pneumonia in immunocompetent individuals, but in patients with more profound immunosuppression less common organisms, or those normally considered to be of low virulence or non-pathogenic, may become 'opportunistic' pathogens. Depending on the clinical context, clinicians should consider the possibility of Gram-negative bacteria, especially *P. aeruginosa*, viruses, fungi, mycobacteria, and less common organisms such as *Nocardia* spp. Infection is often due to more than one organism.

Clinical features

These typically include fever, cough and breathlessness but are influenced by the degree of immunosuppression, and the presentation may be less specific in the more profoundly immunosuppressed. The onset of symptoms tends to be swift in those with a bacterial infection but more gradual in patients with opportunistic organisms such as *Pneumocystis jirovecii* and mycobacterial infections. In *P. jirovecii* pneumonia, symptoms of cough and breathlessness can be present several days or weeks before the onset of systemic symptoms or the appearance of radiographic abnormality. The clinical features of invasive pulmonary aspergillosis are dealt with on p. 525.

Investigations

The approach is informed by the clinical context and severity of the illness. Invasive investigations, such as bronchoscopy, BAL, transbronchial biopsy or surgical lung biopsy, are often impractical, as many patients are too ill to undergo these safely; however, 'induced sputum' (p. 487) offers a relatively safe method of obtaining microbiological samples. HRCT can be helpful:

- focal unilateral airspace opacification favours bacterial infection, mycobacteria or *Nocardia*
- bilateral opacification favours *P. jirovecii* pneumonia, fungi, viruses and unusual bacteria, e.g. *Nocardia*
- cavitation may be seen with *N. asteroides*, mycobacteria and fungi
- the presence of a 'halo sign' (a zone of intermediate attenuation between the nodule and the lung parenchyma) may suggest aspergillosis or other invasive fungal infection
- pleural effusions suggest pyogenic bacterial infections and are uncommon in *P. jirovecii* pneumonia.

ß-1,3-D-glucan levels are characteristically elevated in *P. jirovecii* pneumonia.

Management

In theory, treatment should be based on an established aetiological diagnosis; in practice, however, the causative agent is frequently unknown. Factors that favour a bacterial aetiology include neutropenia, rapid onset and deterioration. In these circumstances, broad-spectrum antibiotic therapy should be commenced immediately, e.g. a third-generation cephalosporin, or a quinolone, plus an antistaphylococcal antibiotic, or an antipseudomonal penicillin plus an aminoglycoside. Thereafter, treatment may be tailored according to the results of investigations and the clinical response. Depending on the clinical context and response to treatment, antifungal or antiviral therapies may be added. The management of *P. jirovecii* infection is detailed on page 361 and that of invasive aspergillosis on page 527.

Tuberculosis

Epidemiology

Tuberculosis (TB) is caused by infection with *Mycobacterium tuberculosis* (MTB), which is part of a complex of organisms including *M. bovis* (reservoir cattle) and *M. africanum* (reservoir humans). The resurgence in TB in the UK observed over the latter part of the 20th century has been reversed. Following a 44% drop between 2011 and 2018, the number of new cases of TB in England has dropped to the lowest levels since records began in 1960. Nevertheless, its impact on world health remains significant. An estimated 10 million new cases were recorded in 2018, with the majority of these presenting in the world's poorest nations, which struggle to cover the costs associated with management and control programmes (Fig. 17.34). In the same year, 1.5 million men, women and children died of TB, compared to 1 million of HIV/AIDS, making TB the worldwide leading cause of death from a single infectious agent that year.

Pathology and pathogenesis

M. tuberculosis is spread by the inhalation of aerosolised droplet nuclei from other infected patients. Once inhaled, the organisms lodge in the alveoli and initiate the recruitment of macrophages and lymphocytes. Macrophages undergo transformation into epithelioid and Langhans cells, which aggregate with the lymphocytes to form the classical tuberculous granuloma (Fig. 17.35). Numerous granulomas aggregate to form a primary lesion or 'Ghon focus' (a pale yellow, caseous nodule, usually a few millimetres to 1–2 cm in diameter), which is characteristically situated in the periphery of the lung. Spread of organisms to the hilar lymph nodes is followed by a similar pathological reaction, and the combination of the primary lesion and regional lymph nodes is referred to as the 'primary complex of Ranke'. Reparative processes encase the primary complex in a fibrous capsule, limiting the spread of bacilli. If no further complications ensue, this lesion eventually calcifies and is clearly seen on a chest X-ray. Lymphatic or haematogenous spread may occur before containment is established, however, seeding secondary foci in other organs, including lymph nodes, serous membranes, meninges, bones, liver, kidneys and lungs, which may lie dormant for years. The only clue that infection is

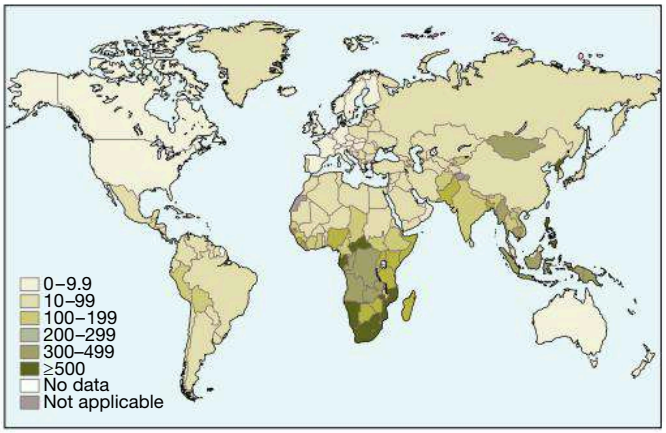


Fig. 17.34 Worldwide incidence of tuberculosis (2019). Estimated new cases (all forms) per 100 000 population. *From Global tuberculosis report 2020. Geneva: World Health Organization; 2020.*

