Tuberculosis

This disease is notifiable in the UK, see Tuberculosis (TB) is a chronic granulomatous disease. In humans it is caused by bacteria of the *Mycobacterium tuberculosis* complex (which includes *M. tuberculosis*, *M. bovis* and *M. africanum*). It is most commonly spread by inhalation of infected droplets (accounts for almost all cases in the UK). Infectious patients cough up huge numbers of mycobacteria, which can survive in the environment for long periods of time.\(^1\)

When *M. tuberculosis* is first encountered (primary infection), host macrophages in the lung engulf the organisms and carry them to hilar lymph nodes in an attempt to control infection. Some organisms may disseminate via the lymphatics or bloodstream to distant sites. Small granulomas (tubercles) are formed around the body to contain the mycobacteria. These may heal spontaneously and the bacteria are eliminated (in 80% of cases)\(^2\) or bacteria are encapsulated in a defensive barrier but persist in an otherwise healthy individual where the disease is considered dormant. Only a small proportion of patients progress to overt (active) TB.

- Miliary TB occurs when primary infection is not adequately contained and invades the bloodstream, resulting in severe disease.
- Secondary TB is due to subsequent reactivation of semi-dormant *M. tuberculosis* and is usually precipitated by impaired immune function such as malnutrition, AIDS or immunosuppressive therapy. Reactivation usually occurs in the apex of the lungs and can spread locally or to distant sites.

### Epidemiology\(^3\)

- The rates of TB have stabilised in the UK over a period of seven years, following the increase in the incidence from 1990 to 2005. However, the incidence of TB in the UK remains high compared to most other Western European countries, with 8,751 cases reported in 2012, an incidence of 13.9 per 100,000 population.\(^4\)
  - The majority of TB cases occurred in large urban centres, amongst young adults, those from countries with high TB burdens, and those with social risk factors for TB.
  - Similarly to 2011, 73% of TB cases were born outside the UK and mainly originated from South Asia (60%) and sub-Saharan Africa (22%).
  - The rate of TB among the non UK-born population was almost 20 times the rate in the UK-born, at 80 per 100,000 but has continued to decline over the last seven years.
  - In the UK-born population, the incidence of TB has not declined in the past decade, with rates remaining stable at 4.1/100,000 per year. Within this population, those most at risk remain individuals from ethnic minority groups, those with social risk factors and the elderly.
  - The proportion of TB cases with resistance to any first-line drug (7.4%) was slightly lower in 2012 than in 2011, while the proportion of multidrug-resistant (MDR) TB cases (1.6%) remained stable.

- About one third of the world's population has latent TB infection (LTBI). Over 95% of TB deaths occur in low- and middle-income countries.\(^5\)
- TB causes one fifth of all deaths of people with HIV infection.\(^5\)
- TB is still a leading cause of death, particularly in sub-Saharan Africa. In large parts of Africa, TB is epidemic because of the increased susceptibility conferred by HIV infection.\(^6\)
- TB in children accounts for 20% or more of all TB cases in many countries with high TB incidence.\(^7\)
**Risk factors**[1, 2]

- **Close contact of TB patient**: a patient with untreated, infectious pulmonary TB will infect a further 10-15 people each year. The risk of infection is related to the nature and duration of exposure, with household members of a TB index case having a 1 in 3 chance of contracting the infection. Risk also extends to healthcare workers and close contacts at school or work.

- **Ethnic minority groups**: 72% of TB patients are from ethnic minority backgrounds (predominantly from South Asia and sub-Saharan Africa). Those individuals born in, or who have arrived or returned from high-prevalence areas within the last five years, are particularly at risk. Most of these patients are diagnosed within five years of entering the UK but their lifetime risk of developing TB remains higher than average and extends to their children and close contacts born in the UK. Rates of infection are particularly high in people from the Indian subcontinent and sub-Saharan Africa.

- **Homeless patients, alcoholics and other drug abusers**: poverty, malnutrition, overcrowding and poor housing encourage the spread of TB. Accurate estimates of the rates of TB in homeless people are unknown but thought to be more than 150 times the UK average. Persons who have recently been in prison may also be at increased risk.

- **HIV-positive and other immunocompromised patients**: worldwide, up to 60% of AIDS patients develop TB and the disease accounts for a third of all AIDS-related deaths. Rates of such concurrent infections in the UK are proportionally low but at least 3% of people with TB are HIV-positive. Patients on immunosuppressant drugs are particularly at risk (eg, infliximab and etanercept, azathioprine, ciclosporin, etc).

- **Elderly patients**: LTBI may reactivate in elderly patients.

- **Other conditions**: debilitating disease (especially haematological and some solid cancers), long-term steroids, diabetes, end-stage renal disease, silicosis and gastrectomy/jejuno-ileal bypass all confer an increased risk.

