TUBERCULOSIS

• Tuberculosis (TB) is a bacterial infection, treatable by anti-TB drugs. Adequate and effective treatment is essential, both clinically for patients and also to control TB, as the BCG vaccine does not prevent infection.

ETIOLOGY

• TB is caused by tubercle bacilli, which belong to the genus *Mycobacterium*. These form a large group but only three relatives are obligate parasites that can cause TB disease.

• *Mycobacterium* species include:
  - *M. tuberculosis* complex: *M. tuberculosis, M. bovis, M. africanum*
  - *Mycobacteria other than tuberculosis*: Around 15 are recognized as *pathogenic to humans and some cause* pulmonary disease resembling TB. They have been found in soil, milk and water. They are also referred to as atypical mycobacteria.
  - *Mycobacterium leprae*: The cause of leprosy.

CLINICAL ASPECTS

• Infection with tubercle bacilli occurs in the vast majority of cases by the respiratory route. The lung lesions caused by infection commonly heal, leaving no residual changes except occasional pulmonary or tracheobronchial lymph node calcification.

• Pulmonary (respiratory) TB is more common in the UK than extrapulmonary (non-respiratory) TB.

• Sites of extrapulmonary disease include the pleura, lymph nodes, pericardium, kidneys, meninges, bones and joints, larynx, skin, intestines, peritoneum and eyes.

• In the UK, the lymph nodes are the most common site for extrapulmonary disease.

• Pulmonary TB may arise from exogenous reinfection or endogenous reactivation of a latent focus remaining from the initial infection. If untreated, about 65% of patients will die within 5 years, the majority of these within 2 years. Completion of chemotherapy using drugs to which the tubercle bacilli are sensitive almost always results in a cure, even with HIV infection.

*Incubation period*

• The incubation period from infection to demonstrable primary lesion or significant tuberculin reaction ranges from 2 to 10 weeks. Latent infection may persist for a lifetime.
Transmission

- Transmission occurs through exposure to tubercle bacilli in air-borne droplet nuclei produced by people with pulmonary or respiratory tract TB during expiratory efforts such as coughing or sneezing.
- In general, only the respiratory forms of TB are infectious. Most infections are acquired from adults with post-primary pulmonary TB. The greatest risk of infection is to close, prolonged contacts, mainly household contacts. TB cannot be acquired from individuals with latent TB infection (LTBI).

Risk groups

- Certain groups are at increased risk of LTBI and possibly TB disease if exposed. These include:
  - close contacts of patients with TB, especially those with sputum smear-positive pulmonary disease (i.e. they produce sputum containing sufficient tubercle bacilli to be seen on microscopic examination of a sputum smear)
  - casual contacts (e.g. work colleagues) if they are immunosuppressed
  - people from countries with a high incidence of TB (40/100,000 population or greater).

DIAGNOSIS

Symptoms

- The symptoms and signs of TB include:
  - Cough for 3 weeks or more/productive cough
  - Sputum usually mucopurulent or purulent
  - Hemoptysis not always a feature
  - Fever may be associated with night sweats
  - Tiredness
  - Weight loss variable
  - Anorexia variable
  - Malaise.

- TB should be considered in the differential diagnoses of patients with a chronic cough for which there is no other likely cause, or in individuals with chest infections not responding to treatment.

Clinical diagnosis

- The clinical diagnosis of TB disease is based on the symptoms and signs in the patient together with chest radiography, microscopy of sputum (for acid-fast bacilli) followed by culture and tuberculin skin testing. Blood-based immunological tests, introduced in the last few years, will play an increasingly important role in TB
diagnosis. These tests can distinguish between TB infection and previous BCG vaccination.

**Investigations**

**Microbiological**

- Direct microscopy of sputum is the simplest and quickest method of detecting the infectious patient, by looking for acid-fast bacilli. A minimum of three sputum samples, one of which should be early morning, should be collected from patients with suspected respiratory TB.
- Direct microscopy is not as useful in non-pulmonary disease; any specimens taken should be sent for culture.
- If conventional culture methods are used, such as the Lowenstein–Jensen medium, growth may take up to 6 weeks. Modern liquid cultures can produce results more quickly.
- Polymerase chain reaction (PCR)-based tests can also detect *M. tuberculosis* complex in clinical specimens.