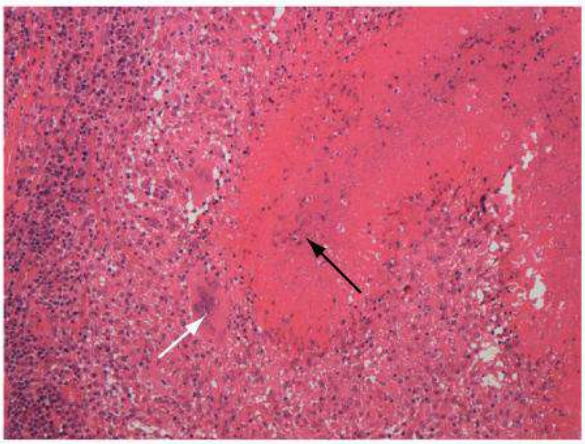


Fig. 17.35 Tuberculous granuloma. Normal lung tissue is lost and replaced by a mass of fibrous tissue with granulomatous inflammation characterised by large numbers of macrophages and multinucleate giant cells (white arrow). The central area of this focus shows caseous degeneration (black arrow). *Courtesy of Dr William Wallace, Department of Pathology, Royal Infirmary of Edinburgh.*

present may be the appearance of a cell-mediated, delayed-type hypersensitivity reaction to tuberculin, demonstrated by tuberculin skin testing or an interferon-gamma release assay (IGRA): so-called latent TB infection (LTBI). If these controlling processes fail, primary progressive disease ensues (Fig. 17.36). The estimated lifetime risk of developing active disease after infection is 10%, with roughly half of this risk occurring in the first 2 years after infection. Factors predisposing to TB are summarised in Box 17.46 and the natural history of infection with TB is summarised in Box 17.47.

Clinical features: pulmonary disease

Primary pulmonary TB

Primary TB refers to the infection of a previously uninfected (tuberculin-negative) individual. A few patients develop a self-limiting febrile illness but clinical disease occurs only if there is a hypersensitivity reaction or progressive infection (Box 17.48). Progressive primary disease may appear during the course of the initial illness or after a latent period of weeks or months.

Miliary TB

Blood-borne dissemination gives rise to miliary TB, which may present acutely but more frequently is characterised by 2–3 weeks of fever, night sweats, anorexia, weight loss and a dry cough. Hepatosplenomegaly may develop and the presence of a headache may indicate coexistent tuberculous meningitis. Auscultation of the chest is frequently normal but in more advanced disease widespread crackles are evident. Fundoscopy may show choroidal tubercles. The classical appearances on chest X-ray are of fine 1–2 mm lesions ('millet seed') distributed throughout the lung fields, although occasionally the appearances are coarser. Anaemia and leucopenia reflect bone marrow involvement.

Post-primary pulmonary TB

Post-primary disease refers to exogenous ('new' infection) or endogenous (reactivation of a dormant primary lesion) infection in a person who has been sensitised by earlier exposure. It is most frequently pulmonary and characteristically occurs in the apex of an upper lobe, where the oxygen tension favours survival of the strictly aerobic organism. The onset is usually insidious, developing slowly over several weeks. Systemic symptoms include fever, night sweats, malaise and loss of appetite and weight, and are accompanied by progressive pulmonary symptoms (Box 17.49). Radiological changes include ill-defined opacification in one or both of the upper lobes, and as progression occurs, consolidation, collapse and cavitation develop to varying degrees (Fig. 17.37). It is often difficult to distinguish active from quiescent disease on radiological criteria alone but the presence of a miliary pattern or cavitation favours active disease. In extensive disease, collapse may be marked and results in significant displacement of the trachea and mediastinum. Occasionally, a caseous lymph node may drain into an adjoining bronchus, leading to tuberculous pneumonia.

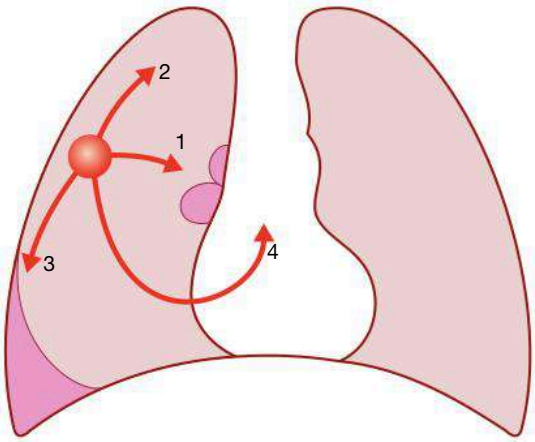


Fig. 17.36 Primary pulmonary tuberculosis. (1) Spread from the primary focus to hilar and mediastinal lymph glands to form the 'primary complex', which heals spontaneously in most cases. (2) Direct extension of the primary focus – progressive pulmonary tuberculosis. (3) Spread to the pleura – tuberculous pleurisy and pleural effusion. (4) Blood-borne spread: *few bacilli* – pulmonary, skeletal, renal, genitourinary infection, often months or years later; *massive spread* – miliary pulmonary tuberculosis and meningitis.

Clinical features: extrapulmonary disease

Extrapulmonary TB accounts for 20% of cases in those who are HIV-negative but is more common in HIV-positive patients.

Lymphadenitis

Lymph nodes are the most common extrapulmonary site of disease. Cervical and mediastinal glands are affected most frequently, followed by axillary and inguinal, and more than one region may be involved. Disease may represent primary infection, spread from contiguous sites or reactivation. Supraclavicular lymphadenopathy is often the result of spread from mediastinal disease. The nodes are usually painless and initially mobile but become matted together with time. When caseation and liquefaction occur, the swelling becomes fluctuant and may discharge through the skin with the formation of a 'collar-stud' abscess and sinus formation. Approximately half of cases fail to show any constitutional features, such as fevers or night sweats. During or after treatment, paradoxical enlargement, development of new nodes and suppuration may all occur but without evidence of continued infection; surgical excision is

i 17.46 Factors increasing the risk of tuberculosis

Patient-related

- Age (children > young adults < old age)
- First-generation immigrants from high-prevalence countries
- Close contacts of patients with smear-positive pulmonary TB
- Overcrowding (prisons, collective dormitories); homelessness (shelters and hostels)
- Chest X-ray evidence of primary TB infection
- Primary infection <1 year previously
- Smoking: cigarettes, bidis (Indian cigarettes made of tobacco wrapped in tembhurni leaves) and cannabis