- **Children**: young children are particularly susceptible to mycobacterial infection, due to their immature immune systems. Children themselves are rarely infectious, as cavitating disease is uncommon but they will often have a close infectious contact.

**Drug-resistant TB**[8]

- MDR TB (resistant to more than one drug) and extensively drug-resistant TB (resistant to more than three drugs) are burgeoning global problems with high mortality which threaten to destabilise TB control programmes in several parts of the world.[9] In 2012, the estimated global burden of MDR TB was 450,000, including 300,000 incident MDR TB cases.

- During a period of five years, there has been an alarming increase in the number of patients with MDR TB and extensively drug-resistant TB in Eastern Europe, Asia, and southern Africa.[10] In 2012, approximately half of the incident cases of MDR TB were in China, India, and Russia.

- Almost 4% of all new TB cases and more than 20% of those with previous history of TB treatment were estimated to be MDR TB.

- By the end of 2012, 92 countries had reported cases of extensively drug-resistant TB, including 13 countries and territories that had reported more than ten extensively drug-resistant TB cases in a single year. The average percentage of extensively drug-resistant TB cases among MDR TB cases was 9.6%.

- Cases with extensively drug-resistant TB may be virtually untreatable, depending on the level of resistance to second-line drugs.

**Presentation**

It is possible to contract TB soon after transmission occurs; however, it is thought that most TB cases in the UK occur from LTBI, from an exposure which occurred a long time before TB developed.[11]

The onset of TB is insidious. Primary infection is usually asymptomatic. The presentation of secondary infection is variable and often nonspecific. A high index of suspicion in patients from particular risk groups is essential to make a diagnosis. TB can affect all organs and body systems. Extrapulmonary TB is more common in children or in the immunosuppressed.

- **General symptoms**: fatigue, malaise, fever, weight loss, anorexia, failure to thrive and pyrexia of unknown origin (PUO).
**Pulmonary:** respiratory TB accounts for 60% of cases in the UK. Symptoms include chronic, productive cough with purulent ± bloodstained sputum. May result in lobar collapse, bronchiectasis, pleural effusion and pneumonia.

**Genitourinary:** the most common site outside the lungs often presents with 'sterile' pyuria. There may be kidney lesions, salpingitis, abscesses and infertility in females and swelling of the epididymis in males.

**Musculoskeletal:** pain, arthritis, osteomyelitis and abscess formation (e.g., loin mass or psoas abscess from spinal TB), nerve root compression, isolated bone or joint lesions (monoarthritis). See also the separate article on Pott's Disease of the Spine.

**Central nervous system:** tuberculous meningitis and tuberculomas - initially nonspecific symptoms (headache, vomiting, altered behaviour) followed by diminished consciousness ± focal neurological signs.

**Gastrointestinal:** mainly ileocaecal lesions (abdominal pain, bloating, obstruction and simulating appendicitis) but occasional peritoneal spread causes ascites.

**Lymph nodes:** hilar, paratracheal or superficial node involvement. Palpable nodes may be initially tender, firm and discrete but later matted and suppurative with discharging sinuses.

**Skin:** erythema nodosum (represents an early immunological response to infection), skin sinus formation ("scrofuloderma"), erythema induratum. See also the separate articles on Erythema Nodosum, Erythema Induratum and Mycobacterial Skin Infections.

**Pericardial:** initially nonspecific; may be signs of pericardial effusion (pulsus paradoxus, elevated JVP) or constrictive pericarditis.

**Differential diagnosis**

TB must not be forgotten and must be suspected amongst the differential diagnosis for carcinoma, lymphoma, pneumonia, PUO, fibrotic lung disease (e.g., sarcoidosis, extrinsic allergic alveolitis, pneumoconiosis and silicosis), chronic diseases such as anorexia nervosa and diabetes.

**Investigations**

- **CXR** is essential even in non-pulmonary disease, as there may have been pulmonary infection:
  - Primary TB usually appears as a central apical portion with a left lower-lobe infiltrate or pleural effusion.
  - Reactivated TB - there is no pleural effusion and lesions are apical in position.
  - Severe disease with poor immune response can produce a picture like millet seeds over the CXR. Hence the name miliary tuberculosis.
  - Pulmonary TB is unlikely with a normal CXR.

Even patients with non-pulmonary disease may have CXR findings due to initial lung infection. Remember that other infections may mimic CXR appearance. Typical TB appearances include:
- Patchy or nodular shadows in the upper zones, loss of volume, fibrosis ± cavitation.
- Uniform 1-10 mm shadows throughout the lung in miliary TB.

