Tuberculosis (TB)

by:

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Etiology

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).

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

Clinical disease occurs only if there is a hypersensitivity reaction or **progressive** infection

Progressive primary disease may appear during the course of the initial illness or after a latent period of weeks or months.

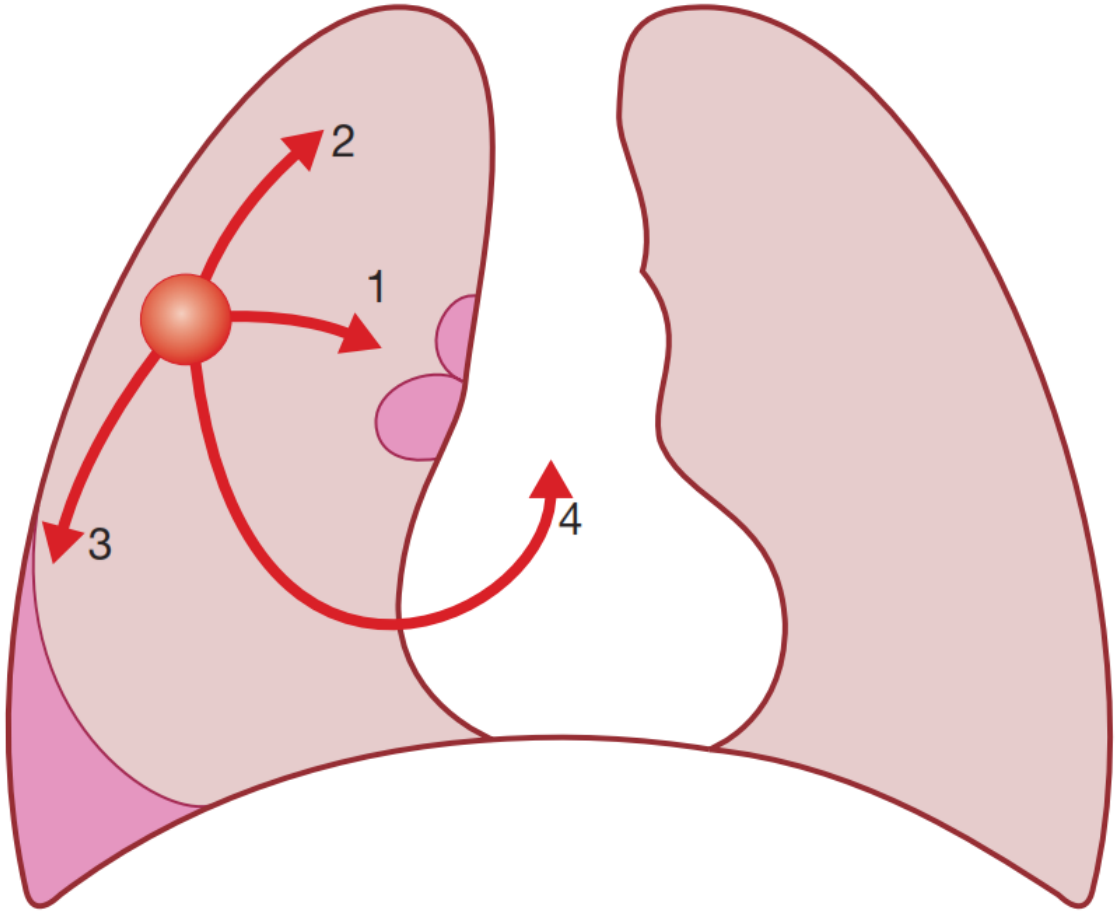


Fig. 17.36 Primary pulmonary tuberculosis. (1) Spread from the primary focus to hilar and mediastinal lymph glands to form the 'primary complex', which heals spontaneously in most cases. (2) Direct extension of the primary focus – progressive pulmonary tuberculosis. (3) Spread to the pleura – tuberculous 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.