Associated diseases

- Immunosuppression: HIV (reduced by ART), anti-tumour necrosis factor (TNF) and other biologic therapies, high-dose glucocorticoids, cytotoxic agents
- Malignancy (especially lymphoma and leukaemia)
- Diabetes mellitus
- Chronic kidney disease
- Silicosis
- Gastrointestinal disease associated with malnutrition (gastrectomy, jejuno-ileal bypass, cancer of the pancreas, malabsorption)
- Deficiency of vitamin D or A
- Recent measles in children

i 17.47 Natural history of untreated primary tuberculosis

Time from infection	Manifestations
3–8 weeks	Primary complex, positive tuberculin skin test
3–6 months	Meningeal, miliary and pleural disease
Up to 3 years	Gastrointestinal, bone and joint, and lymph node disease
Around 8 years	Renal tract disease
From 3 years onwards	Post-primary disease due to reactivation or re-infection

Adapted from Davies PDO, ed. Clinical tuberculosis. London: Hodder Arnold; 1998.

17.48 Features of primary tuberculosis

Infection (4–8 weeks)

- Influenza-like illness
- Skin test conversion
- Primary complex

Disease

- Lymphadenopathy: hilar (often unilateral), paratracheal or mediastinal
- Collapse (especially right middle lobe)
- Consolidation (especially right middle lobe)
- Obstructive emphysema
- Cavitation (rare)
- Pleural effusion
- Miliary disease
- Meningitis
- Pericarditis

Hypersensitivity

- Erythema nodosum
- Phlyctenular conjunctivitis
- Dactylitis

17.49 Clinical presentations of pulmonary tuberculosis

- Chronic cough, often with haemoptysis
- Pyrexia of unknown origin
- Unresolved pneumonia
- Exudative pleural effusion
- Asymptomatic (diagnosis on chest X-ray)
- Weight loss, general debility
- Spontaneous pneumothorax

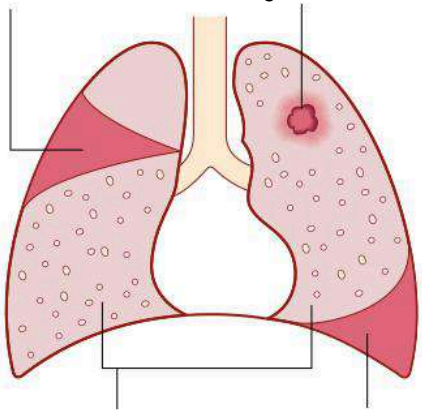
rarely necessary. In non-immigrant children in the UK, most mycobacterial lymphadenitis is caused by opportunistic mycobacteria, especially of the *M. avium* complex.

Pleural tuberculosis

Tuberculous pleural effusions are common. Patients present with pleuritic chest pain in addition to the classic clinical features of pulmonary TB. Effusions are caused by both primary and reactivated TB, but can also result from a delayed hypersensitivity reaction to TB in the pleural cavity. Pseudochylothorax, due to compression from TB lymphadenitis, and empyema occur infrequently. Pleural fluid analysis demonstrates a lymphocytic exudate, with low glucose and pH. Pleural fluid smear and culture have sensitivities of only 10% and 25% respectively, however pleural tissue culture increases this to 80%. Raised adenosine deaminase has high sensitivity but low specificity as it occurs in malignancy and empyema also. Effusion volume fluctuates during treatment, even when successful. Therapeutic drainage is performed when necessary and steroids are sometimes used as an alternative.

Gastrointestinal tuberculosis

TB can affect any part of the bowel and patients may present with a wide range of symptoms and signs (Fig. 17.38). Upper gastrointestinal tract involvement is rare and is usually an unexpected histological finding in an endoscopic or laparotomy specimen. Ileocaecal disease accounts for approximately half of abdominal TB cases. Fever, night sweats, anorexia and weight loss are usually prominent and a right iliac fossa mass may be palpable. Up to 30% of cases present with an acute abdomen. Ultrasound or CT may reveal thickened bowel wall, abdominal lymphadenopathy, mesenteric thickening or ascites. Diagnosis rests on obtaining histology by either colonoscopy or mini-laparotomy. The main differential diagnosis is Crohn's disease. Tuberculous peritonitis is characterised by abdominal distension, pain and constitutional symptoms. The ascitic fluid is exudative and cellular, with a predominance of lymphocytes. Laparoscopy reveals multiple white 'tubercles' over the peritoneal and omental surfaces. Low-grade hepatic dysfunction is common in miliary disease, in which biopsy reveals granulomas.



Consolidation/collapse
Differential diagnosis
- Pneumonia
- Bronchial carcinoma
- Pulmonary infarct

Cavitation
Differential diagnosis
- Pneumonia/lung abscess
- Lung cancer
- Pulmonary infarct
- Granulomatosis with polyangiitis (Wegener's granulomatosis)
- Progressive massive fibrosis

'Miliary' diffuse shadowing
Differential diagnosis
- Sarcoidosis
- Malignancy
- Pneumoconiosis
- Infection (e.g. histoplasmosis, melioidosis)
- Tropical pulmonary eosinophilia (TPE)

Pleural effusion/empyema
Differential diagnosis
- Bacterial pneumonia
- Pulmonary infarction
- Carcinoma
- Connective tissue disorder

Fig. 17.37 Chest X-ray: major manifestations and differential diagnosis of pulmonary tuberculosis. Less common manifestations include pneumothorax, acute respiratory distress syndrome (ARDS), cor pulmonale and localised emphysema.

Pericardial disease

Disease occurs in two forms: pericardial effusion and constrictive pericarditis (see Fig. 17.38 and p. 476). Fever and night sweats are rarely prominent and the presentation is usually insidious, with breathlessness and abdominal swelling. Coexistent pulmonary disease is very rare, with the exception of pleural effusion. Pulsus paradoxus, a raised JVP, hepatomegaly, prominent ascites and peripheral oedema are common to both types. Pericardial effusion is associated with increased pericardial dullness and a globular enlarged heart on chest X-ray, and pericardial calcification occurs in around 25% of cases. Constriction is associated with an early third heart sound and, occasionally, atrial fibrillation. Diagnosis is based on clinical, radiological and echocardiographic findings. The effusion is frequently blood-stained. Open pericardial biopsy can be performed where there is diagnostic uncertainty. The addition of glucocorticoids to antituberculous chemotherapy has been shown to be beneficial in constrictive pericarditis.

