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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 ß-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 varencicline, 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 ß-sympathomimetic agonists, which mimic the action of the sympathetic nervous system by selectively stimulating the $ß_2$ 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 $ß_2$-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

$ß_2$-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_4 inhibitors (*e.g.* roflumilast) which have bronchodilator and anti-inflammatory effects in COPD and the PDE_5 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 $ß_2$-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)
β_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)
		Indicaterol	Onbrez (Novartis)
Antimuscarinic	Short	Ipratropium	Atrovent (Boehringer Ingelheim)
	Long	Tiotropium	Spiriva (Boehringer Ingelheim and Pfizer)
Corticosteroid		Beclomethasone	Becotide (GSK), Qvar (Teva), Clenil (Chiesi)
		Budesonide	Pulmicort (AstraZeneca)
		Fluticasone	Flixotide (GSK)
		Mometasone	Asmanex (Merck, Sharpe and Dohme)
		Ciclesonide	Alvesco (Takeda)
Compound preparations		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 ß-lactam (penicillin) family. However, combinations of antibiotics are used when pneumonia is more severe

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.

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

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 carbocisteine 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

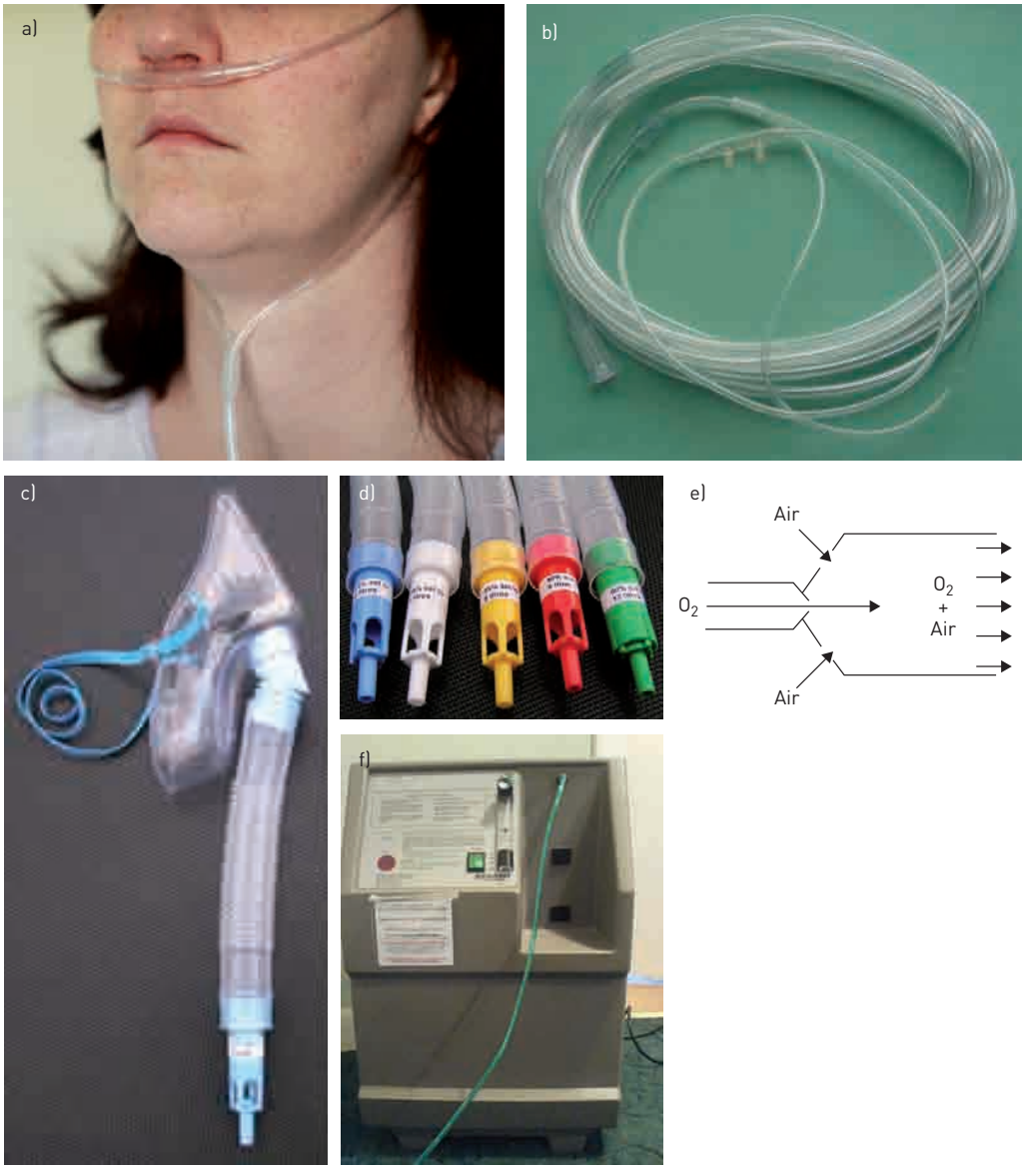

Figure 2 – Common modes of oxygen administration. a and b) Nasal cannulae ('prongs'), which allow control of oxygen flow rate but not inspired concentration. c–e) Venturi masks, which allow precise control of inspired oxygen concentration: the flow of oxygen through a nozzle entrains air *via* holes 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).

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

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

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

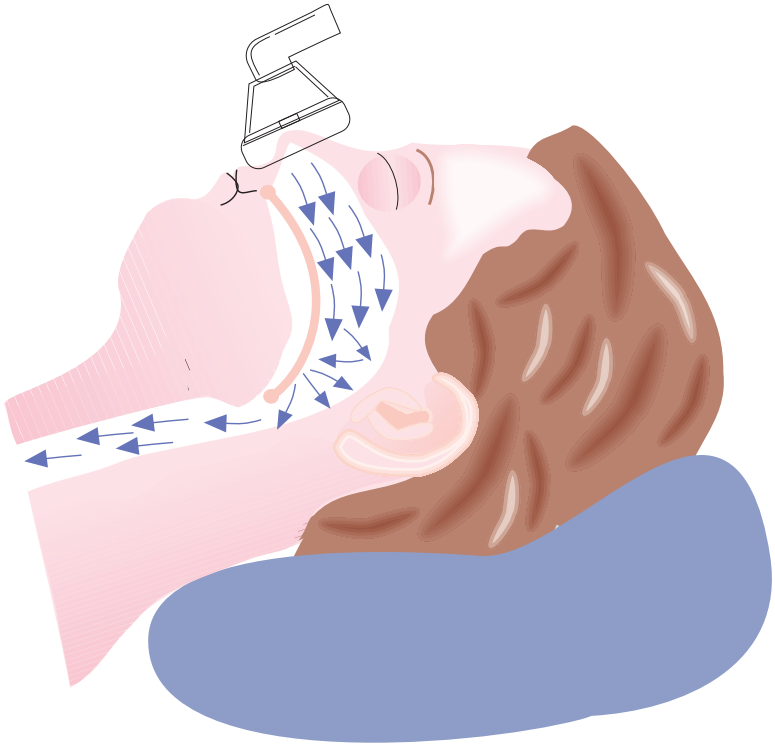

Figure 3 – Principle of continuous positive airway pressure (CPAP) for treating obstructive sleep apnoea syndrome: a modest pressure (*e.g.* 5–15 cm water) applied continuously at the nose and/or mouth during sleep supports the floppy pharyngeal airway (arrows), preventing it narrowing and closing during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

Further reading

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