- **Microbiological samples:** firm diagnosis rests on isolating the infecting organism, and subsequent sensitivity testing can be used to guide antibiotic therapy. Isolation of the organism can be difficult.
  - **Respiratory TB:**
    - Send at least three spontaneous sputum samples for culture and microscopy (including one early morning sample).
    - If spontaneous sputum samples are not possible then consider bronchoscopy and lavage or, in children, gastric washings.
    - Take samples before starting treatment or within seven days of starting.
    - Start treatment without culture results if there are clinical signs and symptoms of TB, and complete treatment even if the culture results are negative.
    - Send autopsy samples for culture if respiratory TB is suspected.
    - If sputum cannot be expectorated or repeated specimens are negative, bronchoscopy and bronchial washings should be considered.
Non-respiratory TB:
- Discuss the advantages and disadvantages of biopsy and needle aspiration with the patient.
- Send samples in a dry pot for TB culture. These may be lymph node biopsies, aspirated pus, early morning urine or any other samples.
- Start drug treatment, if the histology and clinical picture are consistent with TB, before culture results are available.
- Continue treatment even if culture results are negative.
- CXR should be done for co-existing respiratory TB in all patients with non-respiratory TB. Other investigations should also be considered.

Samples are analysed by:
- Staining with Ziehl-Neelsen (ZN) stain and rapid direct microscopy for acid/alcohol-fast bacilli.
- Culture on a Löwenstein-Jensen slope which takes 4-8 weeks due to slow bacterial growth.

Antibiotic sensitivity cultures take a further 3-4 weeks. Rapid detection of rifampicin resistance from cultured *M. tuberculosis* is now possible using molecular techniques. Results are fairly accurate and allow appropriate treatment to begin more promptly; however, results must still be confirmed with conventional techniques.

- Laboratory tests:
  - Risk factors - check HIV, hepatitis B and hepatitis C status.
  - Only perform rapid diagnostic tests (molecular probes) on primary specimens:
    - When rapid confirmation of TB would alter care of the patient.
    - Before conducting large contact-tracing initiatives.
  - If clinical signs and test results suggest TB meningitis, start treatment even when rapid test results are negative (false negatives may well occur).
  - If risk assessment suggests MDR TB then:
    - Do rapid diagnostic tests for rifampicin resistance.
    - Start infection control measures and treat the MDR TB whilst awaiting test results.

Contact screening
See the separate article on Tuberculosis Prevention and Screening.

- Offer Mantoux testing to diagnose LTBI in people who are either household contacts or close work or school contacts (aged 5 years and older) of all patients diagnosed with active TB.\(^1\)
- As the Mantoux test may be positive in patients who have had the bacillus Calmette-Guérin (BCG) vaccine, interferon gamma testing is recommended as a second-line test for people whose Mantoux testing shows positive results, or instead of Mantoux test in people for whom Mantoux testing may be less reliable - for example, BCG-vaccinated people.
- If Mantoux testing is inconclusive, refer the person to a TB specialist.

Management of active tuberculosis\(^2\)

- **Notification**: all cases of TB must be notified under under the Public Health (Infectious Diseases) Regulations 1988, to provide surveillance data and to initiate contact tracing and nursing input. The doctor suspecting the diagnosis is legally responsible for notification of the consultant in communicable disease control (CCDC).
- **Staff and services**: all health authorities should have an integrated policy for prevention and control of TB. Most cases can be managed as outpatients but occasional admission may be needed. Patients with suspected TB should be admitted to a single side-room vented to the outside until they are proven to be non-infectious. Consideration should also be given to the likelihood of MDR TB and the immune status of the other patients on the ward. Only physicians with full training and expertise in management of TB with access to TB nurse specialists and health visitors should be responsible for patients with respiratory TB.
Drug treatment

- A six-month, four-drug initial regimen (six months of isoniazid and rifampicin supplemented in the first two months with pyrazinamide and ethambutol) should be used to treat active respiratory TB.
- Patients with active meningeal TB should be offered:
  - A treatment regimen, initially lasting for 12 months, comprising isoniazid, pyrazinamide, rifampicin and a fourth drug (eg, ethambutol) for the first two months, followed by isoniazid and rifampicin for the rest of the treatment period; and
  - A glucocorticoid at the normal dose range (adults: equivalent to prednisolone 20-40 mg if on rifampicin, otherwise 10-20 mg; children: equivalent to prednisolone 1-2 mg/kg, maximum 40 mg) with gradual withdrawal of the glucocorticoid considered, starting within 2-3 weeks of initiation.
- Patients with HIV co-infection should be treated in line with the British HIV Association guideline.

Compliance

This is a major determinant of the success of drug treatment, as it is essential to prevent treatment failure and acquisition of drug resistance. A patient should always be aware of their diagnosis and be prepared for a long course of treatment. Supervised therapy can improve compliance in some treatment groups. Directly observed therapy (DOT) is not usually necessary - but patients should be assessed for compliance at the initiation of therapy; DOT may be appropriate for homeless street dwellers, etc. All patients should have a key worker whom they can contact for more information.

