practice in respiratory medicine and is described as an 'individually tailored and designed, multidisciplinary programme of care' for patients with chronic respiratory impairment. There are several guidelines that define pulmonary rehabilitation practice.

### Definition



Pulmonary rehabilitation has been defined by the European Respiratory Society (ERS) and American Thoracic Society (ATS) as 'an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Pulmonary rehabilitation is designed to reduce symptoms, optimise functional status, increase participation, and reduce healthcare costs through stabilising or reversing systemic manifestations of the disease.'

“*Pulmonary rehabilitation should be included in the comprehensive treatment of COPD and other chronic respiratory diseases*”

## Rationale

Patients with severe COPD become progressively less mobile and reduce their activities of daily living (ADL). Peripheral muscle wasting is a common finding and has a negative impact on survival. Gains in body weight, muscle mass and strength are associated with better exercise tolerance and longer survival; consequently, improving peripheral muscle function is an appropriate therapeutic target in patients with COPD. Physical activity is the strongest predictor of all-cause mortality in COPD patients, and increased activity is associated with better prognosis, physical and cognitive status, and survival. It is therefore not surprising that rehabilitation has a beneficial effect on symptoms and health-related quality of life (HRQoL) in stable COPD patients. Multidisciplinary rehabilitation can improve peripheral and respiratory muscle function, nutrition and ADL.

## Application

According to Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, pulmonary rehabilitation should be offered to all COPD patients of stage II or greater severity. Professional societies, including the American College of Physicians (ACP), the American College of Chest Physicians (ACCP), the ATS and the ERS, recommend that clinicians should prescribe pulmonary rehabilitation for symptomatic patients with a forced expiratory volume in 1 s (FEV<sub>1</sub>) of less than 50% of the predicted value, and should consider it for symptomatic or exercise-limited patients with an FEV<sub>1</sub> greater than 50% of predicted. However, because of the high prevalence of GOLD stage II COPD or higher, healthcare systems are unable to meet the need for pulmonary rehabilitation in all eligible patients.

More information on COPD can be found in chapter 13.

## Outcome

Published studies provide a sound scientific basis for the overall intervention, as well as its specific components (albeit at a lower level of evidence).

## Clinical outcome

After rehabilitation, patients report improvement in HRQoL, a reduction in respiratory symptoms, increases in exercise tolerance and their ability to perform ADL, and greater independence. However, pulmonary rehabilitation has no effect on lung function or gas exchange (table 1).

Most COPD patients benefit from a pulmonary rehabilitation programme. Although some reports suggest that one-quarter to one-third of patients show no response, studies have failed to identify important predictors of treatment success or failure.

## Health resources

Studies (mostly uncontrolled) evaluating the costs of pulmonary rehabilitation have reported a positive cost/benefit ratio, mostly due to a reduction in hospitalisation frequency after rehabilitation. A recent health economic analysis performed by the London School of Economics, the British Thoracic Society (BTS) and the Primary Care Respiratory Society UK (PCRS-UK) suggested that pulmonary rehabilitation is one of the most cost-effective treatments available. In fact, its cost per quality-adjusted life-year (QALY) is less than that of most long-term inhaled therapy.

## Mortality

A large, prospective, controlled trial would be necessary to examine the possible effect of pulmonary rehabilitation on mortality, but given that a great deal of evidence already exists showing its health benefits, such a trial would be impossible to carry out as it would be considered unethical to deny rehabilitation to a control group. The effect of pulmonary rehabilitation on survival is therefore likely to remain unquantified. Nevertheless, as COPD patients with better exercise tolerance, less breathlessness and lower rates of hospitalisation have higher survival rates and pulmonary rehabilitation provides these benefits, it is reasonable to assume that it is likely to result in a survival advantage.

Outcome	Evidence for expected improvements
Breathlessness	+++
Exercise tolerance	+++
Health-related quality of life	+++
Health resource consumption	++
Respiratory muscle function	++
Survival	+
Lung function	-

**Table 1** – Expected results of pulmonary rehabilitation. +++: based on randomised clinical trials and meta-analyses; ++: encouraging results but further evidence is needed; +: indirect evidence; -: no improvement.

