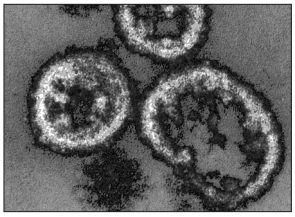
CHAPTER 14



Tuberculosis

Epidemiology

Tuberculosis (TB) is the most common infectious disease in the world, with an estimated one-third of the population infected and 2.5 million deaths annually. A falling incidence has been reversed, with increases in both developed and developing nations since the mid-1980s: human immunodeficiency virus (HIV) fuels much of the new epidemic. *Mycobacterium tuberculosis*:

- infected 8.7 million new cases in 2000 with a global incidence rate that increases by 0.4% per year. The bulk of new infections are in southeast Asia (3 million) and Africa (2 million). One-third of patients with tuberculosis in Africa are coinfected with HIV. By 2005, the World Health Organization predict there will be 10.2 million new cases and Africa will have more cases than any other region (up 10% annually). In the UK numbers are increasing, with London seeing a 40% increase between 1999 and 2000
- is commoner in certain conditions where susceptibility is increased: HIV, silicosis, immunocompromise, malignancy (especially leukaemia and lymphoma), insulin-dependent diabetes mellitus, chronic renal failure and gastrointestinal (GI) disease with malnutrition
- is increasing as a result of many factors—see Table 14.1
- is seen more frequently in children, close contacts of patients with smear-positive pulmonary tuberculosis, persons with chest X-ray (CXR) evidence of healed tuberculosis, and where primary infection occurred < 1 year previously
- causes pulmonary (75%) and extrapulmonary disease (lymph node, bone and joint, meningeal, pericardial, genitourinary and GI tract)
- can result in occasional large outbreaks in institutions (schools, paediatric wards)
- is transmitted by aerosol from smear-positive pulmonary cases: 10% of close contacts develop primary tuberculosis, 5% of those infected develop progressive primary infection, and another 5% will reactivate in later life (postprimary tuberculosis)
- is rarely infectious in primary disease; in immunocompetent adults, tuberculosis is usually a result of reactivation (70%)
- in HIV-positive persons results in a greater likelihood of contracting disease if exposed (30%), of developing progressive primary disease (30%), of developing extrapulmonary and atypical pulmonary manifestations (50%), of being due to reinfection (50%) and of reacting to standard drugs
- can be resistant to one or more of the antituberculosis drugs. Primary and secondary (past treatment) resistance is uncommon in the UK (<5%) but is frequent in many developing countries. Multidrug-resistant strains (MDRTB) are usually seen in previously suboptimally treated patients from abroad and in HIV care facilities

Developed countries	Developing countries
HIV[1]	HIV
Immigration from high-prevalence areas[2]	Population increase[4]
Increasing life expectancy of the elderly	Lack of access to health-care
Social deprivation	Poverty, civil unrest
Drug resistance (MDRTB)[3]	Ineffective control programmes
	Drug resistance (MDRTB)[3]

1 Mainly urban; 3% of cases in 1998 were coinfected in the UK.
2 One-third of new cases in the UK in 1998 were born outside the country.
3 Rifampicin/isoniazid resistance (with/without additional drugs). MDRTB, multidrug-resistant tuberculosis.
4 75% predicted increase in India over 30 years.

Table 14.1 Factors resulting in an increase in tuberculosis.

- has an incubation period (IP) for primary infection of 4–16 weeks
- is one of a large number of mycobacterial species (mostly environmental), many of which can also cause disease in humans—see Table 14.2.

Pathology and pathogenesis

Following inhalation of *M. tuberculosis*, the disease progresses as follows.

- A small subpleural lesion, termed a Ghon focus, develops
- Infection then spreads to the hilum and mediastinal lymph glands to produce a primary complex. These enlarge with an inflammatory granulomatous reaction, which may caseate
- In 95% of cases, the primary complex heals spontaneously in 1–2 months, sometimes with calcification, and the individual becomes tuberculin skin test positive
- In 10–15%, the infection spreads from the primary complex, locally to a bronchus causing pressure on (collapse, obstructive emphysema) or rupture into (endobronchial, bronchopneumonia) a bronchus, via the lymphatics to the pleura causing a pleural effusion, or via the bloodstream to cause disseminated lesions

Table 14.2 Non-tuberculous mycobacteria causing human disease.