Central nervous system disease

Meningeal disease represents the most important form of central nervous system (CNS) TB. Unrecognised and untreated, it is rapidly fatal. Even when appropriate treatment is prescribed, mortality rates of 30% have been reported, while survivors may be left with neurological sequelae. Clinical features, investigations and management are described on p.1173.

Bone and joint disease

The spine is the most common site for bony TB (Pott disease), which usually presents with chronic back pain and typically involves the lower thoracic and lumbar spine (see Fig. 17.38). The infection starts as a discitis and then spreads along the spinal ligaments to involve the adjacent anterior vertebral bodies, causing angulation of the vertebrae with subsequent kyphosis. Paravertebral and psoas abscess formation is common and the disease may present with a large (cold) abscess in the inguinal region. CT or MRI is valuable in gauging the extent of disease, the degree of cord compression, and the site for needle biopsy or open exploration,

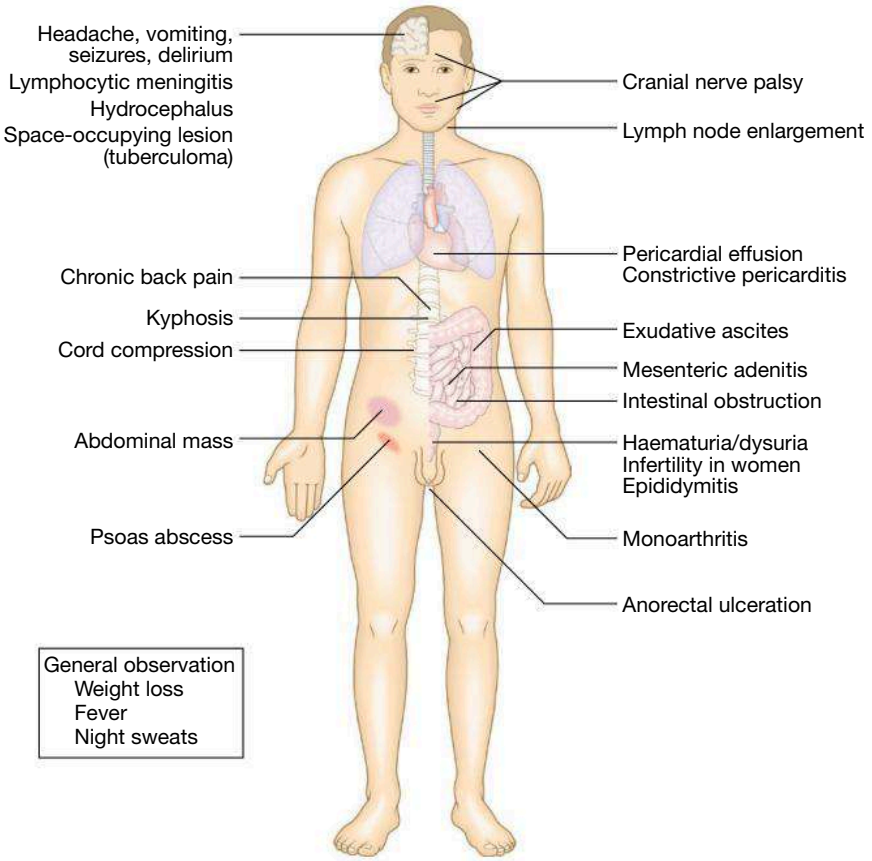


Fig. 17.38 **Systemic presentations of extrapulmonary tuberculosis.**

if required. The major differential diagnosis is malignancy, which tends to affect the vertebral body and leave the disc intact. Important complications include spinal instability or cord compression.

TB can affect any joint but most frequently involves the hip or knee. Presentation is usually insidious, with pain and swelling; fever and night sweats are uncommon. Radiological changes are often non-specific but, as disease progresses, reduction in joint space and erosions appear. Poncet arthropathy is an immunologically mediated polyarthritis that usually resolves within 2 months of starting treatment.

Genitourinary disease

Fever and night sweats are rare with renal tract TB and patients are often only mildly symptomatic for many years. Haematuria, frequency and dysuria are often present, with sterile pyuria found on urine microscopy and culture. In women, infertility from endometritis, or pelvic pain and swelling from salpingitis or a tubo-ovarian abscess occurs occasionally. In men, genitourinary TB may present as epididymitis or prostatitis.

Investigations

The presence of an otherwise unexplained cough for more than 3 weeks, particularly in regions where TB is prevalent, or typical chest X-ray or CT changes (Fig. 17.39) should prompt further investigation (Box 17.50). Direct microscopy of a sputum smear remains the most important first step. At least two sputum samples (including at least one obtained in the early morning) from a spontaneously produced deep cough should be obtained. Induced sputum may be used in those unable to expectorate. In selected cases, bronchoscopy and lavage or aspiration of a lymph node by EBUS may be used.

Light-emitting diode fluorescent microscopy with auramine staining (Fig. 17.40) is increasingly replacing the more traditional standard light microscopy and Ziehl–Neelsen stain. A positive smear is sufficient for the presumptive diagnosis of TB but definitive diagnosis requires either culture or the detection of *M. tuberculosis* DNA. The probability of visualising acid-fast bacilli is proportional to the bacillary burden in the sputum. Smear-negative sputum should also be cultured, as only 10–100 viable organisms are required for sputum to be culture-positive. A diagnosis of smear-negative TB may be considered in advance of culture if the chest X-ray appearances are typical of TB.

The slow growth of MTB on solid (typically between 4 and 6 weeks) and liquid (typically around 2 weeks) culture media has prompted the development of rapid NAATs. For example, the Cepheid GeneXpert MTB/RIF has the capacity to detect MTB (and certain molecular markers of rifampicin resistance) in less than 2 hours. However, while it is specific to MTB, it is not sufficiently sensitive to have replaced culture.