## Setting and content

### Location

The principles of pulmonary rehabilitation apply regardless of location; consequently, it has been shown to be effective across the various settings studied so far, although few clinical trials offer direct comparisons between different settings.

Inpatient pulmonary rehabilitation may consist of a planned programme to which a patient is admitted directly, or care provided during an admission for an acute exacerbation. This clinical setting is better suited to patients with severe disease and/or a lack of home management support, or difficulties in transport to outpatient settings. Inpatient rehabilitation can provide similar benefits to those seen in outpatient settings. Potential disadvantages include the higher cost and, in some countries, lack of health insurance coverage.

Outpatient pulmonary rehabilitation is the most common setting employed, and can be based in the hospital or the community. Potential advantages include cost-effectiveness, a safe clinical environment and availability of trained staff. The majority of studies describing the benefits of pulmonary rehabilitation are derived from hospital-based outpatient programmes.

Home-based rehabilitation is the most convenient method for the patient. This method may prolong the benefits of rehabilitation, although in severely disabled patients, it might not be as effective. The potential disadvantages of home-based rehabilitation include the lack of opportunity for group support, limited presence of a multidisciplinary team, variable availability of exercise equipment, lack of safe facilities and the cost of visits by healthcare professionals.

### Rehabilitation in the intensive care unit

Early mobilisation of critically ill patients is a relatively new management approach that is advocated as a method of addressing acute respiratory failure and reducing the disability associated with intensive care unit-acquired weakness. It has been shown that early physiotherapy benefits patients receiving intensive care. This therapeutic approach has been reported in clinical trials and is recommended by the ERS and the European Society of Intensive Care Medicine (ESICM) Task Force on Physiotherapy for Critically Ill Patients.

### Availability and personnel

As outlined by the recent ERS COPD audit performed in 13 countries, 50% of European respiratory units have access to a pulmonary rehabilitation programme for patients with COPD after hospital admission but only 30% of eligible patients receive pulmonary rehabilitation. 35% of hospitals implement hospital-based pulmonary rehabilitation, 16% implement home-based rehabilitation and 30% implement both.

The effectiveness of pulmonary rehabilitation is more likely to be related to the structure and components of the programme and the quality of the team than to the setting in which it occurs. Pulmonary rehabilitation should be delivered by a multidisciplinary team that includes at least a physiotherapist, an occupational therapist, a psychologist and a dietician, although the exact structure will vary depending on patient population, programme budget and local reimbursement rules. The reported median availability of such personnel in Europe is two per respiratory

unit, with wide variations between countries. Overall, 60% of patients admitted to a respiratory unit are seen by a chest physiotherapist.

## Components

The improvements attributable to individual elements of a programme are difficult to assess due to the multidisciplinary nature of pulmonary rehabilitation and to the wide range of therapeutic modalities used (table 2).

### Exercise training

Physical aerobic training, particularly of the lower extremities, is mandatory. Any patient capable of undergoing training will benefit from a programme that includes leg exercise. Most rehabilitation programmes include endurance training. In patients unable to tolerate high-intensity exercise, an alternative is interval training, which consists of 2–3 minutes of high-intensity training alternating with equal periods of rest. The optimal exercise intensity, modality, level of supervision, duration and maintenance programme remain to be determined. Although high-intensity training is often prescribed, lower-intensity physical training up to the tolerance level of the individual patient can still produce benefits; in fact, greater emphasis on individual prescription of the appropriate amount of exercise is recommended.

Although different exercise training programmes have been safely used in various respiratory diseases, they should not be considered in COPD patients until optimal medical control of the disease has been achieved. The varying severity and complexity of different COPD phenotypes suggest that different options should be used for training respiratory and/

Component	Evidence for expected positive results
Exercise training	+++
Supplemental oxygen during exercise	++
Breathing low-density gas mixtures	+
Mechanically assisted ventilation	+
Nutritional supplementation and advice	++
Anabolic steroids	+
Education	+
'Breathing retraining' techniques	-
Respiratory muscle training	++
Neuromuscular electrical stimulation	++

**Table 2** – Components of pulmonary rehabilitation. +++: based on randomised clinical trials and meta-analyses; ++: encouraging results but further evidence is needed; +: indirect evidence; -: no improvement.

