Current approaches to the management of tuberculosis

Navin Venkatraman MRCP, DTM&H, Thomas Morris MRCP, DTM&H and Martin Wiselka PhD, MD, FRCP

Tuberculosis is the second leading infectious cause of death worldwide and cases are increasing in the UK. Here, the authors consider the pathogenesis and recommended management of TB.

Tuberculosis (TB) remains one of global health's biggest challenges with one-third of the world’s population infected and nine million new cases annually. Worldwide, the highest rates of infection are in South-east Asia and sub-Saharan Africa. In recent years UK numbers have steadily increased, with 9042 new cases reported during 2011.1

How is tuberculosis transmitted?
TB is caused by a group of resilient bacteria known as the 'Mycobacterium tuberculosis complex'. The commonest agent is M. tuberculosis.

TB is primarily a respiratory disease, with at least 50 per cent of cases involving the lungs (see Table 1).2 Transmission is by spread of aerosolised respiratory droplets that establish infection within alveolar macrophages. Depending on the infectious dose and the host immune response, these bacilli can be cleared, lie dormant (latent infection) or reproduce to cause active primary disease. This may manifest locally in the lung or disseminate in the bloodstream to other organs.

The other mechanism is by reactivation of latent infection following weakening of the immune system. This postprimary disease or secondary TB also has the potential for further spread through the lymphatic system or via the bloodstream.

There is a significant degree of variability in infectivity between patients. Characteristics of highly infectious individuals are summarised in Table 2. Patients with smear-positive pulmonary TB, ie acid-fast bacilli visible on sputum smear microscopy, are at higher risk of transmission compared with those who are smear negative or have extra-pulmonary TB.3

Which patients are most at risk?
Given a high enough infecting dose, TB can affect anyone. From epidemiological data, however, there are certain risk factors for acquisition.4 As with any communicable disease these can be grouped based on the epidemiological triangle:
environmental factors, host factors and infectious agent.

**Environmental factors**
Close household contacts of patients with smear-positive pulmonary disease are at high risk of TB. overcrowding, poverty, malnutrition and lack of access to medical services are significant contributors worldwide in maintaining its spread. People who travel to or live in high-incidence countries are also at increased risk. The majority of UK immigrants who develop TB present within five years of their arrival.

**Host factors**
The majority of host factors are theoretically modifiable, although male gender, old age and certain chronic diseases such as diabetes mellitus also increase risk. Substance abuse is a significant predisposition and is likely to be linked with associated socioeconomic factors. Vitamin D has long been implicated in the immune response, and diminished levels may be associated with an increased risk of developing active TB.

The worldwide spread of HIV has played a significant role in the resurgence of TB. Approximately 1 in 14 new cases occur in HIV-positive individuals and the risk is strongly influenced by the level of immunosuppression. Through similar mechanisms, agents including steroids, anti-TNF therapy and immunosuppressants for autoimmune diseases and post-transplant patients also increase the risk.

**First- and second-line treatment options**
Since streptomycin was first used in 1944 as an anti-TB drug, numerous other agents have been discovered. During this time there has been a paradigm shift from monotheraphy to multidrug regimens. NICE guidelines inform the current UK management of TB. Specialist multidisciplinary teams including doctors, health visitors and nurses should manage all patients.

A minimum of six months’ treatment is recommended in all cases of active TB, with a two-month initial phase followed by a four-month continuation phase. A 12-month regimen is recommended for disease affecting the central nervous system. In high-risk patients treatment should not be deferred until microbiological confirmation if clinical, radiological and/or histological features are consistent with TB.

The use of four drugs in the initial phase aims to reduce bacterial load rapidly and decrease the risk of drug resistance. The recommended first-line regimen (see Table 3) for the initial phase is rifampicin (R), isoniazid (H), ethambutol (E) and pyrazinamide (Z). Rifampicin and isoniazid, the most potent drugs, are given for the continuation phase.

