

7. Disorders of the Lungs

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Introduction

A large number of lung disorders are covered in this chapter; they are grouped mainly according to the 'surgical sieve' approach, that is in categories reflecting the type of disorder (e.g. congenital) or underlying pathology (e.g. infection). The aim is to provide a clear structure for revision, allowing the disorders to be worked through in a logical fashion. However, this may make it difficult to see which are the common or important diseases. Therefore, set out below is a list of key disorders; this is necessarily brief but includes some of the diseases commonly seen in clinical practice plus others that illustrate an important pathological process.



The surgical sieve can be a tool for formulating a differential diagnosis, making sure that no possible cause has been forgotten. A number of mnemonics exist for the categories. One is: TIN CAN BED PAN. This is short for: **T**rauma **I**nflammatory **N**eoplastic **C**ongenital **A**rteriovenous **N**eurological **B**lood **E**ndocrine **D**rugs **P**sychogenic **A**llergic **N**ot known.

The key disorders

Asthma

- A chronic inflammatory disorder of the airways, characterized by symptoms that are intermittent and have a diurnal variation (p. 137).

Chronic obstructive pulmonary disease (COPD)

- Chronic bronchitis and emphysema in the same patient, who is almost always a smoker (p. 133).

Lung cancer

- Accounts for 20% of all cancers; the risk is directly related to tobacco exposure (p. 156).

Pneumonia

- An infection of peripheral lung tissue associated with significant morbidity and mortality worldwide (p. 126).

Pulmonary embolism

- The most serious complication of venous thrombosis; prophylaxis is important in high risk patients (p. 146).

Bronchiectasis

- Permanent dilatation of the bronchi secondary to chronic infection (p. 141).

Cystic fibrosis

- An autosomal recessive condition predisposing to chronic lung infection and bronchiectasis (p. 142).

Pneumothorax

- Air in the pleural space; the tension type is a medical emergency (p. 165).

Pleural effusion

- Fluid in the pleural space; a complication of several common lung disorders (p. 163).

Pulmonary fibrosis

- End point of many different lung diseases and an example of the basic pathology of restrictive disorders (p. 149).

Sarcoidosis

- A multisystem disorder; pulmonary features include bilateral hilar lymphadenopathy (p. 152).

Occupational lung diseases

Certain disorders with common themes are dealt with separately under the surgical sieve approach. One category that is important, and that you should consider as a whole, is that of occupational lung disorders. More details on this group of diseases is given in Chapter 9 (Fig. 9.1, p. 183).

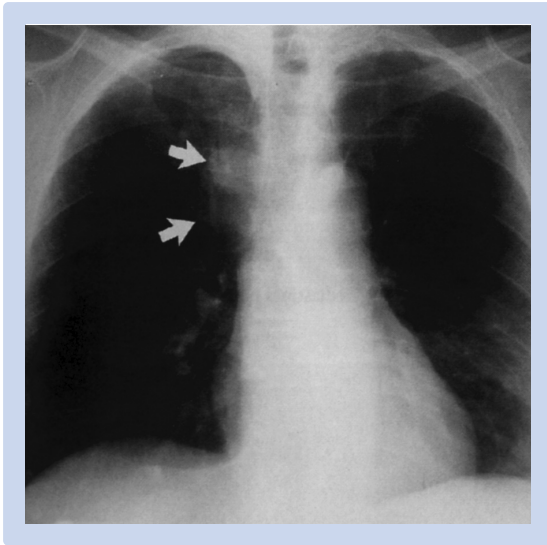


Fig. 7.1 Radiograph of a bronchogenic cyst. There is a right paratracheal mass (arrows). Courtesy of Dr D. Sutton and Dr J.W.R. Young.

Congenital abnormalities

Congenital cysts

The respiratory system is an outgrowth of the ventral wall of the foregut. Bronchogenic cysts may result from abnormal budding of the tracheobronchial tree. They are lined by bronchial elements: cartilage, smooth muscle and ciliated respiratory epithelium. Cysts are classified according to position:

- Central (mediastinal)—85%
- Peripheral (intrapulmonary)—15%.

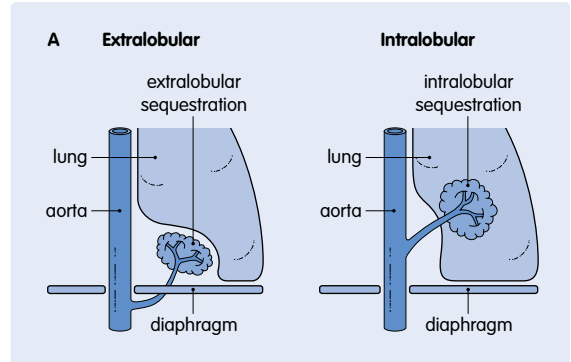
Cysts are usually single, spherical or oval, unilocular masses. They are mainly asymptomatic and can present at any age, although they are more common in men. Surgical excision is recommended. Radiologically, it is impossible to differentiate between a bronchogenic cyst and malignancy (Fig. 7.1).

Lobar sequestrations

Lobar sequestrations are masses of pulmonary tissue that do not communicate anatomically with the tracheobronchial tree (Fig. 7.2).

Vascular abnormalities

Vascular abnormalities include absent pulmonary artery trunk, absent unilateral pulmonary artery,



B Comparison between intralobular and extralobular sequestrations		
	Intralobular	Extralobular
incidence	more common	less common
male-to-female ratio	1 : 1	4 : 1
side of thorax	60% left	90% left
arterial supply	70% thoracic aorta	40% thoracic aorta
venous drainage	pulmonary veins	systemic
position	within normal lung and its pleural covering	separate from normal lung in its own pleural cover
other congenital defects	uncommon	frequent

Fig. 7.2 (A and B) Differences between extralobular and intralobular sequestrations.

pulmonary artery stenosis, pulmonary arteriovenous malformations, anomalous origin of the left pulmonary artery and anomalous pulmonary venous drainage.

Congenital lobar emphysema

Lobar emphysema is an overdistension of a lobe (usually an upper lobe) caused by intermittent bronchial obstruction. Symptoms in early life are caused by pressure effects. Pathogenesis includes defects in the bronchial cartilage, mechanical causes of bronchial obstruction and idiopathic causes. Prognosis is good.

Agnesis and hypoplasia

Agnesis

Agnesis is a complete absence of one or both lungs with no trace of bronchial or vascular supply.



Hypoplasia

In hypoplasia, the bronchus is fully formed, but reduced in size; there is failure of alveolar development. Hypoplasia is associated with other congenital abnormalities such as Potter's syndrome and diaphragmatic hernia.

Abnormalities of trachea or bronchi

Abnormalities of trachea or bronchi include tracheal agenesis, tracheo-oesophageal fistula, tracheal stenosis, tracheal narrowing caused by extrinsic pressure, tracheomalacia and tracheobronchomegaly.

Atelectasis

Atelectasis (from the Greek *ateles* imperfect + *ektasis* expansion) is classified as primary or secondary:

- Primary—lung fails to expand at birth
- Secondary—caused by obstruction or compression (Fig. 7.3).

Obstructive atelectasis

Obstruction is the commonest cause of atelectasis; this is also known as resorptive atelectasis (Fig. 7.4).

Obstructive atelectasis follows an acute and complete obstruction of a large bronchus. Air in the collapsed area of the lung is absorbed and secretions distal to the obstruction accumulate; subsequently, these bronchial secretions become infected and suppurate. Distal to the blockage, the bronchi mechanically distend.

If the collapse has been present for some time, irreversible pulmonary fibrosis occurs. Pulmonary artery branches may have narrowed lumens.

Compressive atelectasis

In compressive atelectasis, bronchial obstruction does not occur; therefore, bronchial secretions are free to drain up the bronchial tree. As such, the collapsed lung does not become seriously infected.

Compressive atelectasis results from external compression of the lung. Causes of compression include pleural effusion, haemothorax, empyema, pneumothorax, space-occupying intrathoracic lesion and abdominal distension.

Haemodynamic and vascular changes occur. High inflation pressures on inspiration are required to

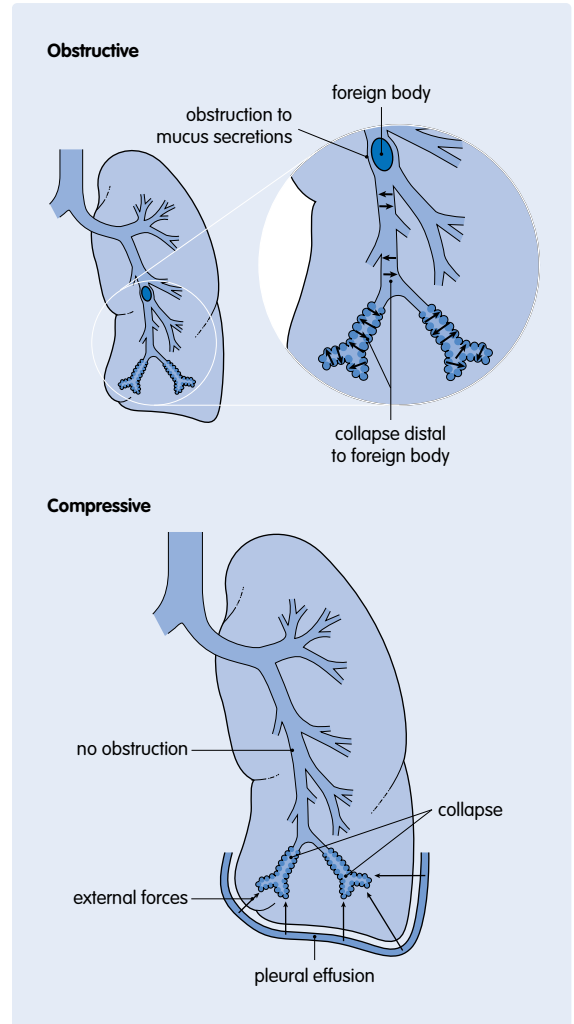


Fig. 7.3 Obstructive and compressive atelectasis.