17.45 Factors increasing the risk of tuberculosis

Patient-related

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

Associated diseases

- Immunosuppression: HIV, 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

17.46 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.

Miliary TB

Blood-borne dissemination gives rise to miliary TB

characterised by 2–3 weeks of fever, night sweats, anorexia, weight loss and a dry cough.

Hepatosplenomegaly may develop

Headache may indicate coexistent tuberculous meningitis

The classical appearances on chest X-ray are of fine 1–2 mm lesions (‘millet seed’) distributed throughout the lung fields

Anaemia and leucopenia reflect bone marrow involvement.

Post-primary pulmonary TB

exogenous (‘new’ infection)
or
endogenous (reactivation of a dormant primary lesion) infection

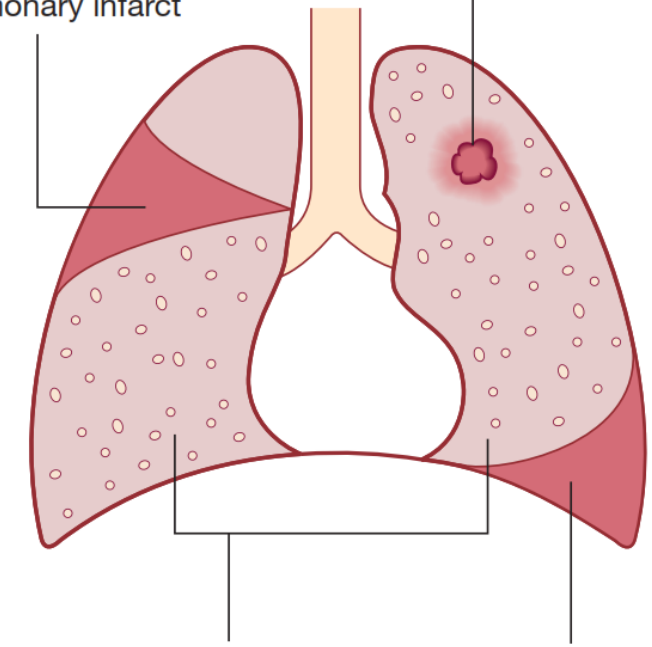
It is most frequently pulmonary and characteristically occurs in the apex of an upper lobe, where the oxygen tension favours survival of the strictly aerobic organism.

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

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

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



'Miliary' diffuse shadowing
Differential diagnosis
- Sarcoidosis
- Malignancy
- Pneumoconiosis
- Infection (e.g. histoplasmosis)

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; p. 198), cor pulmonale and localised emphysema.

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

17.50 Complications of chronic pulmonary tuberculosis

Pulmonary

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

Non-pulmonary

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

*From swallowed sputum.

Clinical features: extra-pulmonary 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.

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.

Gastrointestinal tuberculosis

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.

Tuberculous peritonitis is characterised by abdominal distension, pain and constitutional symptoms.

Pericardial disease

Disease occurs in two forms : pericardial effusion and constrictive pericarditis.

Central nervous system disease

Meningeal disease represents the most important form of central nervous system TB.

Bone and joint disease

The spine is the most common site for bony TB (Pott's disease), which usually presents with chronic back pain

TB can affect any joint but most frequently involves the hip or knee.