**Tuberculin testing**

- In this test, 0.1 mL of the appropriate solution is injected intradermally, usually on the forearm, so that a bleb of around 7 mm is produced. The results are read 48–72 h later, although a valid reading can be obtained up to 96 h later. The transverse diameter of the area of induration is measured with a ruler and the result recorded in millimeters.
- A diameter of induration of less than 6 mm is negative, that is, there is no significant hypersensitivity to tuberculin protein.
- In the absence of specific risk factors for TB, induration of between 6 and 15 mm diameter may be due to previous TB infection, or BCG vaccination or exposure to non-tuberculous mycobacteria.
- An induration of more than 15 mm is strongly suggestive of TB infection or disease.

**Chest radiography**

- The chest radiograph is a non-specific diagnostic tool, as TB may present as virtually any abnormality on chest radiography.
- Pulmonary TB may appear as bronchopneumonia with confluent shadowing, without cavitation. Cavitation may be seen, the incidence can vary between 10% and 30%.

**TREATMENT**

- In treating TB, a number of factors are important:
  - Choice of drugs
• Length of treatment
• Co-morbidity especially HIV infection, liver and renal diseases
• Adherence to treatment by the patient.

• Treatment with anti-TB drugs has two main purposes:
  • to cure people with TB, provided the bacilli are drug sensitive;
  • to control TB, by either preventing the development of infectious forms or reducing the period of infectivity of people with infectious disease.

• Most regimens in the developed world now contain isoniazid and rifampicin, which are the two most important drugs. These are prescribed together with pyrazinamide and possibly with another agent, such as ethambutol.

• The recommended standard treatment regimen for respiratory and most other forms of TB in the UK is:
  • rifampicin, isoniazid, pyrazinamide and ethambutol for the initial 2 months (initial phase)
  • a further 4 months of rifampicin and isoniazid (continuation phase).

• The purpose of the concurrent use of four drugs in the initial phase is to reduce the bacterial population as rapidly as possible and prevent the emergence of drug-resistant bacteria.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Forms available</th>
<th>Dosage</th>
<th>Reduce dose in</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adults intermittent (doses per week)</td>
<td>Children daily (doses per week)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adults daily</td>
<td>Children daily</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Capsules 150 mg, 300 mg&lt;sup&gt;a&lt;/sup&gt;&lt;br&gt; Liquid 100 mg in 5 mL  &lt;br&gt; Injection for infusion 300 mg</td>
<td>450 mg/kg (&lt;50 kg)&lt;br&gt; 600 mg (&gt;50 kg)</td>
<td>15 mg/kg (3)</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Tablets 50 mg&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt; Injection 25 mg/mL  &lt;br&gt; Elixir (special order)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>300 mg</td>
<td>15 mg/kg (3)</td>
</tr>
<tr>
<td>Ethambutol&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Tablets 100 mg, 400 mg&lt;sup&gt;e&lt;/sup&gt;&lt;br&gt; Mixture&lt;sup&gt;f&lt;/sup&gt;</td>
<td>15 mg/kg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>As adult dose</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Tablets 500 mg</td>
<td>1.5 g (&lt;50 kg)&lt;br&gt; 2.0 g (≥50 kg)</td>
<td>2.0 g&lt;sup&gt;f&lt;/sup&gt; (&lt;50 kg) (3)&lt;br&gt; 2.5 g&lt;sup&gt;f&lt;/sup&gt; (≥50 kg)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Injection 1 g</td>
<td>750 mg (&lt;50 kg)&lt;br&gt; 1 g (&lt;50 kg)</td>
<td>750 mg–1 g&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Some of the doses quoted are not licensed but have been recommended by the British Thoracic Society.<br><sup>b</sup>Also available as combined oral preparations.<br><sup>c</sup>Mixture may be prepared extemporaneously.<br><sup>d</sup>Doses refer to patients under 50 kg. Reduce by 500 mg for patients weighing less than 50 kg.<br><sup>e</sup>Drug levels should be monitored to prevent toxicity.<br><sup>f</sup>A dose calculation is required to reduce the risk of toxicity.
**Respiratory TB**
- Respiratory TB is defined as active TB affecting any of the following:
  - lungs
  - pleural cavity
  - mediastinal lymph nodes
  - larynx.
- The standard 6-month regimen, as set out earlier, is recommended for the treatment of active respiratory TB in:
  - adults not known to be HIV positive
  - adults who are HIV positive
  - children.