Comparison of acute and chronic obstruction	
Acute	Chronic
inhalation and impaction of foreign bodies	tumours
mucus plugging of bronchi (e.g. after anaesthesia)	lymphadenopathy
after tracheostomy	aneurysm
lung infections	

Fig. 7.4 Causes of acute and chronic obstruction.



overcome retractive forces. Re-expansion of the lung usually occurs after compression is resolved.

Patchy atelectasis

Depending on the cause, atelectasis may occur in a patchy or diffuse distribution.

Infections of the lung

Pneumonia

Pneumonia is defined as an infection of peripheral lung parenchyma (as opposed to infection of the central conducting airways—bronchitis). Clinically, pneumonia is an acute illness in which there are signs of consolidation in the chest or new changes on chest X-ray. In the UK, pneumonia is responsible for approximately 60000 deaths a year.

Pneumonia can be classified on the basis of:

- The setting or circumstances in which it originated (community or hospital acquired or pneumonia in immunocompromised hosts)
- Anatomy (lobar or bronchopneumonia)
- Organisms (bacterial, atypical, viral, fungal, protozoal).

It is now common to use the first classification as this has more clinical significance (whilst the anatomical site is of limited use in guiding treatment and the organism may never be known).



The anatomical classification for pneumonia is not used here, but if you come across it elsewhere:

lobar pneumonia occurs when organisms widely colonize alveolar spaces, whereas bronchopneumonia occurs when organisms colonize bronchi and extend into alveoli.

Community acquired pneumonia (CAP)

Pathogenesis of CAP

Organisms enter the lungs usually having been inhaled from the environment or nasopharynx. These organisms may be eliminated by the lung's defence

mechanisms (see Chapter 3) or they may survive and multiply. Factors that undermine the lung's defences will therefore increase the risk of pneumonia. These factors include:

- Alcohol excess
- Cigarette smoking
- Chronic heart and lung diseases
- Bronchial obstruction
- Immunosuppression
- Drug abuse.

The pathogen stimulates host defences and alveolar airspaces become filled with eosinophilic oedematous fluid containing neutrophil polymorphs. The oedema transports organisms through the pores of Kohn into the alveoli.

In days 2–4, a red hepatization occurs; there is accumulation in alveolar spaces of polymorphs, lymphocytes and macrophages. The alveolar exudate contains a fine network of fibrin and large numbers of extravasated red cells. The lung is red, solid and airless. Red hepatization corresponds to an area of oedema and haemorrhage.

In days 4–8, a grey hepatization occurs. Fibrinous pleurisy is present. Alveolar spaces are microscopically distended and filled by a dense network of fibrin-containing neutrophil polymorphs. Grey hepatization represents a zone of advanced consolidation with destruction of red and white blood cells. The lung is grey or brown and solid.

Resolution occurs after 8–10 days in untreated cases. When bacteria have been eliminated, macrophages enter and replace granulocytes. The exudate is liquefied by fibrinolytic enzymes and coughed up or absorbed. There is preservation of the underlying alveolar wall architecture.

Aetiology

Figure 7.5 shows the key pathogens in CAP.

S. pneumoniae is the causative organism in 55–75% of cases. Note, however, that in around a third of cases, no cause is found.



Community acquired pneumonia is usually caused by Gram-positive bacteria, whereas hospital acquired pneumonias are mainly caused by Gram-negative bacteria.



Causes and features of community acquired pneumonia		
Organism	Features of pneumonia	% cases
<i>Streptococcus pneumoniae</i>	Gram +ve alpha-haemolytic; polysaccharide capsule determines virulence and is detectable serologically; responsible for a high mortality (especially in the setting of bacteraemia) unless treated appropriately; vaccine available	55–75
<i>Mycoplasma pneumoniae</i>	epidemics every 3–4 years usually in young patients; 50% have cold agglutinins; associated with many extrapulmonary manifestations; penicillin ineffective as no bacterial cell wall	5–18
<i>Influenza</i>	epidemics common; affects patients with underlying lung disease; can be severe; <i>S. aureus</i> , <i>S. pneumoniae</i> , <i>H. influenzae</i> occur secondarily; a vaccine is available	8
<i>Legionella pneumophila</i>	gram –ve; found in cooling towers and air-conditioning; causes very severe pneumonia with high mortality and is frequently associated with extrapulmonary features; antigen may help in diagnosis	2–5
<i>Chlamydia pneumoniae</i>	headache very common; usually serological diagnosis	2–5
<i>Haemophilus influenzae</i>	gram –ve rod; more commonly associated with exacerbations of COPD	4–5
Viruses other than influenza		2–8
<i>Staphylococcus aureus</i>	gram +ve coccus; often follows flu; alcoholics and patients with mitral valve disease are susceptible; often causes severe, often cavitating pneumonia; commonly fatal	1–5
<i>Klebsiella pneumoniae</i>	gram –ve; seen in alcoholics; severe and often cavitates	1

Fig. 7.5 Organisms causing community acquired pneumonia.

Clinical features

The common respiratory symptoms are shown in Fig. 7.6. Note that the presence of confusion is a poor prognostic factor (see below).

On examination the patient is typically pyrexial, tachycardic and tachypnoeic. Lung expansion is reduced and signs of consolidation are found (see Chapter 9). Coarse crackles may be heard as the infection resolves.



If you suspect pneumonia, ask about alcohol intake and comorbidities (especially chronic heart and lung disease and diabetes mellitus); foreign travel (i.e. risk of legionella) and upper respiratory tract infection are so common that positive answers are unlikely to narrow down the list of possible organisms.

Complications

The key complications are:

- Respiratory failure
- Parapneumonic effusions
- Empyema
- Lung abscess
- Pulmonary fibrosis, after resolution.

Investigations

- Sputum—culture and Gram stain
- Blood—full blood count, blood culture (low sensitivity, high specificity)
- Pleural fluid—culture and Gram stain
- Chest radiography
- Bronchoscopy with BAL if diagnosis uncertain
- Assessment of oxygenation
- Other specific tests—mycoplasma, legionella and chlamydia antibodies; pneumococcal antigen testing by counter-immunoelectrophoresis (CIE) of the sputum, urine and serum.



Typical clinical features of bacterial pneumonia	
Clinical feature	Incidence (%)
respiratory features	
cough	90
sputum	70
dyspnoea	70
chest pain	65
upper respiratory tract symptoms	33
haemoptysis	13
nonrespiratory features	
vomiting	20
confusion	15
diarrhoea	15
rash	5
abdominal pain	5
signs	
fever	80–90
tachypnoea	80–90
tachycardia	80–90
abnormal chest signs	80–90
hypotension	20
confusion	15
herpes labialis	10

Fig. 7.6 Typical clinical features of bacterial pneumonia.

Management

Antibiotic treatment should be started immediately, without waiting for microbiology results.

For most cases use:

- Combined oral treatment with amoxicillin and a macrolide (erythromycin or clarithromycin).

For severe cases, admit to hospital and start:

- IV combination of broad spectrum antibiotic or cephalosporin, together with a macrolide as above.

In addition, pleuritic pain should be relieved with simple analgesia and oxygen therapy administered if appropriate.

Prognosis

It is important to assess the severity of CAP as this impacts on prognosis and therefore treatment planning. British Thoracids Society guidelines state the key adverse prognostic features are:

- New mental confusion
- Urea >7mmol/L
- Respiratory rate ≥ 30 /min
- Systolic blood pressure <90mmHg or diastolic ≤ 60 mmHg.

Patients with two or more of these features are at high risk of mortality and should be managed aggressively.

Hospital acquired pneumonia

Hospital acquired or nosocomial pneumonia refers to a new lower respiratory tract infection at least two days after hospital admission. It occurs in 1–5% of admissions and is a serious cause of morbidity and mortality.

Aetiology

In addition to the risk factors discussed above, factors predisposing to hospital acquired infections are:

- Intubation
- Suppressed cough leading to aspiration (e.g. postoperatively)
- Reduced host defences
- Long stays in hospital, with associated exposure to pathogens.