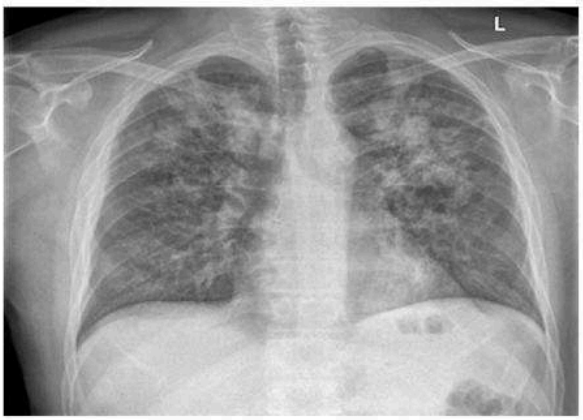


Fig. 17.39 **Typical changes of tuberculosis.** The chest X-ray shows bilateral upper lobe airspace shadowing with cavitation.

The diagnosis of extrapulmonary TB can be more challenging. There are generally fewer organisms (particularly in meningeal or pleural fluid), so culture, histopathological examination of tissue and/or NAAT may be required. Stimulation of T cells by mycobacterial antigens leads to increased levels of adenosine deaminase (ADA) in pleural, pericardial, cerebrospinal and ascitic fluid, so measuring ADA in these fluids may support a diagnosis of TB, but should not replace culture. IGRA and tuberculin skin tests have low sensitivity and specificity, are not routinely used in the diagnosis of active TB infection.

Drug sensitivity testing

The rapid detection of drug resistance is central both to the management of the individual with TB and to control of the disease in the population. The gold standard remains culture. Molecular tests are increasingly used to provide rapid drug sensitivity testing (DST), particularly with regard to the detection of rifampicin resistance, which is important because rifampicin forms the cornerstone of 6-month chemotherapy. Rapid identification of rifampicin resistance is provided by Xpert MTB/RIF. Line probe assays (LPAs) use PCR and reverse hybridisation to detect genetic sequences linked to resistance to both rifampicin and isoniazid, and increasingly to resistance to pyrazinamide, ethambutol and second-line agents.

Whole genome sequencing is now being used routinely in resource-rich settings both for identification of mycobacterium and to predict antimicrobial susceptibility, at least to first-line agents.

Management

Chemotherapy

The treatment of TB is based on the principle of an initial intensive phase to reduce the bacterial population rapidly, followed by a continuation phase to destroy any remaining bacteria (Box 17.51). Standard treatment involves 6 months' treatment with isoniazid and rifampicin, supplemented in the first 2 months with pyrazinamide and ethambutol. Fixed-dose tablets combining two, three or four drugs are preferred. Unless there is reason to suspect drug resistance or non-tuberculous mycobacterium, treatment should be commenced immediately in any patient who is smear-positive, and in those who are smear-negative but with typical chest X-ray changes and no response to standard antibiotics. Where drug resistance is not anticipated, patients can be assumed to be non-infectious after 2 weeks of appropriate therapy.

17.50 Diagnosis of tuberculosis

Specimens required

Pulmonary

- Sputum* (induced with nebulised hypertonic saline if patient not expectorating)
- Bronchoscopy with washings or BAL
- Gastric washing* (mainly used for children)

Extrapulmonary

- Fluid examination (cerebrospinal, ascitic, pleural, pericardial, joint): yield classically very low
- Tissue biopsy (from affected site or enlarged lymph node): bone marrow/liver may be diagnostic in disseminated disease

Diagnostic tests

- Stain
  Auramine fluorescence
  Ziehl–Neelsen
- Nucleic acid amplification
- Culture
  Solid media (Löwenstein–Jensen, Middlebrook)
  Liquid media (e.g. MGIT)
- Pleural fluid: adenosine deaminase
- Response to empirical antituberculous drugs

Baseline blood tests

- Full blood count, C-reactive protein, urea and electrolytes, liver function tests

*Preferably three early morning samples.
(BAL = bronchoalveolar lavage; MGIT = mycobacteria growth indicator tube)

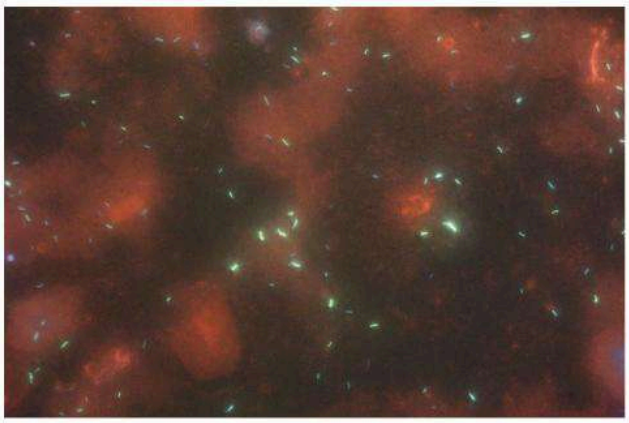


Fig. 17.40 Auramine-stained sputum sample. *Mycobacterium tuberculosis* and other mycobacteria retain the auramine stain after washing with acid and alcohol and are therefore seen as fluorescent organisms against a dark background. *Courtesy of Richard Hobson.*

17.51 Treatment of new tuberculosis (TB) patients (World Health Organization recommendations)

Intensive phase	Continuation phase	Comments
Standard regimen		
2 months of HRZE	4 months of HR	
2 months of HRZE	4 months of HRE	Applies only in countries with high levels of isoniazid resistance in new TB patients, and where isoniazid drug susceptibility testing in new patients is not done (or results are unavailable) before the continuation phase begins
Dosing frequency		
Daily*	Daily	Optimal
Daily*	3 times/week	No longer recommended but sometimes used in practice for patients receiving directly observed therapy
3 times/week	3 times/week	No longer recommended but sometimes used in practice for patients receiving directly observed therapy, provided the patient is *not* living with HIV or living in an HIV-prevalent setting

*Daily (rather than 3 times weekly) intensive-phase dosing may help to prevent acquired drug resistance in TB patients starting treatment with isoniazid resistance. (H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol; HIV = human immunodeficiency virus)
Adapted from World Health Organization. Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update.