**TB of peripheral lymph nodes**
- Trials have shown that 6 months of treatment are just as effective as 9 months for fully susceptible bacilli. The standard 6-month treatment regimen is recommended.

**Meningeal TB**
- Patients with active meningeal TB (tuberculous meningitis) should be treated with rifampicin and isoniazid for 12 months together with pyrazinamide, and normally ethambutol, for the first 2 months. Ethambutol (and streptomycin if used in preference) only reach cerebrospinal fluid through inflamed meninges.
- The use of glucocorticoids is also recommended in the management of meningeal TB and is commenced at the same time as anti-tuberculous drugs. Consideration should be given to their gradual withdrawal within 2–3 weeks of initiation.

**Bone and joint TB**
- The spine is the most common site for bone TB. Bone and joint TB are treated effectively with standard agents such as isoniazid and rifampicin for 6 months, together with pyrazinamide and a fourth drug, usually ethambutol in the initial phase (for 2 months).

**Disseminated TB**
- Generalized (disseminated or miliary) TB must be treated promptly as there is appreciable mortality from delayed diagnosis and treatment. The standard 6-month regimen containing both isoniazid and rifampicin, with pyrazinamide and ethambutol in the first 2 months, is used. If there is evidence of CNS involvement, treatment should be the same as for meningeal TB.
Pericardial TB

• Although TB of the pericardium is rare in the UK, it is potentially important because of the possibility of cardiac tamponade (pressure on the heart that occurs when blood or fluid builds up in the space between the heart muscle (myocardium)) and the outer covering sac of the heart (pericardium) and constrictive pericarditis, which are associated with a significant morbidity and mortality. The standard 6-month treatment regimen is recommended for patients with active pericardial disease. Glucocorticoids should also be prescribed.

Treatment of Tb in Special Circumstances

TB in children

• Doses are generally estimated to facilitate prescription of easily administered volumes of liquid or tablets of appropriate strength. Ethambutol should not routinely be used in young children, who would be unable to report visual disturbances should they occur. However, it may be used if there is toxicity or resistance to other agents.

Pregnancy

• Standard therapy should be given, although streptomycin should not be used as it may be ototoxic to the fetus. It is considered safe for mothers to breast feed while taking anti-tuberculous treatment. Pyridoxine (vitamin B6) supplementation (10–25 mg/day) is recommended for breastfeeding women taking isoniazid. Patients should be warned of the reduced effectiveness of oral contraceptives in regimens containing rifampicin, and advised to use other, non-hormonal contraceptives.

Monitoring Treatment

• In pulmonary TB, sputum examination and culture are the most sensitive markers of treatment success.
• Patients taking regimens containing rifampicin and isoniazid should be non-infectious within 2 weeks. If a patient does not become culture negative, it may be due to either drug resistance or non-adherence, the latter being more likely.

Adverse Reactions

• Rifampicin, isoniazid and pyrazinamide are all potentially hepatotoxic, and liver function should be checked before treatment commences with these drugs. Transient increases in transaminases and bilirubin commonly occur at the start of treatment although there is no need to continue to monitor liver function in patients where pre-treatment liver function was normal.
• Rifampicin is usually well tolerated, but gastro-intestinal upsets, fever and rash can occur. It will colour the urine orange-red within approximately 4 h of a dose.
• *Isoniazid* can cause fever, skin rashes and a dose-dependent peripheral neuropathy, probably due to depletion of vitamin B6. This reaction is rare at recommended doses, but certain patient groups which include problem drinkers (‘alcoholics’) and pregnant women are at greater risk and should receive pyridoxine supplementation at a dose of 10–25 mg/day.

• *Pyrazinamide* can cause hepatitis. This is not increased when the drug is given with isoniazid and rifampicin in the standard 6-month treatment regimen.

• *Ethambutol* ocular toxicity (optic neuritis) is by far the most important side effect of ethambutol.

**CHEMOPROPHYLAXIS**

• The use of chemoprophylaxis is important in preventing vulnerable individuals with LTBI from developing active TB disease.

• Prophylaxis is usually with isoniazid alone for 6 months or rifampicin and isoniazid for 3 months.

**BCG VACCINE**

• BCG (Bacillus Calmette–Guérin) vaccine contains a live, attenuated strain derived from *M. bovis*. It does not protect against infection, but it prevents the more serious forms of disease such as miliary TB and meningeal TB.