Genitourinary disease

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

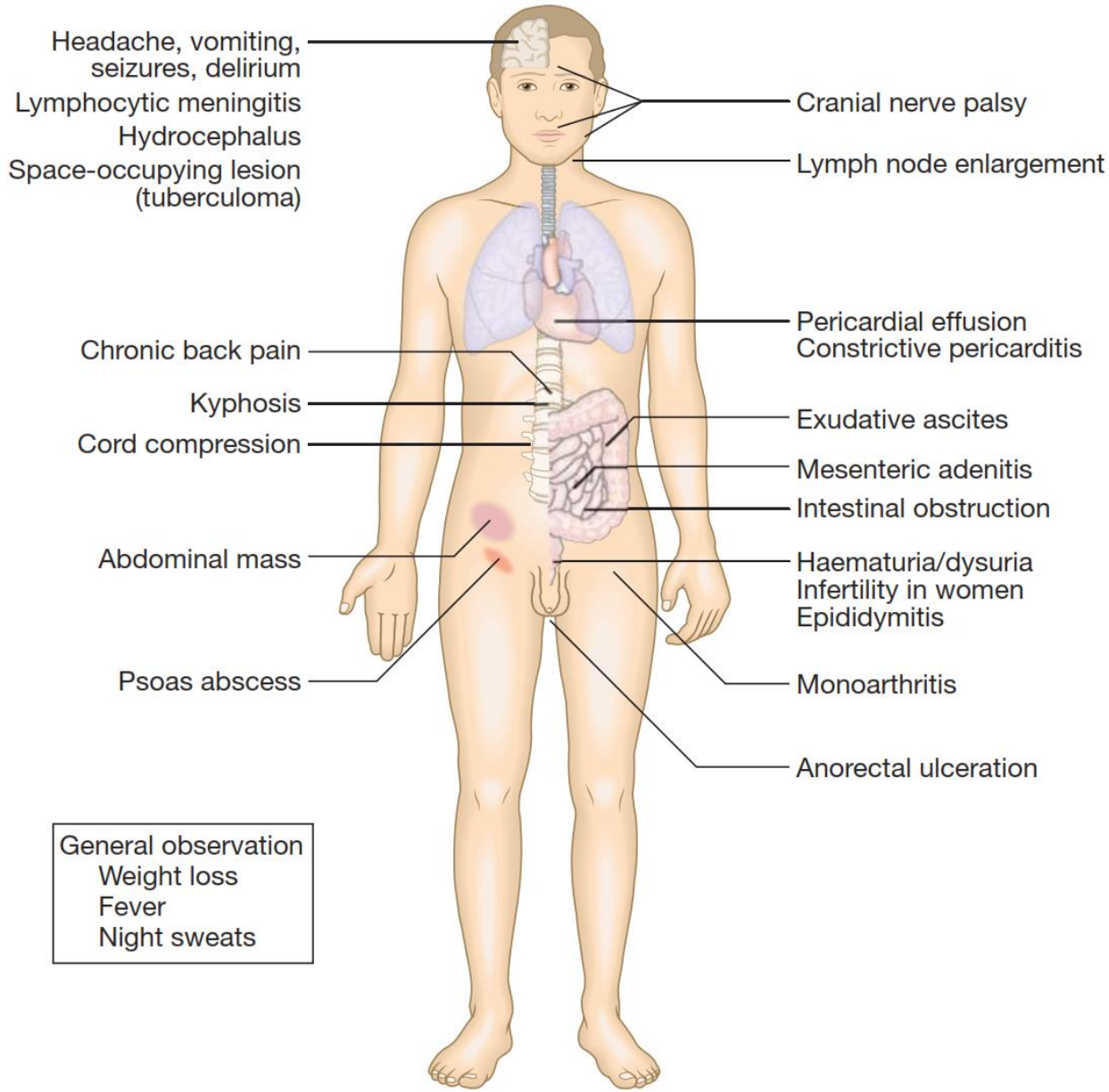


Fig. 17.38 Systemic presentations of extrapulmonary tuberculosis.

Investigations

The presence of an otherwise unexplained cough for more than 2–3 weeks, particularly in regions where TB is prevalent, or typical chest X-ray or CT changes should prompt further investigation

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.