“50% of European respiratory units have access to a programme for patients with COPD, but only 30% of patients receive rehab”

or peripheral muscles; thus, although it is not possible to generalise, modalities such as interval training, supported exercise and neuromuscular electrical stimulation have been proposed, in order to include the most disabled individuals.

Recent studies have shown that, following acute COPD exacerbations requiring hospital admission, pulmonary rehabilitation is associated with clinically meaningful improvement in exercise tolerance. Deterioration in performance after the event may be prevented by peripheral muscle training during acute care.

### **Adjunctive strategies to exercise**

The effects of oxygen supplementation during exercise training are still being debated, although peripheral muscle function has been shown to deteriorate in COPD patients with long-term hypoxaemia. The results of oxygen supplementation during exercise training in patients with or without exercise hypoxaemia, in order to allow them to reach a higher exercise intensity, are also the subject of debate. The use of low-density gas mixtures to improve exercise performance in moderate-to-severe COPD patients is still under investigation.

There is experimental evidence that mechanically assisted ventilation may reduce breathlessness and increase exercise tolerance in COPD patients (allowing them to reach a higher exercise intensity), possibly by 'unloading' respiratory muscles and reducing 'air trapping' in the lungs – although the exact underlying pathophysiological mechanism remains unclear. In selected patients with severe chronic respiratory disease and suboptimal response to exercise, assisted ventilation may be considered as adjunctive therapy as it may allow for greater training intensity by unloading the respiratory muscles. However, delivering assisted ventilation during exercise is costly, very difficult and labour-intensive, and therefore should only be used in those who will particularly benefit from this therapy. Further studies are needed to further define its role in routine pulmonary rehabilitation.


### **Other interventions**

Supportive strategies, including nutritional supplementation and advice, and/or pharmacological agents (e.g. testosterone or anabolic drugs), can help improve functional outcome, especially in patients suffering from weight loss and muscle wasting. The contribution of education alone remains unclear.

A physiotherapy technique that was previously used as part of rehabilitation encouraged patients to coordinate the breathing process; this technique now receives less emphasis. The term 'breathing retraining' generally refers to such techniques, including pursed-lip and diaphragmatic breathing. Pursed-lip breathing is often used subconsciously by COPD patients to enhance exercise tolerance in the face of severe breathlessness and increased ventilatory demand. Pursed-lip breathing results in slower and deeper breaths with a shift in respiratory muscle recruitment from the diaphragm to the accessory muscles of breathing, leading to decreased breathlessness and improved oxygenation on exercise. Physiological studies of diaphragmatic breathing have failed to show any benefits.

Respiratory muscle training increases the strength and endurance of the respiratory muscles. However, the beneficial effect of respiratory muscle training on the exercise capacity and ADL of COPD patients is still an issue of debate. A recent meta-analysis showed that inspiratory muscle training improves muscle strength and endurance, functional exercise capacity, dyspnoea and HRQoL in COPD patients. Inspiratory muscle endurance training has been shown to be less effective than respiratory muscle strength training. Most guidelines still do not recommend this as a method of training.





Neuromuscular electrical stimulation is a possible therapy method for patients with severe chronic respiratory disease who are bed-bound or suffering from extreme skeletal muscle weakness.

### *What is needed?*

- Healthcare delivery systems should make conventional pulmonary rehabilitation available to all patients who are likely to benefit.
- Strategies for maintaining the benefits of pulmonary rehabilitation on a long-term basis are needed.
- Further research is required in order to optimise pulmonary rehabilitation. It should be tailored to the needs of the individual patient; the optimal schedule (intensity and duration of exercise training) should be defined; and the usefulness of other components beyond exercise should be clarified.
- More research is required in order to evaluate the benefits of pulmonary rehabilitation in respiratory diseases other than COPD.
- Telehealthcare in COPD seems to have an impact on the HRQoL of patients, reducing the frequency of hospital attendance. However, further research is needed to clarify its role as telehealthcare trials have included it as part of more complex packages.