Pathogens

Gram-negative bacteria (e.g. *Escherichia*, *Klebsiella* and *Pseudomonas*) are the cause of hospital acquired pneumonia in many cases, although *Staph. aureus* (particularly drug resistant strains) is also common.

Clinical features and investigations

These are similar to those described above under CAP.

Management

Good Gram-negative coverage is achieved with an aminoglycoside plus anti-pseudomonal penicillin or a third generation cephalosporin. Most hospital acquired pneumonia is serious and these drugs are frequently given intravenously.

Pneumonia in the immunocompromised

Pneumocystis carinii pneumonia

Pneumocystis carinii pneumonia (PCP) is a fungal infection that is largely confined to the lung. It is the commonest opportunistic infection in the immunocompromised.

Infection occurs by inhalation of the organism. The patient presents with an insidious or abrupt onset of dry cough, fever and dyspnoea.

Pleural effusions are rare.



Pathology

There is an interstitial infiltrate of mononuclear cells and alveolar airspaces are filled with foamy eosinophilic material.

Diagnosis

Bilateral pneumonia in an immunocompromised patient should raise suspicion of PCP.

Diagnosed in 90% of cases by staining using Giemsa, methanamine–silver, papanicocou, or Gram–Weigert stains with monoclonal antibodies.

Chest radiography shows diffuse bilateral alveolar and interstitial shadowing, beginning in peripheral regions and spreading in a butterfly pattern.

Treatment

High-dose co-trimoxazole is given, intravenously at first. Prophylaxis is recommended in patients with low CD4 counts or where previous infection has occurred.

Mortality of untreated patients is 100%; in treated patients, mortality is 20–50%.

Cytomegalovirus

Cytomegalovirus (CMV) is a DNA virus in the herpes group. Of patients with AIDS, 90% are infected with CMV. CMV also occurs in recipients of bone marrow and solid organ transplants. Only occasionally does CMV cause pneumonia.

Usual symptoms are a non-productive cough, dyspnoea and fever. Disseminated infection occurs, causing encephalitis, pneumonitis, retinitis and diffuse involvement of the gastrointestinal tract.

Pathology

Features in the pathology of CMV infection include:

- Interstitial inflammatory infiltrate of mononuclear cells
- Scattered alveolar hyaline membranes
- Protein-rich fluid in alveoli
- Intranuclear inclusion bodies found in alveolar epithelial cells.

Diagnosis

CMV infection can be diagnosed by the identification of characteristic intranuclear owl's eye inclusions in tissues and by direct immunofluorescence.

Treatment

Treatment is by ganciclovir 5mg/kg daily for 14–21 days.

Aspergillus

Four pulmonary diseases are caused by the fungus

Aspergillus fumigatus:

- Allergic aspergillosis
- Mucoid impaction
- Aspergilloma
- Invasive aspergillosis.

Invasive aspergillosis

Invasive aspergillosis occurs in immunocompromised individuals with severe neutropenia or T-lymphocyte deficiency. It is confined to the lungs and may present as a necrotizing pneumonia, lung abscess, or solitary granuloma. Microabscesses contain the characteristic fungal filaments.

Recovery may occur after vigorous treatment with intravenous amphotericin. Prognosis is generally poor.

Cryptococcus

Cryptococcus is a budding, yeast-like fungus that may disseminate to all organs. Pulmonary lesions commonly involve the lower lobes, are nodular, and may simulate carcinoma. Other pulmonary manifestations include:

- Cavitation within lung nodules
- Calcification
- Pneumonitis
- Pleural effusions
- Intrathoracic lymph node enlargement.

Meningeal involvement is the commonest form of cryptococcosis.

Varicella zoster

Varicella zoster is an uncommon cause of pneumonia. The associated pustular rash confirms diagnosis. Treatment is with aciclovir.

Kaposi's sarcoma

Kaposi's sarcoma is included here because may be a differential diagnosis in the immunocompromised host. It is a multifocal neoplastic condition typically seen in patients with AIDS. Lesions of the pleura, parenchyma, lymph nodes and airways occur. Overall prognosis is poor.

Lung abscess

Lung abscess is a localized area of infected parenchyma, with necrosis and suppuration.



Aetiology

A lung abscess may occur due to:

- Aspiration of infected material (e.g. in alcoholism, unconscious patients)
- Complications of pneumonia
- Infection of cavities in bronchiectasis or TB
- Bronchial obstructions (e.g. tumours or foreign body)
- Pulmonary infarction.

Clinical features

Onset may be acute or insidious, depending on the cause of the abscess. Acute symptoms include malaise, anorexia, fever and a productive cough. Copious foul-smelling sputum is present, caused by the growth of anaerobic organisms.

In large abscesses there may be dullness to percussion. Pallor is common, caused by anaemia. Clubbing is a late sign.

Complications

Abscesses can heal completely leaving a small fibrous scar. Complications include empyema, bronchopleural fistula, pyopneumothorax, pneumatoceles, haemorrhage caused by erosion of a bronchial or pulmonary artery, meningitis and cerebral abscess.

Investigations

- Investigations must exclude necrosis in a malignant tumour or cavitation caused by tuberculosis; bronchoscopy may be indicated to sample cells or exclude an obstruction. Chest radiography shows a walled cavity with fluid level
- Sputum culture may identify a causative organism
- Blood culture and full blood count show that the patient is often anaemic with high erythrocyte sedimentation rate. Patients usually have mild to moderate leucocytosis.

Treatment

Follow disease carefully with regular chest radiographs and sputum collections. Resolution of disease is prompt after institution of appropriate antibiotics. Postural drainage should be used. Surgery is not usually indicated.

Tuberculosis

Tuberculosis is the world's leading cause of death from a single infectious disease. It is a notifiable

disease and the prevalence is on the increase, primarily due to the arrival of the human immunodeficiency virus (HIV). In the UK, 6000 new cases occur per year, with the highest incidence among immigrants, who are 40 times more likely to develop the disease than the native Caucasian population. Their UK-born children are regarded as being at high risk and as such are immunized soon after birth. The discussion below deals only with pulmonary tuberculosis, and does not consider the extra-pulmonary effects.

The causative agent in most cases of tuberculosis is *Mycobacterium tuberculosis*. Patients with pre-existing lung disease or the immunosuppressed may also be infected by opportunistic mycobacteria. These are also known as atypical mycobacteria or non-tuberculous mycobacteria and include:

- *Mycobacterium kansasii*
- *Mycobacterium avium* complex (MAC).

Transmission and dissemination

Transmission is through the air or from direct contact. The pulmonary or bronchial focus ulcerates into an airway. A cough, sneeze or exhalation then discharges droplets of viable mycobacterium. The droplet nuclei are then inhaled by an uninfected person and can lodge anywhere in the lungs or airways. Initial infection usually occurs in childhood.

Primary tuberculosis

The initial lesion is usually solitary, 1–2 cm in diameter, and subpleural in the middle or upper zones of the lung. The focus of primary infection is called a Ghon complex. The primary infection has two components:

- The initial inflammatory reaction
- Resultant inflammation in lymph nodes draining the area.

Within 3–8 weeks, the process becomes a tubercle, a granulomatous form of inflammation. The granulomatous lesion commonly undergoes necrosis in a process called caseation and is surrounded by multinucleated giant cells and epithelioid cells (both derived from macrophage). The caseous tissue may liquefy, empty into an airway, and be transmitted to other parts of the lung. Lymphatic spread of mycobacterium occurs. The combination of tuberculous lymphadenitis and the Ghon complex is termed the primary complex.



In most cases, the primary foci will organize and form a fibrocalcific nodule in the lung with no clinical sequelae.

Secondary tuberculosis (postprimary tuberculosis)

Secondary tuberculosis results from reactivation of a primary infection or re-infection. Any form of immunocompromise may allow reactivation. The common sites are posterior or apical segments of the upper lobe or the superior segment of the lower lobe. Tubercle follicles develop and lesions enlarge by formation of new tubercles. Infection spreads by lymphatics and a delayed hypersensitivity reaction occurs.

In secondary tuberculosis, the lesions are often bilateral and usually cavitated. Most lesions are connected to fibrocalcific scars.

Progressive tuberculosis

Progressive tuberculosis may arise from a primary lesion or may be caused by reactivation of an incompletely healed primary lesion or re-infection. Tuberculosis progresses to widespread cavitation, pneumonitis and lung fibrosis. Early symptoms are seldom diagnostic.

Miliary tuberculosis

In miliary tuberculosis, an acute diffuse dissemination of tubercle bacilli occurs through the bloodstream. Numerous small granulomas form in many organs, with the highest numbers found in the lungs. These granulomas often contain numerous mycobacteria and are usually the result of a delay in diagnosis or commencement of treatment.

Miliary tuberculosis may be a consequence of either primary or secondary tuberculosis and is universally fatal without treatment.

The pathology of tuberculosis is shown in Fig. 7.7; complications are shown in Fig. 7.8.