Light-emitting diode fluorescent microscopy with auramine staining is increasingly replacing the more traditional standard light microscopy and Ziehl–Neelsen stain

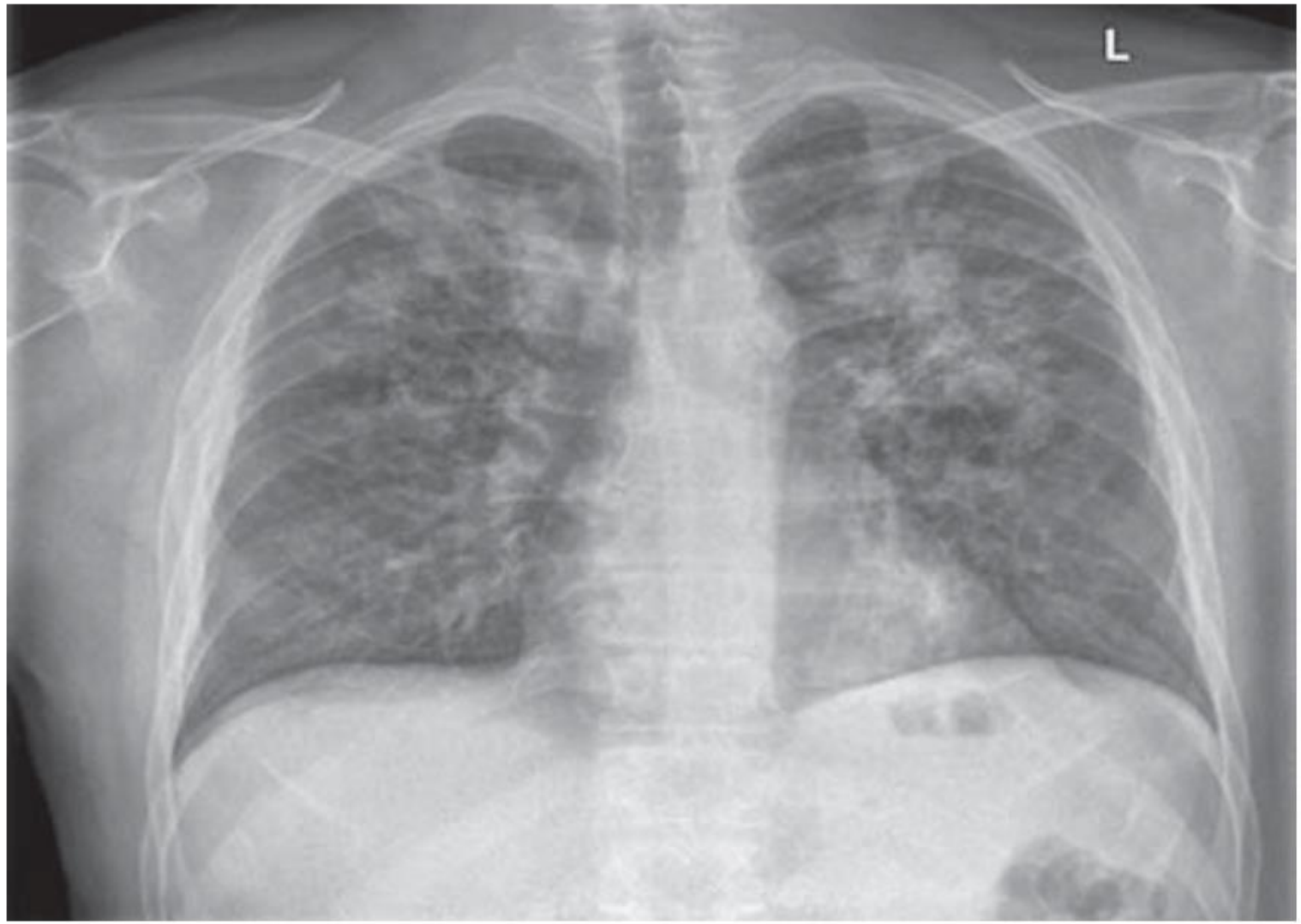


Fig. 17.39 Typical changes of tuberculosis. The chest X-ray shows bilateral upper lobe airspace shadowing with cavitation.