**Table 1.** Distribution (percentage) of TB cases in UK by disease site

<table>
<thead>
<tr>
<th>Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>51.6</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>31.7</td>
</tr>
<tr>
<td>Pleura</td>
<td>7.5</td>
</tr>
<tr>
<td>Bone</td>
<td>6.5</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>4.9</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>3.1</td>
</tr>
<tr>
<td>Miliary (disseminated)</td>
<td>3.0</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>1.6</td>
</tr>
</tbody>
</table>

**Table 2.** Characteristics of people highly contagious with TB

<table>
<thead>
<tr>
<th>Characteristic</th>
</tr>
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<tbody>
<tr>
<td>Vigorous cough</td>
</tr>
<tr>
<td>High cough frequency</td>
</tr>
<tr>
<td>Good performance status</td>
</tr>
<tr>
<td>Smear positivity</td>
</tr>
<tr>
<td>Short time to culture positivity</td>
</tr>
<tr>
<td>Poor compliance with treatment</td>
</tr>
</tbody>
</table>

**Table 3.** Dosages of first-line anti-TB drugs and their side-effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>&lt;50kg 450mg od 50kg 600mg od</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liver enzyme induction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Orange discoloration of urine and contact lenses</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>300mg od</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psychosis (rare)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>&lt;50kg 1.5g od 50kg 2g od</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gout/arthritis</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15mg/kg od</td>
<td>Loss of visual acuity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colour blindness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visual field defect</td>
</tr>
<tr>
<td>Rifinah</td>
<td>&lt;50kg 3 tabs of 150/100 50kg 2 tabs of 300/150</td>
<td>As above for rifampicin and isoniazid</td>
</tr>
<tr>
<td>Rifater</td>
<td>&lt;40kg 3 tabs od 40-49kg 4 tabs od 50-64kg 5 tabs od 65kg 6 tabs od</td>
<td>As above for rifampicin, isoniazid and pyrazinamide</td>
</tr>
<tr>
<td>Voractiv</td>
<td>30-39kg 2 tabs od 40-54kg 3 tabs od 55-70kg 4 tabs od &gt;70kg 5 tabs od</td>
<td>As above for rifampicin, isoniazid, pyrazinamide and ethambutol</td>
</tr>
</tbody>
</table>

**Drug**

- Rifampicin
- Isoniazid
- Pyrazinamide
- Ethambutol
- Rifinah
- Rifater
- Voractiv

**Dosage**

- Rifampicin
  - <50kg 450mg od
  - >50kg 600mg od
- Isoniazid
  - 300mg od
- Pyrazinamide
  - <50kg 1.5g od
  - >50kg 2g od
- Ethambutol
  - 15mg/kg od
- Rifinah
  - <50kg 3 tabs of 150/100
  - >50kg 2 tabs of 300/150
- Rifater
  - <40kg 3 tabs od
  - 40-49kg 4 tabs od
  - 50-64kg 5 tabs od
  - >65kg 6 tabs od
- Voractiv
  - 30-39kg 2 tabs od
  - 40-54kg 3 tabs od
  - 55-70kg 4 tabs od
  - >70kg 5 tabs od

**Adverse effects**

- Hepatotoxicity
- Liver enzyme induction
- Orange discoloration of urine and contact lenses
- Peripheral neuropathy
- Hepatitis
- Psychosis (rare)
- Gout/arthritis
- Loss of visual acuity
- Colour blindness
- Visual field defect
- As above for rifampicin and isoniazid
- As above for rifampicin, isoniazid and pyrazinamide
- As above for rifampicin, isoniazid, pyrazinamide and ethambutol

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resistance to one of the first-line agents, and multidrug resistance (MDR) implies resistance to both rifampicin and isoniazid. Extensively drug-resistant (XDR) TB is MDR plus resistance to a fluoroquinolone and at least one injectable second-line drug (amikacin, capreomycin or kanamycin). A risk assessment for drug resistance (see Table 4) should be made in all cases.

A specialist team should manage drug-resistant TB with at least five second-line drugs including an injectable agent. The precise drug regimen depends on final sensitivities. The initial phase lasts for at least eight months and a total length of at least 20 months’ treatment is recommended.9

### The GP’s role in management

The primary-care physician has important roles to play including timely recognition and diagnosis of TB, prompt referral to specialist care and support of patients through prolonged treatment. Constitutional symptoms such as anorexia, fever, night sweats and weight loss should trigger the suspicion of active TB. A cough lasting more than three weeks, chest pain or haemoptysis are common symptoms of pulmonary TB; Table 5 summarises features of extrapulmonary disease.