Clinical features

Primary tuberculosis is usually asymptomatic but may cause a mild febrile illness, with or without erythema nodosum. If the illness follows the progressive course, other symptoms then appear either immediately or gradually over weeks or months. Symptoms range from tiredness, anorexia and malaise to bronchopneumonia with fever, cough, dyspnoea and respiratory distress. Sputum is purulent, mucoid or blood-stained.

A pleural effusion or pneumonia may be the presenting complaint; often the disease is discovered due to an abnormal chest radiograph in an asymptomatic patient.

Diagnosis

Chest radiographs show upper zone shadows and fibrosis. Sequential sputum samples are taken:

- Stain with Ziehl–Neelson stain for acid-fast and alcohol-fast bacilli
- Culture on Lowenstein–Jensen medium, which takes up to 8 weeks.

Bronchoscopy is useful if no sputum is available. Biopsies from pleura, lymph nodes and solid lesions within the lung may be necessary.

Prevention

BCG (bacille Calmette–Guérin) vaccination is a vaccine made from non-virulent tubercle bacilli. The BCG vaccination is offered to schoolchildren at 12–13 years in the UK and to newborns of high-risk groups (e.g. Asians). It is given to individuals who are tuberculin negative (Mantoux, Heaf or tuberculin test). A positive tuberculin test indicates prior infection and those testing positive are screened with a chest X-ray. A 0.1 mL intradermal dose of the vaccine (chosen dilution is usually 1:1000) is given to children and adults. Immunization decreases the risk of developing tuberculosis by up to 70%. Once an individual has been vaccinated, subsequent tuberculin tests are positive.

Treatment

Most patients are treated on an outpatient basis with combination therapy, involving four drugs: isoniazid, rifampicin, pyrazinamide and ethambutol.

Treatment lasts 6 months and is in two phases:

- Initial phase lasting 2 months (rifampicin, isoniazid, pyrazinamide plus streptomycin or ethambutol)
- Continuation phase lasting 4 months (isoniazid and rifampicin).

The fourth drug (streptomycin or ethambutol) may be omitted in the initial phase except in drug resistant strains. In adults the daily doses in the initial phase are: rifampicin 600mg (taken 30 min before breakfast), isoniazid 300mg, pyrazinamide 1.5–2.0g.

Patients should be regularly followed up because lack of compliance is a major reason for treatment

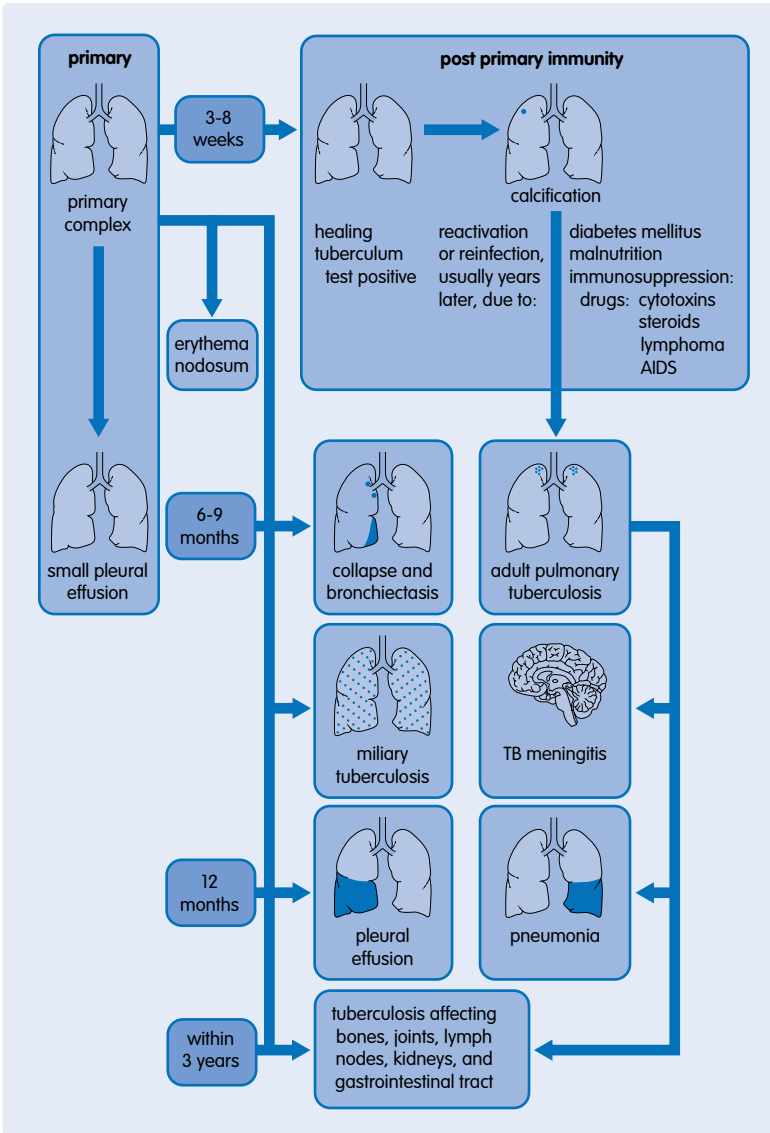


Fig. 7.7 Pathology of tuberculosis. Note the different routes from primary systems (via progression, reactivation or re-infection). (From *Clinical Medicine* 3e, by P. Kumar and M. Clark. Baillière Tindall, 1994.)

Early and late complications of tuberculosis	
Early	Late
pneumonia	bronchiectasis
empyema	mycetomas in cavities
haemoptysis	colonization of fibrotic lung with a non-tuberculous mycobacterium
laryngitis	extra-pulmonary disease
pneumothorax	

Fig. 7.8 Complications of tuberculosis.

failure. Drug toxicity is a problem in a minority of cases.

Disorders of the airways

Obstructive and restrictive defects

Obstructive defects

Airway obstruction and resultant airflow limitation may be caused by local or diffuse lesions; examples include asthma and COPD. Airways are widened distal to the diseased airway. Symptoms include coughing, wheezing and dyspnoea.



Pulmonary function tests show the following results:

- Increased residual volume and total lung capacity
- Reduced vital capacity, FEV_1 , peak expiratory flow rate and $FEV_1:FVC$ ratio.

Restrictive defects

Examples of defects that restrict normal lung movement during respiration include pulmonary fibrosis, pleural disease and consolidation. Patients' breathing is shallow and rapid.

Characteristically, all lung volumes are reduced. $FEV_1:FVC$ ratio is normal, but vital capacity is decreased.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a gradually progressive disease of the lungs involving airway obstruction. Unlike in asthma, the airway obstruction does not change over several months and is only partially reversible (e.g. with a bronchodilator). COPD is a very common disease and is a leading cause of death in the UK (30000 deaths per year). The disease is strongly associated with cigarette smoking.

Two disorders comprise COPD—chronic bronchitis and emphysema. Although by definition these are both present in a patient with COPD, they differ in pathology and site and are dealt with separately below. Clinical presentation varies widely, depending on which of the two diseases predominates; two clinical groups of patient can be identified, although these represent the two ends of a spectrum of illness and in practice most patients will fall between the two (Fig. 7.9).

Aetiology

Cigarette smoking is the major aetiological factor; all others are minor in comparison. Cigarette smoking has three major effects:

- Impairs ciliary movement
- Causes mucus gland hypertrophy
- Alters the structure and function of alveolar macrophages.

Atmospheric pollution, occupational exposure and recurrent bronchial infections are also implicated. Recurrent bronchial infections are frequent causes of acute exacerbations; their role in development rather than progression of the condition is less clear.

'Pink puffers' and 'blue bloaters'		
	Pink puffer	Blue bloater
body size	thin	obese
chest hyperinflation	marked	present
predominant disease	emphysema	chronic bronchitis
postmortem finding	panacinar emphysema	centrilobular emphysema
cor pulmonale	absent	present
secondary polycythaemia	absent	present
cyanosis	absent	centrally
blood gases	low P_aCO_2	raised P_aCO_2

Fig. 7.9 'Pink puffers' and 'blue bloaters'.

Genetic abnormalities play a small role in the aetiology of emphysema (see below) but a genetic component of COPD is likely since only 15% of smokers will develop the disease.

Diagnosis

A diagnosis of COPD is based on:

- History of chronic symptoms, without intervening periods when the patient is well
- Exposure to risk factors (primarily smoking)
- Evidence of airways obstruction (preferably using spirometry) that is not completely reversible.

Clinical features depend on the severity of the disease (Fig. 7.10) but can be summarized as:

- Productive cough
- Breathlessness, with or without wheeze
- Recurrent low-grade infective exacerbations.

Typical signs found on examination are shown in Chapter 9 (Fig. 9.42, p. 199).