17.51 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): bone marrow/liver may be diagnostic in disseminated disease

Diagnostic tests

- Tuberculin skin test: low sensitivity/specificity; useful only in primary or deep-seated infection
- Stain
  - Ziehl–Neelsen
  - Auramine fluorescence
- Nucleic acid amplification
- Culture
  - Solid media (Löwenstein–Jensen, Middlebrook)
  - Liquid media (e.g. MGIT)
- Pleural fluid: adenosine deaminase
- Response to empirical antituberculous drugs (usually seen after 5–10 days)

Baseline blood tests

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

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*At least two but preferably three, including an early morning sample.
(BAL = bronchoalveolar lavage; MGIT = mycobacteria growth indicator tube)

17.52 Treatment of new tuberculosis patients (World Health Organisation 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	Acceptable alternative for any new patient receiving directly observed therapy
3 times/week	3 times/week	Acceptable alternative, provided that the patient is receiving directly observed therapy and 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)
Adapted from World Health Organisation. Treatment of tuberculosis guidelines, 4th edn; 2010.

Control and prevention

Detection of latent TB

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.

Latent TB may be identified by the presence of immune responses to *M. tuberculosis antigens.*

Contact tracing is a legal requirement in many countries.

Cases are commonly identified using the **tuberculin skintest (TST) or an IGRA**

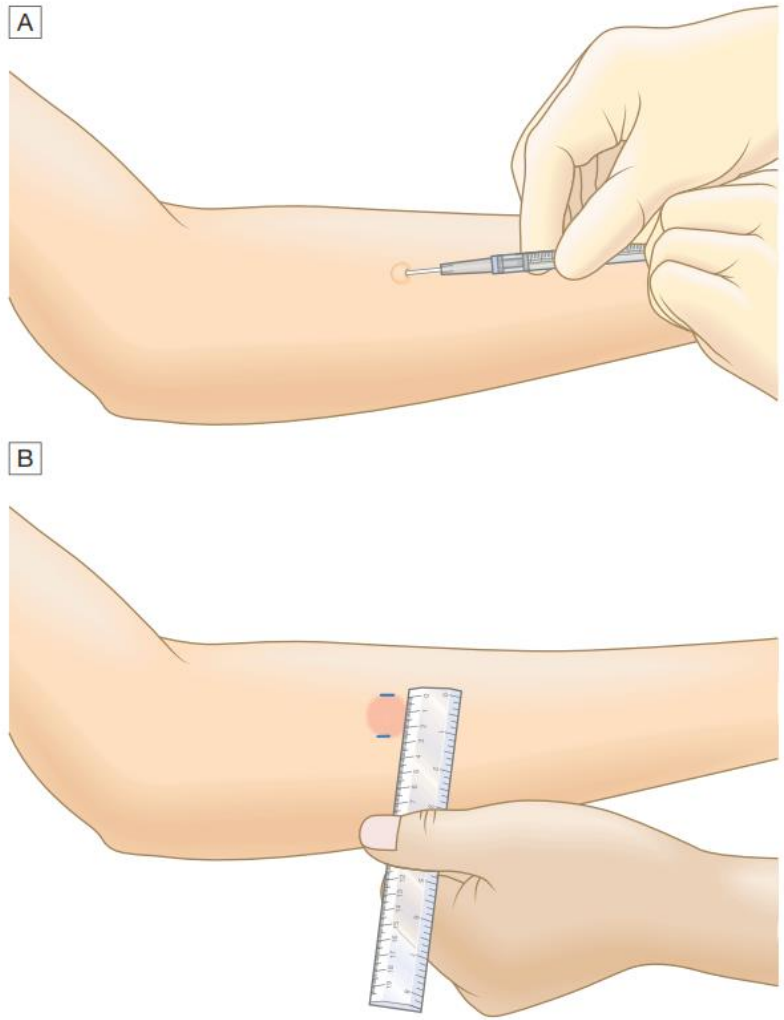

Fig. 17.41 The tuberculin skin test. A The reaction to the intradermal injection of tuberculin purified protein derivative (PPD) on the inner surface of the forearm is read between 48 and 72 hours. B The diameter of the indurated area should be measured across the forearm and is positive when ≥5 mm.