Pulmonary	Lymph node	Soft tissue/skin	Disseminated[1]
M. bovis/*M. africanum*[2]	MAC[3]	*M. leprae*	MAC[5]
M. xenopi	*M. bovis*[2]	*M. ulcerans*[4]	*M. haemophilum*
M. kansasii	*M. malmoense*	*M. marinum*	*M. genavensae*
M. malmoense	*M. fortuitum*	*M. fortuitum*	Bacille Calmette–Guérin (BCG)
MAC	*M. chelonei*	*M. chelonei*	

1 Seen in immunodeficiency states.
2 Cause 'classical' tuberculosis. *M. bovis* reservoir is in cattle. *M. africanum* is restricted to west/central Africa.
3 *Mycobacterium avium* complex (*M. scrofulaceum*, *M. intracellulare* and *M. avium*).
4 Causes Buruli ulcer, prevalent in Africa, northern Australia, and south-east Asia.
5 HIV-associated.

• In some, disease then progresses with the development of miliary or meningeal tuberculosis. In others, dormant foci are created in the bone, lungs, kidneys, etc., which reactivate in later life
• Occasionally, the tonsil, intestine and skin may be the site of primary disease
• The virulence factors of *M. tuberculosis* have not been fully elucidated. The organism is versatile, with the ability to multiply rapidly outside cells within cavities, to survive inside macrophages and prevent fusion of the lysosome and phagosome, and to survive in a relatively inactive state with only infrequent bursts of division.

Clinical features

Pulmonary disease

• The primary pulmonary complex is often asymptomatic or marked only by a self-limiting febrile illness. Clinical disease results either from the development of a hypersensitivity reaction or from the infection pursuing a progressive course. Erythema nodosum may be the presenting feature and is associated with a strongly positive tuberculin skin test. Progressive primary disease may appear during the course of the initial illness or after a latent interval of weeks or months. Endobronchial tuberculosis may result in wheezing and cough. Collapse and/or consolidation from obstruction or tuberculous bronchopneumonia is usually associated with constitutional symptoms, cough and sputum
• Miliary tuberculosis is a severe infection, often diagnosed late. The patient usually has a 2–3-week history of fever, night sweats, anorexia, weight loss and a dry cough. Hepatosplenomegaly may be present (25%). Auscultation of the chest may be normal but with advanced disease widespread crackles are evident. Choroidal tubercles occur in 5%. The CXR shows fine 1–2-mm 'millet-seed' appearances through both lungs
• Cryptic tuberculosis is often associated with a normal CXR and affects the elderly, presenting with unexplained weight loss, fevers, hepatosplenomegaly and blood film abnormalities and is usually confirmed by liver or bone marrow biopsy
• Postprimary adult pulmonary tuberculosis is the most frequent presentation. Cough, haemoptysis, dyspnoea, anorexia and weight loss associated with fevers and sweats is typical. The history is subacute (4–8 weeks) in the majority. Auscultation of the chest usually reveals localized signs
• In HIV where the CD4 count is >350 cells/mm^3, disease is more likely to be reactivated upper lobe open cavitatory disease; as immunosuppression increases, miliary, atypical pulmonary and extrapulmonary (especially pericardial, abdominal and meningeal) tuberculosis become progressively more common, as does mycobacteraemia. Constitutional symptoms of fever and night sweats are usually present. MDRTB in HIV centres caused major nosocomial outbreaks initially in the USA in the early 1990s with very high mortalities. These are now rare in developed countries.

Table 14.3 Complications of pulmonary tuberculosis.

Acute	Chronic
Respiratory failure, adult respiratory distress syndrome	Aspergilloma
Haemoptysis (occasionally massive)	Lung fibrosis, cor pulmonale
Pleural effusion, empyema	Lung/pleural calcification
Pericardial effusion	Amyloidosis
Laryngitis	Atypical mycobacterial colonization (e.g. *M. malmoense*)

Complications
See Table 14.3.