Complications of COPD

Exacerbations

An acute worsening of the patient's condition is usually due to infection, which can be viral (e.g. influenza) or bacterial (commonly *H. influenzae*). A mild exacerbation may only require an increase in



Fig. 7.10 Clinical features and management of COPD. (Redrawn with permission from, Clinical Features and Management of COPD, *Thorax*; 52: suppl 5. British Thorax Society, 1997)

	Clinical features signs and symptoms	Improve function bronchodilator therapy
80% Lung Function (% Predicted)	Mild No abnormal signs 'Smokers cough'. Little or no breathlessness.	<ul style="list-style-type: none"> • Short acting β_2-agonist or inhaled anticholinergic as required depending upon symptomatic response
60%	Moderate Breathlessness (\pm wheeze) on moderate exertion. Cough (\pm sputum). Variable abnormal signs – general reduction in breath sounds, presence of wheezes.	<ul style="list-style-type: none"> • As for mild disease but regular therapy with either drug or a combination of the two may be needed. • Consider steroid trial
40% FEV ₁	Severe Breathlessness on any exertion/ at rest. Wheeze and cough often prominent. Lung overinflation usual; cyanosis, peripheral oedema, and polycythaemia in advanced disease, especially during exacerbations.	<ul style="list-style-type: none"> • Combination therapy with regular β_2-agonist and anticholinergic • Consider addition of other agents • Perform steroid trial • Assess for home nebuliser

medication at home. If the exacerbation is severe, the patient may deteriorate rapidly and require hospitalization.

Respiratory failure

In severe exacerbations the patient may be unable to maintain normal blood gases. This state is known as respiratory failure and is discussed in more detail elsewhere. Respiratory failure is the leading cause of death in patients with COPD and is often hypercapnic (type II).

Cor pulmonale

Mortality increases in those patients with COPD who develop cor pulmonale, or right ventricular enlargement secondary to disorders affecting the lungs. In COPD it is pulmonary hypertension that causes the right ventricle to hypertrophy and eventually fail. Further details are found under pulmonary hypertension below.

Investigations

Lung function tests show an obstructive pattern. Transfer factor/diffusing capacity is low (note that it is normal in asthma). Exercise testing assesses the extent of disability.

Chest radiography typically shows hyperinflation or flat hemidiaphragms, reduced peripheral vascular markings, and bullae. Alternatively, radiographs may appear normal.

Full blood counts may show secondary polycythaemia, but blood gas tests are often normal. α_1 Antitrypsin levels should be measured.

Treatment

The most important intervention is to encourage smoking cessation, thus reducing the rate of deterioration. Self-administration of inhaled drugs is the key to management of COPD: patients must be taught correct inhaler technique. Treatment options are summarized in Fig. 7.10 and include:



- Bronchodilators—combining drugs may be useful (N.B. anticholinergics are more effective than in asthma)
- Xanthines—e.g. theophylline (but remember narrow therapeutic window)
- Corticosteroids—only if there is a documented spirometric response or if FEV₁ is <50% of predicted or best. Combination therapies may again be more useful
- Antibiotics—shorten exacerbations and should always be given in acute episodes
- Vaccine—annual flu vaccine
- Long-term domiciliary oxygen therapy—if necessary, administer for 19 hours per day at a flow rate of 1–3L/min. Arterial oxygen saturation needs to be above 90%
- Surgery—may be indicated to remove emphysematous lung.

In addition, severe exacerbations may be treated by:

- Oxygen (24–28% by mask at 2L/min)
- Ventilatory support if pH < 7.6 and P_aCO₂ is rising (intubation or NIV).

Chronic bronchitis

Chronic bronchitis is defined clinically as a persistent cough with sputum production for at least 3 months of the year for 2 consecutive years.

Pathology

Hyperplasia and hypertrophy occur to the mucus-secreting glands found in the submucosa of the large cartilaginous airways. Mucous gland hypertrophy is expressed as gland–wall ratio or by the Reid index (normally, <0.4). Hyperplasia of the intraepithelial goblet cells occurs at the expense of ciliated cells in the lining epithelium. Regions of epithelium may undergo squamous metaplasia.

Small airways become obstructed by intraluminal mucus plugs, mucosal oedema, smooth muscle hypertrophy and peribronchial fibrosis. Secondary bacterial colonization of retained products occurs (Fig. 7.10).

The effect of these changes is to cause obstruction, increasing resistance to airflow. A mismatch in ventilation:perfusion occurs, impairing gas exchange.

Emphysema

Emphysema is a permanent enlargement of the air spaces distal to the terminal bronchiole accompanied by destruction of their walls. As alveolar walls are destroyed, bullae form which may rupture causing pneumothorax. Destruction of the parenchyma increases compliance of the lung and causes a mismatch in ventilation:perfusion.

Classification of emphysema is based on anatomical distribution (Fig. 7.11). The two main types are: centriacinar and panacinar.

Centriacinar (centrilobular) emphysema

This is the form of emphysema that is associated with chronic bronchitis in COPD ('blue bloater') (Fig. 7.9); it occurs predominantly in male smokers. As the name suggests, damage (i.e. septal destruction and dilatation) is limited to the centre of the acinus, around the terminal bronchiole. The upper lung lobes are affected more commonly than the lower lobes. Respiratory bronchiolitis is frequently present.

Panacinar (panlobular) emphysema

Panacinar (panlobular) emphysema is a characteristic lesion of α_1 antitrypsin deficiency. Loss of lung parenchyma, including pulmonary capillaries, occurs. The whole of the acinus is involved distal to the terminal bronchioles. Panacinar emphysema usually affects the lower lobes.

Enlarged air spaces may become cystic and form bullae. This form of emphysema is not usually associated with chronic bronchitis (Fig. 7.12C).

Irregular emphysema

Irregular emphysema is associated with scarring and damage affecting lung parenchyma, commonly found around old healed tuberculosis scars in the lung apices. Air trapping caused by fibrosis is thought to be the pathogenesis.

Irregular emphysema overlaps clinically with paraseptal emphysema (Fig. 7.12D).

Paraseptal (distal acinar) emphysema

In paraseptal (distal acinar) emphysema, alveolar wall destruction is restricted to the periphery of the acinus, with the upper lobes more frequently

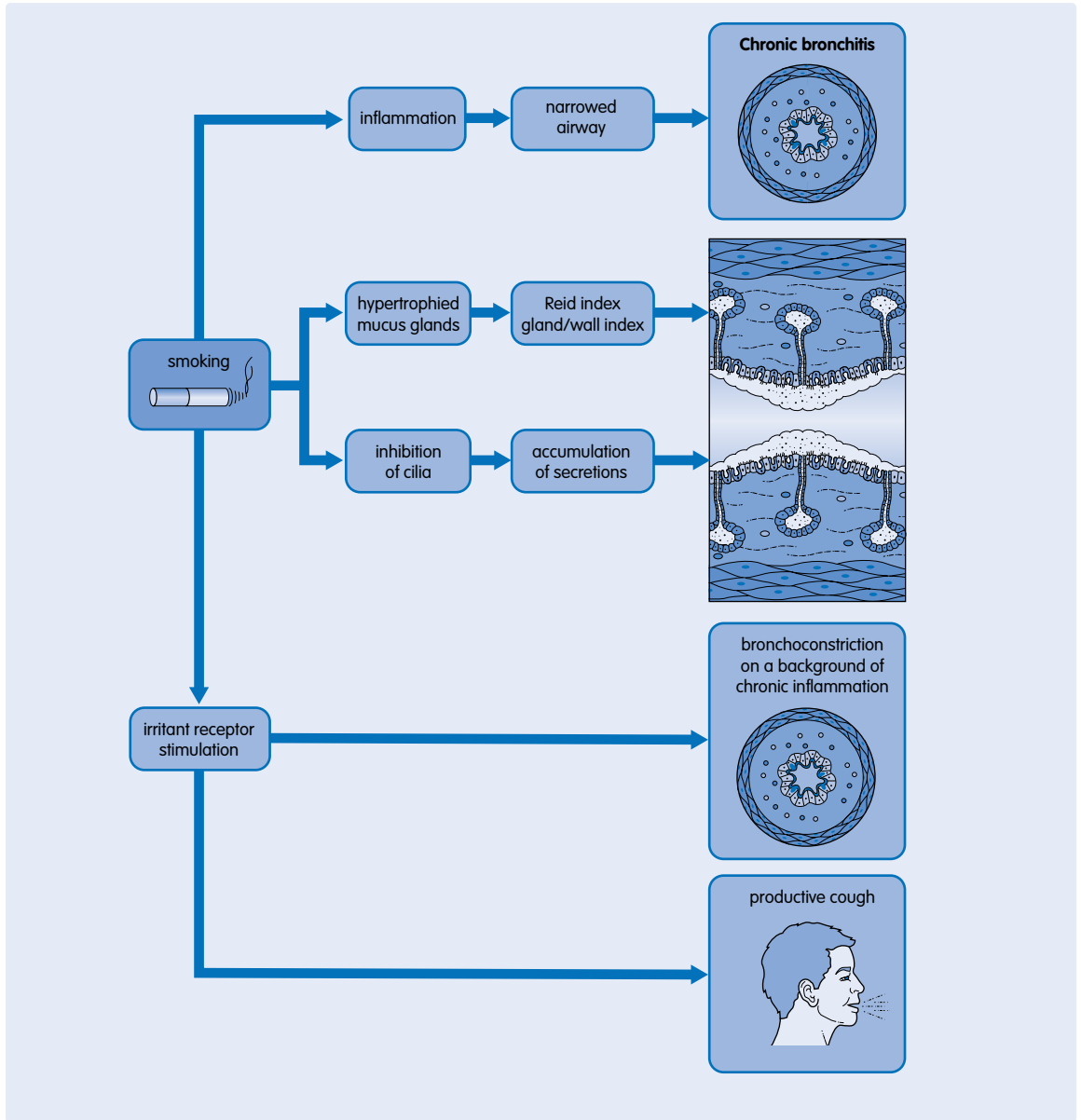


Fig. 7.11 Pathogenesis of chronic bronchitis.

affected. If dilated airspace measures more than 10mm in diameter, the condition is termed bullous (Fig. 7.12E).