Active screening for TB should be performed in high-risk groups, particularly new UK entrants from high-incidence areas. Appropriate screening investigations include Mantoux (tuberculin) test or interferon-γ release assay (IGRA). A positive result should be referred to a specialist and a negative test should prompt education about the symptoms of TB, with vaccination if appropriate (see Table 6).

### BCG (Bacillus Calmette-Guérin) is a live attenuated vaccine and should therefore not be given in impaired cellular immunity. Conversely, the vaccine is highly immunogenic and should therefore not be given to those with induration of 6mm or more following Mantoux testing owing to a risk of severe skin blistering.

Anyone diagnosed with active or latent TB should be offered HIV testing in a primary healthcare setting.

### Conclusion

TB remains a significant global health problem. Poverty, HIV and the emergence of drug resistance have hindered efforts to achieve control and rising UK numbers reflects this increased global incidence. The rapid diagnosis and treatment of TB should involve a multidisciplinary approach including primary-care physicians, specialist doctors, health visitors and nurses. Clinicians should be aware of the presenting symptoms and indications for referral, testing and vaccination.

### References

8. Tuberculosis: Clinical diagnosis and management of tuberculosis, and measures for its prevention and control. CG117. NICE, March 2011.

### Table 4. Risk factors for drug-resistant TB in the UK

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache &gt;6 days</td>
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<tr>
<td>Worsening back or joint pain</td>
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<tr>
<td>Lymphadenopathy</td>
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<tr>
<td>Pleural effusion</td>
</tr>
<tr>
<td>Chronic diarrhoea</td>
</tr>
<tr>
<td>Ascites</td>
</tr>
<tr>
<td>Sterile pyuria</td>
</tr>
<tr>
<td>Urethral stricture</td>
</tr>
</tbody>
</table>

### Table 5. Some clinical features of extrapulmonary TB

(RHEZ), a fixed-dose quadruple tablet, has become available. Rifinah (RH) is used similarly in the continuation phase.

The regimen should be optimised depending on final drug sensitivities. Adjunctive corticosteroids are indicated in pericardial and meningeal disease.

All patients should be counselled about side-effects (see Table 3) and the importance of adherence. Visual acuity plus liver and renal function should be documented beforehand. All patients should be offered HIV testing. In patients where visual acuity cannot be monitored or there is concern about pre-existing eye disease, the fluoroquinolones – levofloxacin or moxifloxacin (Avelox) – are suitable alternatives to ethambutol. Streptomycin is now rarely used except in cases of known isoniazid monoresistance.

Directly observed therapy (DOT) is advised on a thrice-weekly basis for patients felt to be unlikely to comply with daily dosing. Risk factors that should trigger referral for DOT include drug resistance, homelessness, alcoholism, drug abuse, mental illness or a history of non-adherence.

The emergence of drug-resistant TB is well recognised, and increasing UK numbers pose a significant challenge to TB control. Drug-resistant TB is defined as

### Table 6. Indications for BCG vaccination

- all infants (aged 0–12 months) living in areas of the UK where the annual incidence of TB is 40/100 000 or greater
- all infants (aged 0–12 months) with a parent or grandparent who was born in a country where the annual incidence of TB is 40/100 000 or greater
- previously unvaccinated children aged 1–5 years with a parent or grandparent who was born in a country where the annual incidence of TB is 40/100 000 or greater
- previously unvaccinated, tuberculin-negative children aged from 6 to 16 years of age with a parent or grandparent who was born in a country where the annual incidence of TB is 40/100 000 or greater
- previously unvaccinated, tuberculin-negative individuals under 16 years of age who are contacts of cases of respiratory TB
- previously unvaccinated, tuberculin-negative individuals under 16 years of age who were born in or who have lived for a prolonged period (at least 3 months) in a country with an annual TB incidence of 40/100 000 or greater

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Recommended reading

Declaration of interests
None to declare.

Dr Venkatraman and Dr Morris are infectious diseases registrars and Dr Wiselka is consultant and honorary senior lecturer in infectious diseases in the Department of Infectious Diseases and Tropical Medicine, University Hospitals of Leicester.