Lymphadenitis

- The commonest site of extrapulmonary disease
- Disease may represent primary infection, spread from contiguous sites or reactivation of infection
- Cervical and mediastinal glands are affected most commonly, followed by axillary and inguinal: in 5% more than one regional group is involved
- Constitutional disturbance and evidence of associated tuberculosis are usually lacking
- In non-immigrant children in the UK, most mycobacterial cervical lymphadenitis is caused by environmental (atypical) mycobacteria, especially of the *M. avium* complex
- The nodes are usually painless and initially mobile but become matted together with time. When caseation and liquefaction occurs, the swelling becomes fluctuant and may discharge through the skin with the formation of a collar-stud abscess and sinus formation
- During or after treatment, paradoxical enlargement, development of new nodes or suppuration may all occur but without evidence of continued infection; rarely surgical excision is necessary.

Gastrointestinal disease

- Tuberculosis can affect any part of the bowel and patients may present with a wide range of symptoms and signs
- Ileocaecal disease accounts for half the cases of abdominal tuberculosis. Fever, night sweats, anorexia and weight loss are usually prominent and a right iliac fossa mass may be palpable; up to 30% present with an acute abdomen. Abdominal scanning may reveal thickened bowel wall, lymphadenopathy, mesenteric thickening or ascites. Barium and small bowel enemas may reveal narrowing, shortening and distortion of the bowel with caecal involvement predominating. Differentiation is from Crohn's disease
- Tuberculous peritonitis is associated with fevers, abdominal pain and distension. Exudative ascites is common, or there may be palpable masses of matted omentum and loops of bowel
- Diagnosis of abdominal tuberculosis rests on obtaining histology by either colonoscopy (ileocaecal disease), laparoscopy (peritoneal) or minilaparotomy
- Low-grade hepatic dysfunction is common in miliary and cryptic tuberculosis, which often presents as a pyrexia of unknown origin, when biopsy reveals granulomata. Occasionally patients may present frankly icteric with a mixed hepatic/cholestatic picture.

Pericardial disease

- Disease occurs in two main forms: pericardial effusion and constrictive pericarditis
- Fever and night sweats are rare and presentation is insidious with breathlessness and abdominal swelling
- Pulsus paradoxus, a very raised jugular venous pressure, hepatosplenomegaly, prominent ascites and the absence of peripheral oedema are common to both
- Pericardial effusion is associated with increased pericardial dullness and a globular enlarged heart on CXR whereas constriction is associated with atrial fibrillation (<20%), an early third heart sound and pericardial calcification (25%)
- Diagnosis is on clinical, radiological and echocardiographic grounds. The pericardial effusion is bloodstained in 85% of cases.

Central nervous system disease

- By far the most important form of central nervous system tuberculosis is meningeal disease
- This may complicate primary or postprimary tuberculosis. It can be life-threatening and rapidly fatal if not diagnosed early. Accompanying pulmonary disease (usually miliary) is not infrequent
- Onset is insidious with vomiting, headache, fevers and night sweats occurring over 1–2 weeks
- Mental and personality changes follow with

progressive drowsiness, meningism, cranial nerve palsies (particularly 3rd and 6th), focal long-tract signs and eventually coma in the 3rd to 4th week. Hyponatraemia is common

• Lumbar puncture reveals a lymphocytic cellular response (10–400/μL) with raised protein and depressed CSF : serum glucose ratio

• Tuberculomata are uncommon and usually present with focal features.

Bone and joint disease

• Any bone or joint can be affected but the commonest are the spine and the hip

• Tuberculosis of the spine usually presents with chronic back pain and typically involves the lower thoracic and lumbar spine. Disc involvement is the first feature followed by spread along the spinal ligaments to involve adjacent anterior vertebral bodies causing angulation of the vertebrae and kyphosis. Paravertebral and psoas abscess formation are not uncommon

• Computed tomography scanning helps gauge the extent of disease, the amount of cord compression, and the site for needle biopsy or open exploration if required. The major differential diagnosis is malignancy, which tends to affect the vertebral body and leave the disc intact

• In the absence of spinal instability or cord compression, patients can be treated as outpatients

• Presentation of joint disease is insidious with pain and swelling; fever and night sweats are uncommon. Radiological changes are often nonspecific but as disease progresses, reduction in joint space and erosions appear.