α_1 Antitrypsin deficiency

α_1 Antitrypsin is an acute-phase serum protein produced in the liver, which functions as an antiprotease and inhibits the action of:

- Neutrophil elastase—an enzyme released during an inflammatory response, which is capable of destroying alveolar cell wall tissue
- Trypsin
- Collagenase.

In α_1 antitrypsin deficiency, serum levels of the enzyme are reduced. This is an autosomal dominant

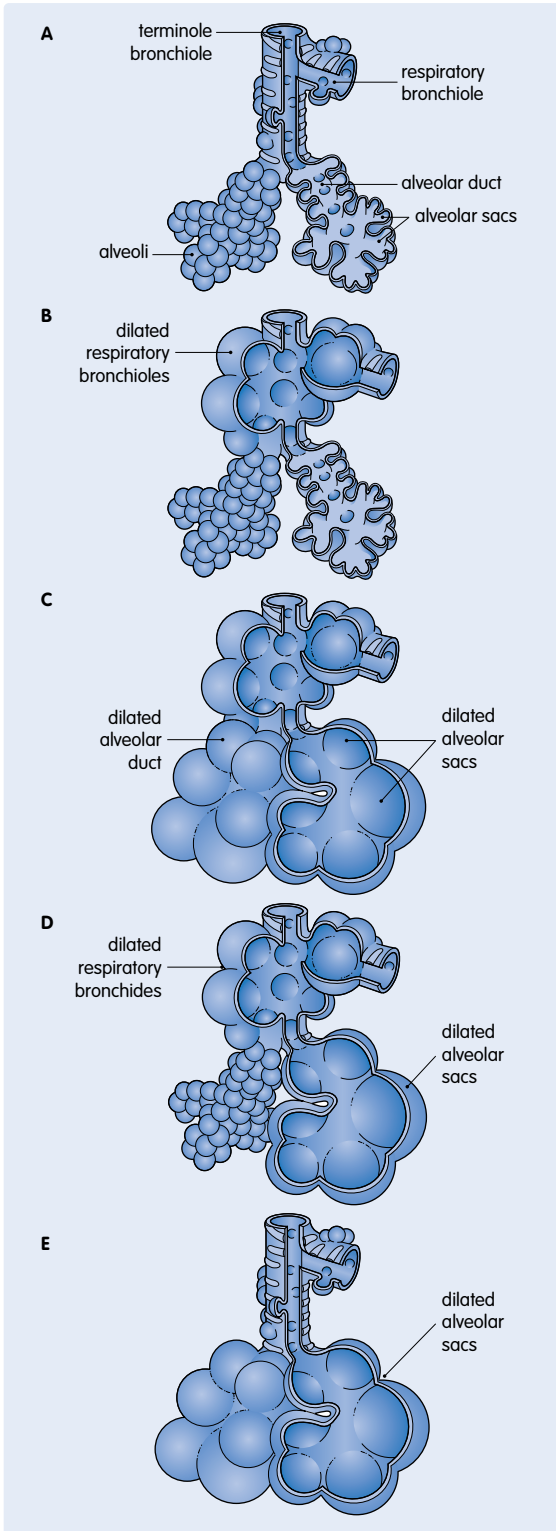


Fig. 7.12 Main types of emphysema. (A) Normal distal lung acinus; (B) centriacinar emphysema; (C) panacinar emphysema; (D) irregular emphysema; (E) paraseptal emphysema.

condition, where homozygous individuals develop severe panacinar emphysema.

α_1 Antitrypsin deficiency develops at an early age (before 40 years of age) with equal distribution between sexes. The homozygous state has an incidence of 1:3630 in Caucasians, but is rarer in dark-skinned people.

Asthma

Asthma is a chronic inflammatory disorder of the lungs characterized by variability in symptoms and lung function.

Prevalence

Five per cent of the adult population are receiving therapy for asthma at any one time. Prevalence of asthma in the Western world is rising, particularly in children; up to 20% have symptoms at some time in their childhood.

Classification

Bronchial asthma may be categorized into two groups on the basis of atopy: extrinsic or intrinsic (Fig. 7.13). Precipitating factors are described in Fig. 7.14.

Occupational asthma is increasing; currently there are over 200 materials encountered at the workplace that are implicated (Fig. 7.15). Occupational asthma may be classified as:

- Allergic (immunologically mediated with a latent period between exposure and symptoms)
- Non-allergic (immediate response after exposure, e.g. to toxic gases).



Take a full history, including occupational history. Do symptoms improve at the weekend or on holiday? If so, there may be an occupational cause.

Pathogenesis of asthma

Pathogenesis of asthma is very complex. Airway inflammation (Fig. 7.16) causes:

- Smooth muscle constriction
- Thickening of the airway wall (smooth muscle hypertrophy and oedema)
- Basement membrane thickening
- Mucus and exudate in the airway lumen.



Fig. 7.13 Classification of asthma.

Asthma		
	Extrinsic asthma	Intrinsic asthma
underlying abnormality	immune reaction (atopic)	abnormal autonomic regulation of airways
onset	childhood	adulthood
distribution	60%	40%
allergens	recognized	none identified
family history	present	absent
predisposition to form IgE antibodies	present	absent
association with chronic obstructive pulmonary disease	none	chronic bronchitis
natural progression	improves	worsens
eosinophilia	sputum and blood	sputum
drug hypersensitivity	absent	present

Precipitating factors for asthma					
Allergens	Occupational sensitizers	Viral infections	Atmospheric factors	Drugs	Other factors
house dust mite (<i>Dermatophagoides pteronyssius</i>)	colophony fumes (from soldering)	para influenza	cigarette smoke	β-blockers	cold air
flour	isocyanates (from polyurethane varnishes)	respiratory syncytial virus	ozone	nonsteroidal anti-inflammatory drugs	emotion
animal danders	acid anhydrides (from industrial coatings)	rhinovirus	sulphur dioxide		fumes
grain					exercise

Fig. 7.14 Precipitating factors for asthma.

Microscopically, the viscid mucus contains:

- Desquamated epithelial cells
- Whorls of shed epithelium (Curshmann’s whorls)
- Charcot Leyden crystal (eosinophil cell membranes)
- Infiltration of inflammatory cells, particularly CD4+ T lymphocytes.

Inflammatory mediators

Inflammatory mediators play a vital role in the pathogenesis of asthma. Inflammatory stimuli activate mast cells, epithelial cells, alveolar macrophages and dendritic cells resident within the airways, causing the release of mediators that are chemotactic for cells derived from the circulation—



Fig. 7.15 Factors implicated in occupational asthma. (Adapted from *Pulmonary Physiology* by G. Criner and G. D'Alonzo. Fence Creek Publishing, 1999, pp. 213 and 398.)

Factors implicated in occupational asthma	
Agents	Workers at risk include:
High-molecular weight agents	
cereals	bakers, millers
animal-derived allergens	animal handlers
enzymes	detergent users, pharmaceutical workers, bakers
gums	carpet makers, pharmaceutical workers
latex	health professionals
seafoods	seafood processors
Low-molecular weight agents	
isocyanates	spray painters, insulation installers etc.
wood dusts	forest workers, carpenters
anhydrides	users of plastics, epoxy resins
fluxes	electronic workers
chloramine	janitors, cleaners
acrylate	adhesive handlers
drugs	pharmaceutical workers, health professionals
metals	solderers, refiners

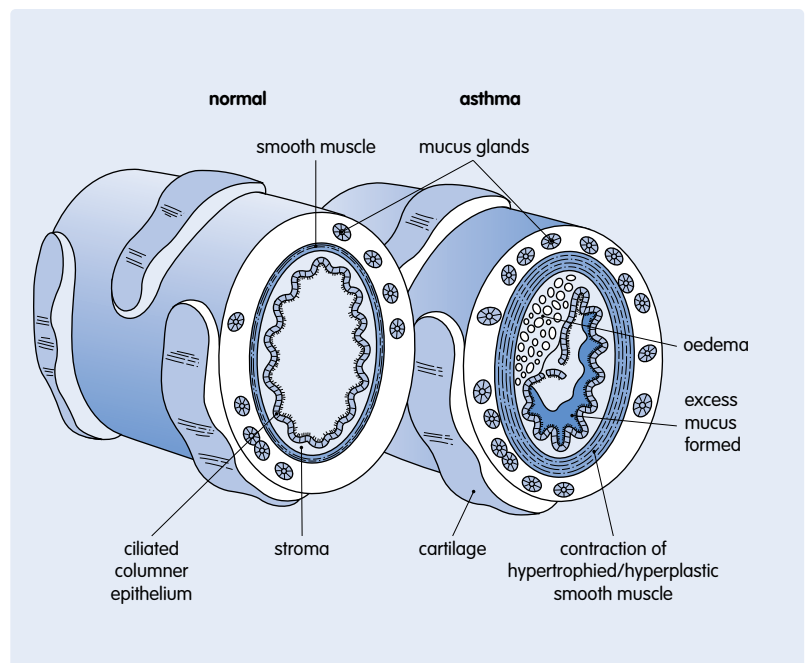


Fig. 7.16 Mechanisms of airway narrowing in asthma. (From *Pulmonary Physiology* by G. Criner and G. D'Alonzo. Fence Creek Publishing, 1999, p. 213.)



secondary effector cells (eosinophils, neutrophils and platelets).