First-line drugs

Isoniazid, rifampicin and pyrazinamide are associated with liver toxicity. Liver function should be checked before treatment with these drugs. Those with pre-existing liver disease or alcohol dependence should have frequent checks, particularly in the first two months. Patients and their carers should be informed carefully how to recognise signs of liver disorders and advised to discontinue treatment and seek immediate medical attention if symptoms of liver disease occur.

Kidney function should be checked before treatment with antituberculous drugs and appropriate dosage adjustments made. Streptomycin and ethambutol should be avoided in patients with renal impairment, but if used, the dose should be reduced and the plasma-drug concentration monitored.

Side-effects of ethambutol are largely confined to visual disturbances in the form of loss of acuity, colour blindness, and restriction of visual fields. Patients should be advised to discontinue therapy immediately if they develop deterioration in vision, and promptly seek further advice. Early discontinuation of the drug is almost always followed by recovery of eyesight. Visual acuity should be tested by Snellen chart before treatment with ethambutol.

Isoniazid is very effective and its only common side-effect is peripheral neuropathy which is more likely to occur where there are pre-existing risk factors such as diabetes, alcohol dependence, chronic kidney disease, pregnancy, malnutrition and HIV infection. In these circumstances pyridoxine 10 mg daily should be given prophylactically from the start of treatment.

During the first two months (‘initial phase’) of rifampicin administration transient disturbance of liver function with elevated serum transaminases is common but generally does not require any change of treatment. Occasionally more serious liver toxicity requires a change of treatment, particularly in those with pre-existing liver disease.

Rifampicin induces hepatic enzymes which accelerate the metabolism of several drugs including oestrogens, corticosteroids, phenytoin, sulfonylureas, and anticoagulants.

Second-line drugs

Second-line agents are used by specialists in certain situations (for example, resistance and intolerance) and include amikacin, capreomycin, cycloserine, macrolides (azithromycin, clarithromycin) and quinolones (moxifloxacin, levofloxacin). Streptomycin is unlicensed and now rarely used in the UK.
Treatment of latent tuberculosis infection

Treatment of LTBI should be considered for people in the following groups, once active TB has been excluded by CXR and examination.

- People identified through screening who are: 35 years or younger, any age with HIV, any age and a healthcare worker, and are either:
  - Mantoux-positive (6 mm or greater), and without prior BCG vaccination; or
  - Strongly Mantoux-positive (15 mm or greater), interferon gamma-positive, and with prior BCG vaccination.

- Children aged 1-15 years identified through opportunistic screening to be: strongly Mantoux-positive (15 mm or greater), and interferon gamma-positive (if this test has been performed), and without prior BCG vaccination.

- People with evidence of TB scars on CXR, and without a history of adequate treatment.

- People with HIV who are in close contact with people with sputum-smear-positive respiratory TB should have active disease excluded and then be given treatment for LTBI.

People who have agreed to receive treatment for LTBI should be started on:

- Either six months of isoniazid or three months of rifampicin and isoniazid for people aged 16-35 not known to have HIV.
- Either six months of isoniazid or three months of rifampicin and isoniazid for people older than 35 in whom treatment for LTBI is recommended, and who are not known to have HIV.
- Six months of isoniazid for people of any age who have HIV.
- Six months of rifampicin for contacts, aged 35 or younger, of people with isoniazid-resistant TB.

For children requiring treatment for LTBI, a regimen of either three months of rifampicin and isoniazid or six months of isoniazid should be planned and started, unless the child is known to be HIV-positive, when six months of isoniazid should be given.

Certain groups of people with LTBI are at increased risk of going on to develop active TB, including people who are HIV-positive, injecting drug users, those who have had solid organ transplantation, have a haematological malignancy, have had a jejuno-ileal bypass, have chronic kidney disease or receive haemodialysis, have had a gastrectomy, are receiving anti-tumour necrosis factor-alpha treatment, or have silicosis.

Further reading & references

- Tuberculosis; NICE Guideline (January 2016)
- Tuberculosis; NICE CKS, January 2015 (UK access only)
- Tuberculosis; NICE Quality Standard, January 2017
- Immunisation against infectious disease - the Green Book (latest edition); Public Health England
- Tuberculosis; NICE Clinical Guideline (March 2011)
- Tuberculosis Fact Sheet; World Health Organization
- Annual report on tuberculosis surveillance in the UK; Health Protection Report, News Archives
- Tuberculosis (TB); World Health Organization
- Tuberculosis (TB) and other mycobacterial diseases: diagnosis, screening, management and data; Public Health England
- Management of co-infection with HIV-1 and hepatitis B or C virus; British HIV Association (2010)
- British National Formulary