Genitourinary disease

• Renal disease is uncommon and is often very insidious with minimal constitutional symptoms

• Haematuria, frequency and dysuria are often present, with sterile pyuria found on urine microscopy and culture

• In men, genitourinary tuberculosis may present as epididymitis or prostatitis

• In women, infertility from endometritis, or pelvic pain and swelling from salpingitis or a tubo-ovarian abscess may occur infrequently.

Diagnosis

• See Table 14.4

• Mycobacterial infection can be confirmed by direct microscopy of samples (positive in 60% of pulmonary and 5–25% of extrapulmonary cases) and culture

• Confirmation that the isolate is *M. tuberculosis* is made through standard culture methods (growth characteristics, pigment production and biochemical tests) or molecular DNA technology (hybridization probes, PCR amplification)

• Drug susceptibility profiles can be obtained within 1–2 weeks of growth using the BACTEC system. Where MDRTB is suspected, molecular methods allow the detection of rifampicin resistance (a marker for multidrug resistance) in cultures as well as primary sputum specimens

• If a cluster of cases suggests a common source, fingerprinting of isolates with restriction fragment length polymorphism (RFLP) or DNA amplification can help confirm this

• Primary tuberculosis in children is rarely confirmed by culture

• In 10–20% of patients with pulmonary and 40–50% of patients with extrapulmonary disease, culture is also negative and the diagnosis is clinical.

Treatment

• Standard therapy consists of 2 months of four drugs (rifampicin, isoniazid, pyrazinamide, and ethambutol) followed by 4 months of rifampicin and isoniazid. It is recommended for all patients with new-onset uncomplicated pulmonary or extrapulmonary tuberculosis. Drugs should be given as a single daily dose before breakfast. Combined drug preparations (including rifampicin and isoniazid with or without pyrazinamide) reduce tablet load and allow relatively simple screening for compliance as the urine can be assessed visually for an orange-pink colour

• Streptomycin is now rarely used in the UK but

Clinical	History of foreign residence, recent immigration or HIV infection Subacute respiratory illness with fever Chest X-ray showing a cavity or bilateral disease (Fig. 14.1)
Standard tests	Raised ESR, CRP or plasma viscosity Normocytic normochromic anaemia Mildly deranged liver function tests Tuberculin skin test[6]
Specimen	*Diagnostic tests*
Respiratory	Microscopy stain
Sputum[1,2]	Ziehl–Neelsen
Gastric washing[1,3]	Auramine fluorescence
Bronchoalveolar lavage	Nucleic acid amplification (PCR)
Transbronchial biopsy	Culture
Non-respiratory	Solid (Lowenstein–Jensen, Middlebrook)
Fluid examination[4]	Liquid (e.g. BACTEC)
Tissue biopsy[5]	Empirical treatment[7]

1 3 × early morning samples.
2 Induced with nebulized hypertonic saline if not expectorating.
3 Mainly used for children.
4 Cerebrospinal, ascitic, pleural, pericardial, joint, blood.
5 From affected site. Also bone marrow/liver may be diagnostic in patients with disseminated disease.
6 Low sensitivity/specificity: useful only in primary or deep-seated infection.
7 Response to antituberculous drugs usually seen after 5–10 days.

Table 14.4 Diagnosis of tuberculosis.

is an important component of short-course treatment regimens in developing nations

• In patients with a history of past treatment, four drugs must be used until the sensitivity results are obtained. In the UK, drug resistance in newly diagnosed patients is uncommon (overall <5%) and is more frequently observed in isolates from ethnic minority patients

• Patients should be given 9–12 months' treatment where meningeal disease is present, where there is HIV coinfection, or where drug intolerance occurs and a second-line agent is substituted

• Most patients can be treated at home. Treatment should be supervised as closely as possible for the first 2 weeks, partly to see that compliance is satisfactory and partly to be alert to drug reactions. After the first 2 weeks of treatment, patients can be regarded as non-infectious

• To improve adherence in patients unlikely to comply (e.g. alcoholics), directly observed therapy (DOT) three times a week using higher doses of the first-line agents is often used. In developing nations, DOT also dispenses with the need for initial hospitalization to receive streptomycin, is cost-effective and is less disruptive to patients' lives