Mediators that are thought to be involved in asthma include (Fig. 7.17):

- Preformed mediators—present in cytoplasmic granules ready for release. Associated with human lung mast cells and include histamine, neutral proteases and chemotactic factors for neutrophils and eosinophils
- Newly generated mediators—manufactured secondary to the initial triggering stimulus after release of preformed mediators. Some of these mediators are derived from the membrane phospholipid and are associated with the metabolism of arachidonic acid (e.g. prostaglandins and leukotrienes). The production of inflammatory cytokines and chemokines is important in the activation and recruitment of inflammatory cells.

Early and late responses

Two patterns of response can be considered; in practice most asthmatics show evidence of both responses, although either may be absent.

Immediate (early) reaction

The release of preformed mediators causes maximal airway narrowing within 10–15 minutes of challenge with a return to baseline within 1–2 hours.

Late reaction

The influx of inflammatory cells and release of inflammatory mediators causes airway narrowing after 3–4 hours and is maximal after 6–12 hours. This is much more difficult to reverse than the immediate reaction and there is an increase in level of airway hyperreactivity.

Clinical features

Symptoms (breathlessness, chest tightness, cough, wheeze) classically show a diurnal variation often being worse at night. For example, nocturnal coughing is a common presenting symptom, especially in children.

Clinical features vary according to the severity of asthma (classified from mild to severe and either intermittent or persistent). Acute severe asthma in adults is diagnosed if:

- Patient cannot complete sentences in one breath
- Respiration rate ≥ 25 breaths/min
- Pulse ≥ 110 beats/min
- PEFR $\leq 50\%$ of predicted or best.

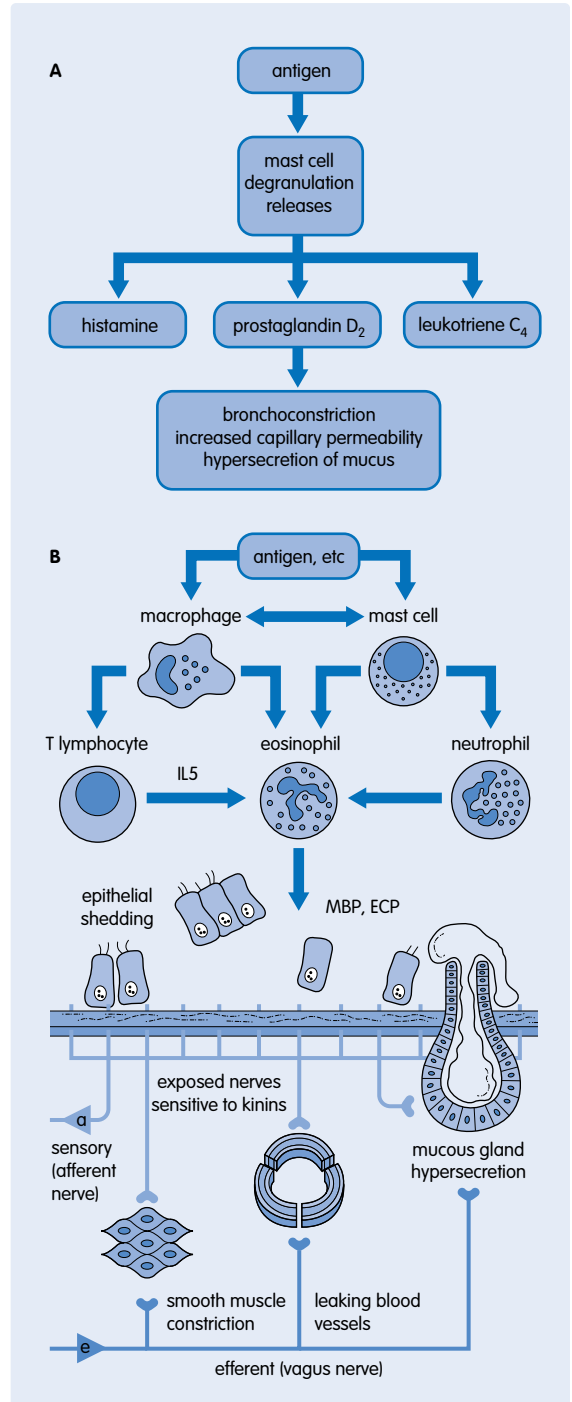


Fig. 7.17 Pathogenesis of asthma. (A) Preformed mediators; (B) newly generated mediators. IL5, interleukin 5; MBP, major basic protein; ECP, eosinophil cationic protein.



Life-threatening asthma is characterized by the following:

- PEFR < 33% of predicted or best
- Silent chest and cyanosis
- Bradycardia or hypotension
- Exhaustion, confusion or coma
- $P_aO_2 < 8\text{kPa}$.

Investigations

Investigations include:

- Lung function tests—FEV₁/FVC is reduced, RV may be increased; tests demonstrate an improvement in FEV₁ of more than 15% after bronchodilator administration
- Peak expiratory flow rate—morning and evening measurements. Useful in the long-term assessment of asthma; a characteristic morning dipping pattern is seen in poorly controlled asthma
- If PEFR < 50%, arterial blood gases should be tested
- Exercise laboratory tests
- Bronchial provocation tests—performed rarely in normal clinical practice, using histamine or methacholine to demonstrate bronchial hyperreactivity
- Chest radiography—no diagnostic features of asthma on chest radiograph; use to rule out a diagnosis of allergic bronchopulmonary aspergillosis
- Skin prick tests—allergen injections into the epidermis of the forearm, which are used to identify extrinsic causes. Look for weal development in sensitive patients.

Treatment

Identify and avoid extrinsic factors. Follow the British Thoracic Society (BTS) guidelines with a stepwise approach to drug treatment:

- Occasional use of short-acting bronchodilators
- Regular inhaled anti-inflammatory agents
- High-dose inhaled steroids or low-dose plus long-acting inhaled bronchodilator
- High-dose inhaled steroids and regular bronchodilators
- Addition of regular steroid tablets.

Drugs used in treating asthma are discussed in Chapter 6.

Bronchiectasis

Bronchiectasis is defined as an abnormal and permanent dilatation of the bronchi and is associated with chronic infection. Most cases arise in childhood.

Aetiology

Bronchiectasis can either be acquired or, less commonly, congenital.

Acquired bronchiectasis

Bronchiectasis is usually caused by a severe childhood infection (e.g. bronchopneumonia, measles or whooping cough). Inflammation can damage and weaken the bronchial wall, leading to dilatation. It may also be caused by bronchial obstruction (e.g. by a foreign body, tuberculous lymph nodes or tumour) followed by infection in the lung distal to the obstruction.

Congenital bronchiectasis

Congenital abnormalities that interfere with ciliary function (e.g. primary ciliary dyskinesia, Kartagener's syndrome and Young's syndrome) impair the transport of mucus and cause recurrent infection. Kartagener's syndrome, which is a rare cause, is also associated with dextrocardia and sinusitis. The viscous mucus and recurrent infections of cystic fibrosis may also lead to bronchiectasis. Recurrent infections are also a feature of immunoglobulin deficiencies (e.g. IgA); therefore these are also associated with bronchiectasis.

Pathology

Infection leads to obstruction, dilation of bronchi and often loss of cilia. Destruction of the alveolar walls and fibrosis of lung parenchyma occur and pulmonary haemodynamic changes can take place. The dependent portions of the lungs, usually the lower lobes, are affected most commonly.

Symptoms

Cough is the most common symptom; this is often persistent and accompanied by sputum which may be mucopurulent or copious, purulent and foul-smelling. Systemic features of infection such as fever and malaise also occur.

Haemoptysis may be present and can be massive. Clubbing occurs and coarse inspiratory crackles are heard on auscultation.