17.52 Main adverse reactions of first-line antituberculous drugs

	Isoniazid	Rifampicin	Pyrazinamide	Ethambutol
Mode of action	Cell wall synthesis	DNA transcription	Unknown	Cell wall synthesis
Major adverse reaction	Peripheral neuropathy[1] Hepatitis[2] Rash	Febrile reactions Hepatitis Rash Gastrointestinal disturbance	Hepatitis Gastrointestinal disturbance Hyperuricaemia	Retrobulbar neuritis[3] Arthralgia
Less common adverse reaction	Lupoid reactions Seizures Psychoses	Interstitial nephritis Thrombocytopenia Haemolytic anaemia	Rash Photosensitisation Gout	Peripheral neuropathy Rash

[1]The risk may be reduced by prescribing pyridoxine. [2]More common in patients with a slow acetylator status and in alcoholics. [3]Reduced visual acuity and colour vision may be reported with higher doses and are usually reversible.

Six months of therapy is appropriate for all patients with pulmonary TB and most cases of extrapulmonary TB. However, 12 months of therapy is recommended for CNS TB. Most patients can be treated at home. Admission to a hospital unit with appropriate isolation facilities should be considered where there is uncertainty about the diagnosis, intolerance of medication, questionable treatment adherence, adverse social conditions or a significant risk of multidrug-resistant TB.

Adverse drug reactions occur in about 10% of patients (Box 17.52). Patients treated with rifampicin should be advised that their urine, tears and other secretions will develop a bright, orange/red coloration. Rifampicin is a cytochrome P450 inducer, it accelerates the metabolism of several drugs, thereby reducing their effective dose. These medications include steroids, oral hypoglycaemics, antiretrovirals, warfarin, opiates (including methadone) and contraceptives. Women taking oral or depot hormonal contraceptives must be warned that their efficacy, and that of emergency hormonal contraception, will be reduced and alternative contraception may be necessary. Standard TB medication is safe during pregnancy, however pregnant women experience an increased rate of side-effects, so conception is not advised. Pyridoxine should be prescribed in pregnant women and malnourished patients to reduce the risk of peripheral neuropathy with isoniazid. Ethambutol should be used with caution in severe renal impairment, with appropriate dose reduction and monitoring of drug levels. Visual acuity and colour vision should be assessed before commencing ethambutol.

Baseline liver function and regular monitoring are important for patients treated with standard therapy. Rifampicin may cause asymptomatic hyperbilirubinaemia but, along with isoniazid and pyrazinamide, may also cause hepatitis. Mild asymptomatic increases in transaminases are common but significant hepatotoxicity occurs in only 2%–5%. It is important to stop treatment and allow any symptoms to subside and the liver function tests to recover before commencing a stepwise re-introduction of the individual drugs. Less hepatotoxic regimens may be considered, including streptomycin, ethambutol and fluoroquinolones.

Glucocorticoids reduce inflammation and limit tissue damage; they are currently recommended when treating constrictive pericarditis or CNS disease, and in children with endobronchial disease. They may confer benefit in TB of the ureter, pleural effusions and extensive pulmonary disease, and can suppress hypersensitivity drug reactions. Embolization should be considered for treatment of massive haemoptysis. Surgery is required for patients with spinal TB causing spinal cord compression.

The effectiveness of therapy for pulmonary TB is assessed by further sputum analysis at 2 months to ensure sputum culture conversion, if the patient is still producing sputum. If sputum is culture-positive at 2 months, repeat sputum should be obtained at month 3. If this sample is culture-positive then DST should be repeated. Treatment failure is defined as a positive sputum culture at 5 months or any patient with a newly converted multidrug-resistant strain, regardless of whether they are smear-positive or negative. Extrapulmonary TB must be assessed clinically or radiographically, as appropriate.

Control and prevention

Active TB is preventable, particularly so in those with latent TB. Supporting the development of laboratory and health-care services to improve detection and treatment of active and latent TB is an important component of this goal.

Latent TB infection (LTBI)

The majority of individuals exposed to MTB harbour the bacteria, which remain dormant. They do not develop any signs of active disease and are non-infectious. They are, however, at risk of developing active TB disease and becoming infectious. The lifetime risk of TB disease for a person with documented LTBI is estimated at 5%–15%, with the majority of cases occurring within the first 5 years after initial infection.

LTBI may be identified by the presence of immune responses to *M. tuberculosis* antigens. Contact tracing is a legal requirement in many countries. It has the potential to identify the probable index case, other cases infected by the same index patient (with or without evidence of disease), and close contacts who should receive BCG vaccination (see below) or chemotherapy. Approximately 10%–20% of close contacts of patients with smear-positive pulmonary TB and 2%–5% of those with smear-negative, culture-positive disease have evidence of TB infection.

Cases are commonly identified using the tuberculin skin test (TST; Fig. 17.41) or an IGRA (Fig. 17.42). An otherwise asymptomatic contact who tests positive but has a normal chest X-ray may be treated with chemoprophylaxis to prevent infection from progressing to clinical disease. Chemoprophylaxis should be offered to adults up to the age of 65 (although age-specific cut-off varies by country). It should also be considered for HIV-infected close contacts of a patient with smear-positive disease. A course of rifampicin and isoniazid for 3 months or isoniazid for 6 months is effective.

Tuberculin skin testing may be associated with false-positive reactions in those who have had a BCG vaccination and in areas where exposure to non-tuberculous mycobacteria is high. The skin tests may also be falsely negative in the setting of immunosuppression or overwhelming TB infection.

IGRAs detect the release of interferon-gamma (IFN-γ) from sensitised T cells in response to antigens, such as early secretory antigenic target (ESAT)-6 or culture filtrate protein (CFP)-10, which are encoded by genes specific to *M. tuberculosis* and are not shared with BCG or opportunistic mycobacteria (see Fig. 17.42). IGRAs are more specific than skin testing and logistically more convenient, as they require a single blood test rather than two clinic visits. In the UK, IGRA represents the first choice investigation, except in children, for whom TST is recommended.