Tuberculin skin testing

False-positive

Those who have had a BCG vaccination

Non-tuberculous mycobacteria

Falsely negative :

Immunosuppression

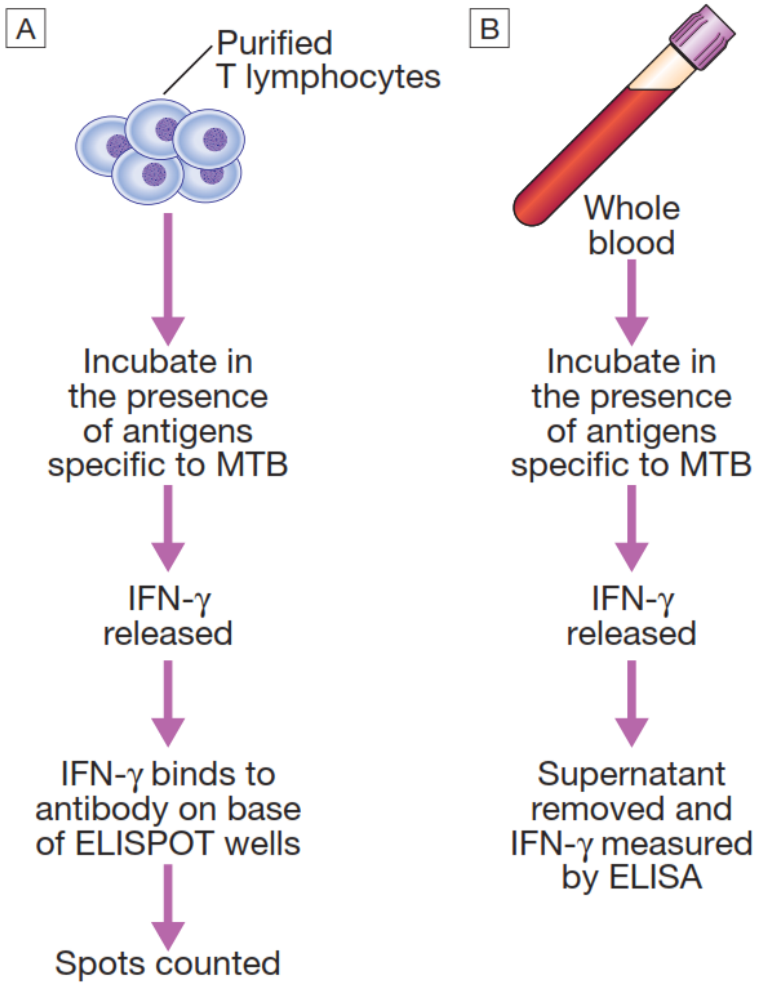

Fig. 17.42 The principles of interferon-gamma release assays (IGRAs). A sample of either (A) purified T cells (T-SPOT.TB test) or (B) whole blood (QuantiFERON–TB Gold test) is incubated in the presence of antigens specific to *Mycobacterium tuberculosis* (MTB). The release of interferon-gamma (IFN-γ)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

IGRAs detect the release of interferon-gamma (IFN-γ) from sensitised T cells in response to antigens

IGRAs are more specific than skin testing

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 :

Rifampicin and isoniazid for 3 months
or isoniazid for 6 months

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 3 times weekly to improve adherence.

It is currently recommended for patients thought unlikely to be adherent to therapy: homeless people and drifters, alcohol or **drug users, patients with serious mental illness and those with a history of non-adherence.**

Vaccines

BCG (the Calmette–Guérin bacillus), a live attenuated vaccine derived from *M. bovis, is the most established TB vaccine.*

It is administered by intradermal injection

BCG appears to be effective in preventing disseminated disease, including tuberculous meningitis, in children, but its efficacy in adults is inconsistent

Contraindications:
immunocompromised (e.g. by HIV) or pregnant.