Complications

Complications of bronchiectasis include:

- Pneumonia
- Pneumothorax
- Empyema
- Meningitis
- Metastatic abscess (e.g. in brain)
- Amyloid formation (e.g. in kidney).

Investigations

Bronchiectasis can be investigated through:

- Radiology—chest radiograph may be normal or show bronchial wall thickening. If disease is advanced, cystic spaces may be seen
- High-resolution CT—the investigation of choice to detect bronchial wall thickening
- Sputum tests—Gram stain, anaerobic and aerobic culture, and sensitivity testing are vital during an infective exacerbation. Major pathogens include *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Haemophilus influenzae* and anaerobes
- Tests for cystic fibrosis where appropriate (cystic fibrosis sweat test)
- Lung function spirometry (may show an obstructive pattern).

Treatment

Aims of treatment are twofold:

- Control of infection
- Removal of secretions.

Infections should be eradicated with antibiotics if progression of the disease is to be halted. Treatment regimens depend on infecting organism (e.g. flucloxacillin 500mg 6-hourly to treat *Staphylococcus aureus* infection). If there is no improvement with treatment, the patient is likely to be infected with *Pseudomonas aeruginosa*: treat with ceftazidime aerosol or parenterally. Secretions are removed by postural drainage for 10–20 minutes, three times a day. Patients are trained in the method by physiotherapists.

Bronchodilators are useful if demonstrable airflow limitation exists. Surgery is of limited value but may be indicated in a young patient with adequate lung function, if disease is localized to one lung or segment.

Cystic fibrosis

Cystic fibrosis is a disorder characterized by the production of abnormally viscid secretions by

exocrine glands and mucus-secreting glands, such as those in the pancreas and respiratory tract. Impaired mucociliary clearance in the airways leads to recurrent infections and bronchiectasis.

Cystic fibrosis is the commonest genetically transmitted disease in Caucasians. It is an autosomal recessive condition occurring in 1:2000 live births. The gene has been identified on the long arm of chromosome 7. Prevalence of heterozygous carriers is 4%.

Aetiology

The commonest mutation is a specific gene deletion in the codon for phenylalanine at position 508 in the amino-acid sequence ($\Delta F508$). This results in a defect in a transmembrane regulator protein known as the cystic fibrosis transmembrane conductive regulator (CFTR). Mutation causes a failure of opening of the chloride channels in response to elevated cAMP in epithelial cells, leading to:

- Decreased excretion of chloride into the airway lumen
- Increased reabsorption of sodium into the epithelial cells
- Increased viscosity of secretions.

Pathology

The thick secretions produced by the epithelial cells cause:

- Small airway obstruction, leading to recurrent infection and ultimately bronchiectasis
- Pancreatic duct obstruction, causing pancreatic fibrosis and ultimately pancreatic insufficiency.

Clinical features

Presentation depends on age. Usually, the condition presents in infancy with gastrointestinal manifestations (Fig. 7.18).

Cystic fibrosis	
Respiratory manifestations	Gastrointestinal manifestations
recurrent bronchopulmonary infection bronchiectasis	meconium ileus rectal prolapse diarrhoea failure to thrive malabsorption

Fig. 7.18 Manifestations of cystic fibrosis.



Complications of cystic fibrosis	
Respiratory complications	Other complications
allergic aspergillosis bronchiectasis cor pulmonale haemoptysis lobar collapse nasal polyps pneumothorax sinusitis wheezing	abdominal pain biliary cirrhosis delayed puberty diabetes mellitus gall stones growth failure male infertility portal hypertension rectal prolapse

Fig. 7.19 Complications of cystic fibrosis.

Summary of treatment	
Respiratory	Gastrointestinal
drain secretions, postural drainage	pancreatic enzyme supplements with all meals and snacks
prevent infection where possible	high-energy, high-protein diet
exercise encouraged	do not restrict fat in diet
regular sputum cultures	vitamin A, D, and E supplements
immunization against measles and influenza	

Fig. 7.20 Summary of treatment cystic fibrosis.

Stools are bulky, greasy, and offensive in smell. Respiratory signs are normal and symptoms are non-specific:

- Lungs are normal at birth
- Frequent infections with cough and wheeze as the child gets older
- Clubbing and dyspnoea occur.

Almost all men with cystic fibrosis are infertile; females may be subfertile.

Investigations

Family history is sought (e.g. affected siblings). Genetic screening is available for couples with a family history.

Prenatal diagnosis is available by chorionic villous sampling or amniocentesis.

Tests include:

- Guthrie test
- Immunoreactive trypsin test (IRT)—positive test shows low levels
- Sweat test—raised levels of sodium and chloride in sweat.

The complications of cystic fibrosis are described in Fig. 7.19.

Treatment

Treatment (Fig. 7.20) is based on:

- Physiotherapy
- Antibiotics (see below)
- DNase (see below)
- Anti-inflammatory drugs (steroids)
- Nutritional support.

IV antibiotics may be given at home (e.g. through implantable venous access devices) to reduce hospital admissions and improve patient independence.

Human DNase has been cloned, sequenced and expressed by recombinant techniques. This is:

- Capable of degrading DNA
- Shown to improve FEV₁
- Expensive.

Heart–lung and liver transplantations are possible in severely affected patients.

Prognosis

Prognosis is improving: currently, mean survival is 29 years. Death is mainly caused by respiratory complications.

Disorders of the pulmonary vessels

Pulmonary congestion and oedema

Pulmonary oedema is defined as an abnormal increase in the amount of interstitial fluid in the lung.

The two main causes are:

- Increased venous hydrostatic pressures
- Injury to alveolar capillary walls or vessels, leading to increased permeability.

Less common causes are blockage of lymphatic drainage and lowered plasma oncotic pressure.



High-pressure pulmonary oedema

High-pressure or haemodynamic pulmonary oedema is cardiogenic; it may occur acutely as a result of a myocardial infarction or chronically in aortic and mitral valve disease.

Fluid movement between intravascular and extravascular compartments is governed by Starling forces (see Fig. 5.11, p. 80). Net fluid flow through a capillary wall (out of the blood) is governed by:

- Hydrostatic pressure (arterial blood pressure) at the arteriole end of the capillary bed
- Capillary permeability
- Opposing oncotic pressure exerted by serum proteins (mainly albumin); interstitial oncotic pressure may also contribute to the outflow.

Reabsorption of interstitial fluid is governed by:

- Plasma oncotic pressure (pulling pressure)
- Hydrostatic pressure in the interstitial space (tissue pressure)
- Fall in hydrostatic pressure at venous end of capillary.

Imbalances in Starling forces and a reduced plasma oncotic pressure will cause expansion of the interstitial spaces.

No pathological conditions cause a local reduction of plasma protein concentration within the lung capillaries. However, many conditions (e.g. left ventricular failure) cause an elevation of hydrostatic pressure. If left arterial pressure rises, so do pulmonary venous and capillary pressures, thereby raising hydrostatic pressure and causing oedema formation. Pulmonary oedema occurs only after the lymphatic drainage capacity has been exceeded. Lymphatic drainage can increase 10-fold without oedema formation. However, if lymphatic drainage is blocked (e.g. in cancer), oedema occurs more readily.

Oedema due to haemodynamic causes has a low protein content.

Oedema caused by microvascular injury

This is the non-cardiogenic form of pulmonary oedema.

Capillary blood is separated from alveolar air by three anatomical layers:

- Capillary endothelium
- Narrow interstitial layer
- Alveolar epithelium.

Damage to capillary endothelium

Normal alveolar capillary endothelial cells are joined by tight junctions containing narrow constrictions. Many conditions can damage the pulmonary capillary endothelium, resulting in movement of fluid and a transcapillary leak of proteins. Interstitial oncotic pressure rises; thus, a natural defence against oedema formation is disabled.

After damage, fibrinogen enters and coagulates within the interstitium. Interstitial fibrosis subsequently occurs, leading to impaired lymphatic drainage. Oedema caused by microvascular damage characteristically has a high protein content.

Progression of pulmonary oedema

Fluid first accumulates in loose connective tissue around the bronchi and large vessels. Fluid then distends the thick, collagen-containing portions of the alveolar wall. The final stage of pulmonary oedema is accumulation of fluid within the alveolar spaces. If pulmonary oedema is chronic, recurrent alveolar haemorrhages lead to the accumulation of haemosiderin-laden macrophages along with interstitial fibrosis.

Clinical features

Clinical features of oedema are as follows:

- Acute breathlessness
- Wheezing
- Anxiety
- Tachypnoea
- Profuse perspiration
- Production of pink sputum while coughing
- Peripheral circulatory shutdown
- Tachycardia
- Basal crackles and wheezes heard on auscultation
- Respiratory impairment with hypoxaemia
- Overloaded lungs predispose to secondary infection.

Treatment

The patient should be placed in a sitting position and 60% O₂ administered. Intravenous diuretics give an immediate and delayed response. Morphine sedates the patient and causes systemic vasodilatation: if systemic arterial pressure falls below 90 mmHg do not use morphine. Aminophylline can be infused over 10 minutes, but should be used only when bronchospasm is present.

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