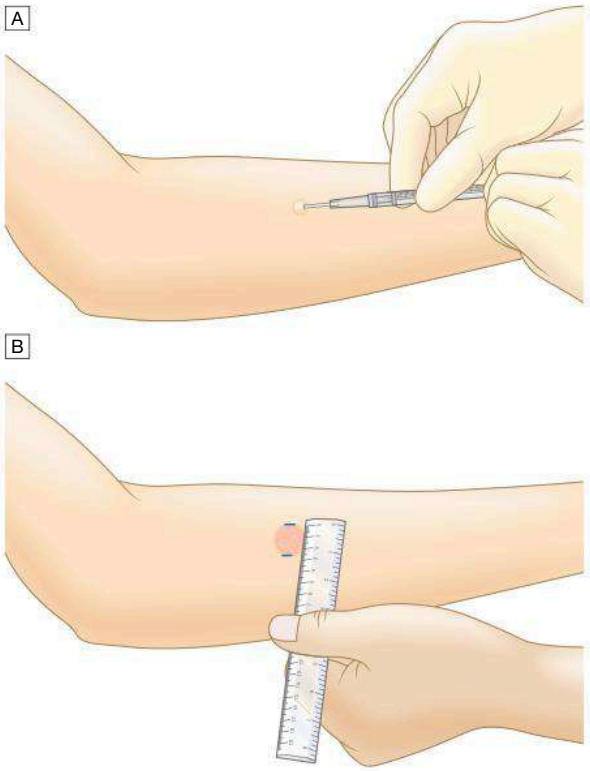


Fig. 17.41 The tuberculin skin test. A The reaction to the intradermal injection of tuberculin purified protein derivative (PPD) on the inner surface of the forearm is read between 48 and 72 hours. B The diameter of the indurated area should be measured across the forearm and is positive when ≥5 mm.

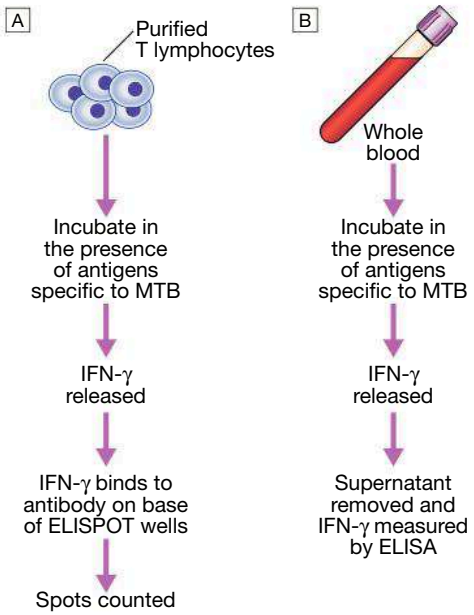


Fig. 17.42 The principles of interferon-gamma release assays (IGRAs). A sample of either A purified T cells (T-SPOT.TB test) or B whole blood (QuantiFERON–TB Gold test) is incubated in the presence of antigens specific to *Mycobacterium tuberculosis* (MTB). The release of interferon-gamma (IFN-γ) by the cells is measured by enzyme-linked immunosorbent assay (ELISA). (ELISPOT = enzyme-linked immunosorbent spot assay)

Directly observed therapy

Poor adherence to therapy is a major factor in prolonged illness, risk of relapse and the emergence of drug resistance. Directly observed therapy (DOT) involves the supervised administration of therapy three times weekly to improve adherence. DOT has become an important control strategy in resource-poor nations. In the UK, it is currently recommended for patients with previous TB, multidrug-resistant TB, poor adherence to treatment, denial of the diagnosis, those with a history of homelessness, alcohol or drug misuse, those currently or recently in prison, and those with major psychiatric, memory or cognitive disorders. DOT can be replaced by video-observed consultation (VOT) if appropriate facilities are available.

TB and HIV/AIDS

The close links between HIV and TB, particularly in sub-Saharan Africa, and the potential for both diseases to overwhelm health-care funding in resource-poor nations, have been recognised, with the promotion of programmes that link detection and treatment of TB with detection and treatment of HIV. It is recommended that all patients with TB should be tested for HIV infection, in addition to hepatits B and C. Mortality is high and TB is a leading cause of death in HIV-positive patients. Full discussion of its presentation and management with antiretroviral therapy (ART) is given in Chapter 14.

ART should be initiated for all HIV-positive patients with TB. ART is usually initiated after 2 weeks of tuberculous therapy, but in patients with a CD4 count under 50 cells/μL or CNS TB is often delayed until 8 weeks of TB therapy has been completed to reduced the risk of IRIS/paradoxical reaction. TB-associated immune reconstitution inflammatory syndrome (TB-IRIS) is a paradoxical increase in pre-existing, or development of new, TB signs or symptoms, due to ART reviving the immune system. TB-IRIS may be self-limiting, but in severe cases steroids are used to reduce symptoms, and patients are advised to continue TB chemotherapy and ART. Choice of initial ART or change in ART should reflect the need to avoid drug interactions.

Drug-resistant TB

Drug-resistant TB is defined by the presence of resistance to any first-line agent. Multidrug-resistant tuberculosis (MDR-TB) is defined by resistance to at least rifampicin and isoniazid, with or without other drug resistance. Globally, an estimated 3.5% of new TB cases and 18% of previously treated cases have MDR-TB. In 2017, an estimated 230 000 people died of MDR-TB. Extensively drug-resistant tuberculosis (XDR-TB) is defined as resistance to at least rifampicin and isoniazid, in addition to any quinolone and at least one injectable second-line agent. An estimated 8.5% of people with MDR-TB have XDR-TB. The prevalence of MDR-TB is rising, particularly in post-Soviet states, Central Asia and South Africa. It is more common in individuals with a prior history of TB, particularly if treatment has been inadequate. Box 17.53 lists the factors contributing to the emergence of drug-resistant TB. Diagnosis is challenging, especially in resource-poor settings, and although cure is possible, it requires prolonged treatment with less effective, more toxic and more expensive second-line therapies. These include injectable drugs (aminoglycosides), fluoroquinolones and various other antibiotics and TB-specific agents (see p. 315). The mortality rate from tuberculosis increases with the level of drug resistance.