### *Conclusion*

Pulmonary rehabilitation reduces breathlessness, increases exercise tolerance and improves HRQoL in patients with COPD and other chronic respiratory diseases. Patients should be carefully selected in order to make the best use of resources and extract the maximum benefits from rehabilitation. Although unresolved questions remain, pulmonary rehabilitation programmes should be included in the comprehensive treatment of patients with COPD and other chronic respiratory diseases.

### *Further reading*



#### **General**

- Casaburi R, ZuWallack R. Pulmonary rehabilitation for management of chronic obstructive pulmonary disease. *N Engl J Med* 2009; 360: 1329–1335.
- Marciniuk DD, Brooks D, Butcher S, *et al.* Optimizing pulmonary rehabilitation in chronic obstructive pulmonary disease – practical issues: a Canadian Thoracic Society Clinical Practice Guideline. *Can Respir J* 2010; 17: 159–168.

- Nici L, Donner C, Wouters E, *et al.* American Thoracic Society/European Respiratory Society Statement on Pulmonary Rehabilitation. *Am J Respir Crit Care Med* 2006; 173: 1390–1413.
- Pulmonary rehabilitation. *In: An international comparison of COPD care in Europe. Results of the first European audit.* Lausanne, European Respiratory Society, 2012; pp. 46–52.
- Ries AL, Bauldoff GS, Carlin BW, *et al.* Pulmonary rehabilitation. Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. *Chest* 2007; 131: Suppl. 5, 4S–42S.

### Location

- Clini E, Foglio K, Bianchi L, *et al.* In-hospital short-term training program in patients with chronic airway obstruction (CAO). *Chest* 2001; 120: 1500–1505.
- Maltais F, Bourbeau J, Shapiro S, *et al.* Effects of home-based pulmonary rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2008; 149: 869–878.

### Nutrition

- Ferreira IM, Brooks D, Lacasse Y, *et al.* Nutritional supplementation for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005; 2: CD000998.

### Respiratory muscle training

- Gosselink R, De Vos J, van den Heuvel SP, *et al.* Impact of inspiratory muscle training in patients with COPD: what is the evidence? *Eur Respir J* 2011; 32: 416–425.
- Vogiatzis I. Strategies of muscle training in very severe COPD patients. *Eur Respir J* 2011; 38: 971–975.

### Tele-assistance

- McLean S, Nurmatov U, Liu JL, *et al.* Telehealthcare for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2011; 6: CD007718.

### ICU physiotherapy

- Ambrosino N, Venturelli E, Vaghegini G, *et al.* Rehabilitation, weaning and physical therapy strategies in chronic critically ill patients. *Eur Respir J* 2012; 39: 487–492.
- Gosselink R, Bott J, Johnson M, *et al.* Physiotherapy for adult patients with critical illness: recommendations of the European Respiratory Society and European Society of Intensive Care Medicine Task Force on Physiotherapy for Critically Ill Patients. *Intensive Care Med* 2008; 34: 1188–1199.

### Acute COPD exacerbations

- Puhan MA, Gimeno-Santos E, Scharplatz M, *et al.* Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2011; 10: CD005305.

### Maintenance

- Spencer LM, Alison JA, McKeough ZJ. Maintaining benefits following pulmonary rehabilitation: a randomised controlled trial. *Eur Respir J* 2010; 35: 571–577.

### Outcomes

- Janaudis-Ferreira T, Beauchamp MK, Goldstein RS, *et al.* How should we measure arm exercise capacity in patients with COPD? A systematic review. *Chest* 2012; 141: 111–112.
- Lacasse Y, Goldstein R, Lasserson TJ, *et al.* Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006; 18: CD003793.

### New strategies

- Ambrosino N, Strambi S. New strategies to improve exercise tolerance in COPD. *Eur Respir J* 2004; 24: 313–322.
- Vivodtzev I, Debigaré R, Gagnon P, *et al.* Functional and muscular effects of neuromuscular electrical stimulation in patients with severe COPD: a randomized clinical trial. *Chest* 2012; 141: 716–725.