• Corticosteroids are beneficial in pericarditis, pleural disease and meningitis, and probably in severe pulmonary disease

• The most important drug reactions are hepatitis (isoniazid, rifampicin, pyrazinamide), optic neuritis (ethambutol), psychosis (isoniazid), peripheral neuropathy (isoniazid) and skin rashes (streptomycin and thiacetazone in HIV patients). They occur in ~10%

• Surgery is still occasionally required (e.g. massive haemoptysis, loculated empyema, constric-

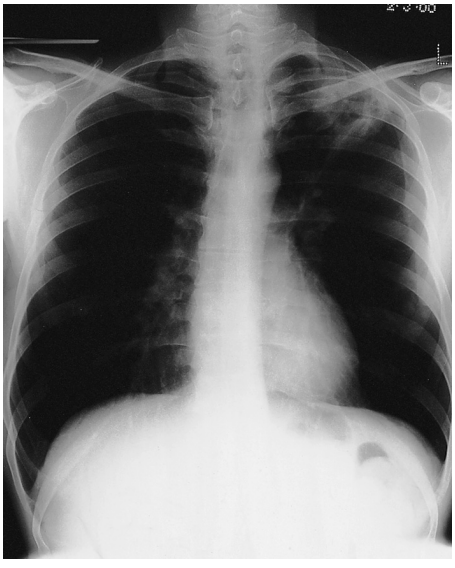


Fig. 14.1 Chest X-ray of a patient with smear-positive pulmonary tuberculosis showing cavity in the left upper lobe.

tive pericarditis, lymph node suppuration, spinal disease with cord compression)

• Relapse is rare when the strain is fully sensitive (<2%) and adherence to the drugs is complete

• Occasionally, paradoxical worsening of disease can occur after commencement of treatment, especially with lymph node disease

• The treatment of MDRTB is complex and depends on the sensitivity of the isolate. Five or more drugs are used and the patient must be admitted to a negative-pressure isolation room for treatment until deemed non-infectious.

Prevention

• The best protection against tuberculosis is the efficient diagnosis and treatment of people with active infections. Tuberculosis of all forms is a notifiable disease in the UK

• Close contacts of patients with pulmonary disease should have their bacille Calmette–Guérin (BCG) and clinical status reviewed, tuberculin skin test (usually Heaf) performed and the need for radiography assessed. The aim of contact tracing is to identify a possible index case with clinical disease, other cases infected by the same index patient (with or without evidence of disease), and close contacts who should receive BCG

• Intradermal tuberculin skin testing is usually performed using the Heaf or Mantoux technique. The response is graded (e.g. Heaf grades 0–4) according to the degree of induration. The test is used to assess whether a person has acquired *M. tuberculosis* following exposure, and is useful in persons not immunized with BCG. It is also used preimmunization with BCG to judge whether or not persons have had previous subclinical primary tuberculosis. Interpretation is more difficult in BCG-vaccinated persons since a mild positive reaction is to be expected

• Chemoprophylaxis is given to prevent infection progressing to clinical disease. It is recommended for children aged <16 years with strongly positive Heaf tests, for children aged <2 years in close contact with smear-positive pulmonary disease, for those in whom recent tuberculin conversion has been confirmed, and for babies of mothers with pulmonary tuberculosis. It should be considered for HIV-infected close contacts of a patient with smear-positive disease. Rifampicin and isoniazid for 3 months, or isoniazid for 6 months are all effective

• BCG is used in some countries as a protective measure for mycobacterial infections. It gives approximately 80% protection for 10–15 years and is greatest for preventing disseminated disease in children. Because of its potential diagnostic value as a measure of recent primary infection, some countries do not use it

• Occasional complications include local BCG abscesses, and disseminated BCG infection in immunocompromised persons.

Prognosis

• With short-course therapy using four first-line drugs, cure is to be expected
• Occasional patients die of overwhelming infection (usually miliary disease, meningitis or bronchopneumonia) and some patients succumb to the later complications of tuberculosis (e.g. cor pulmonale)
• In HIV-associated tuberculosis, mortality is increased, but mainly as a result of superimposed bacterial infections.