Vaccines

BCG (bacille Calmette–Guérin), a live attenuated vaccine derived from *M. bovis*, is the most established TB vaccine. It is administered by intradermal injection and is highly immunogenic. BCG appears to be effective in preventing disseminated disease, including tuberculous meningitis, in children, but its efficacy in adults is inconsistent and new vaccines are urgently needed. Current vaccination policies vary worldwide according to incidence and health-care resources, but usually target children and other high-risk individuals. BCG is very safe, with the occasional

complication of local abscess formation. It should not be administered to those who are immunocompromised (e.g. by HIV) or pregnant.

Prognosis

Following successful completion of chemotherapy, cure should be anticipated in the majority of patients, though complications such as lung scarring and bronchiectasis are not uncommon (Box 17.54). There is a small (<5%) and unavoidable risk of relapse. Most relapses occur within 5 months and usually have the same drug susceptibility. In the absence of treatment, a patient with smear-positive TB will remain infectious for an average of 2 years; in 1 year, 25% of untreated cases will die. Death is more likely in those who are smear-positive and those who smoke. A few patients die unexpectedly soon after commencing therapy and it is possible that some have subclinical hypoadrenalism that is unmasked by a rifampicin-induced increase in glucocorticoid metabolism. HIV-positive patients have higher mortality rates and a modestly increased risk of relapse.

Non-tuberculous mycobacterial infection

Other species of environmental mycobacteria (termed 'non-tuberculous') may cause human disease (Box 17.55). The sites commonly involved are the lungs, lymph nodes, skin and soft tissues. The most widely recognised of these mycobacteria, *M. avium* complex (MAC), is well described in severe HIV disease (CD4 count <50 cells/μL). However, several others (including MAC) colonise and/or infect apparently immunocompetent patients with chronic lung diseases such as COPD, bronchiectasis, pneumoconiosis, old TB, or cystic fibrosis. The clinical presentation varies from a relatively indolent course in some to an aggressive course characterised by cavitatory or nodular disease in others. Radiological appearances may be similar to classical TB, but in patients with bronchiectasis, opportunistic infection may present with lower-zone nodules. The most commonly reported organisms include *M. kansasii*, *M. malmoense*, *M. xenopi* and *M. abscessus* but geographical variation is marked. *M. abscessus* and *M. fortuitum* grow rapidly but the majority of others grow slowly. More rapid diagnostic systems are under development, including DNA probes, high-performance liquid chromatography (HPLC), PCR restriction enzyme analysis (PRA) and 16S rRNA gene sequence analysis. Drug sensitivity testing is often unhelpful in predicting treatment response, with the exception of macrolide susceptibility for MAC and rifampicin sensitivity for *M. kansasii*. In the UK, these organisms are not notifiable to local public health departments as they are not normally communicable; patient-to-patient transmission of *M. abscessus* in cystic fibrosis is a key exception.

17.53 Factors contributing to the emergence of drug-resistant tuberculosis

- Drug shortages
- Poor-quality drugs
- Poor concordance with drugs
- Lack of appropriate supervision
- Transmission of drug-resistant strains
- Prior antituberculosis treatment
- Treatment failure (culture-positive at 5 months)

17.54 Complications of pulmonary tuberculosis

- Bronchiectasis
- Massive haemoptysis
- Cor pulmonale
- Fibrosis/emphysema
- Atypical mycobacterial infection
- Aspergilloma/chronic pulmonary aspergillosis
- Obstructive airways disease
- Bronchopleural fistula
- Lung/pleural calcification and pleural thickening

Non-pulmonary complications

- Empyema necessitans
- Laryngitis
- Enteritis*
- Anorectal disease*
- Amyloidosis
- Poncet's polyarthritis

*From swallowed sputum.

Respiratory diseases caused by fungi

The majority of fungi encountered by humans are harmless saprophytes but in certain circumstances (Box 17.56) some species may cause disease by infecting human tissue, promoting damaging allergic reactions or producing toxins. 'Mycosis' is the term applied to disease caused by fungal infection. The conditions associated with *Aspergillus* species are listed in Box 17.57.

Allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) occurs as a result of a hypersensitivity reaction to germinating fungal spores in the airway wall. The condition may complicate the course of asthma and cystic fibrosis, and is a recognised cause of pulmonary eosinophilia. The prevalence of ABPA is approximately 1%–2% in asthma and 5%–10% in patients with CF. A variety of human leucocyte antigens (HLAs) convey both an increased and a decreased risk of developing the condition, suggesting that genetic susceptibility is important.

Clinical features

Clinical features depend on the stage of the disease. Common manifestations in the early phases include fever, breathlessness, cough

17.55 Site-specific opportunistic mycobacterial disease

Pulmonary

- *M. xenopi*
- *M. kansasii*
- *M. malmoense*
- MAC
- *M. abscessus* (in cystic fibrosis)

Lymph node

- MAC
- *M. malmoense*
- *M. fortuitum*
- *M. chelonei*

Soft tissue/skin

- *M. leprae*
- *M. ulcerans* (prevalent in Africa, northern Australia and South-east Asia)
- *M. marinum*
- *M. fortuitum*
- *M. chelonae*

Disseminated

- MAC (HIV-associated)
- *M. haemophilum*
- *M. genavense*
- *M. chimera* (cardiopulmonary bypass-associated)
- *M. fortuitum*
- *M. chelonae*
- BCG

(BCG = bacille Calmette–Guérin; MAC = *Mycobacterium avium* complex – *M. scrofulaceum*, *M. intracellulare* and *M. avium*)

17.56 Factors predisposing to pulmonary fungal disease

Systemic factors

- Haematological malignancy
- HIV
- Diabetes mellitus
- Chronic alcoholism
- Radiotherapy
- Glucocorticoids, cytotoxic chemotherapy, biologic therapies and other immunosuppressant medication

Local factors

- Tissue damage by suppuration or necrosis
- Alteration of normal bacterial flora by antibiotic therapy