Current recommended management of tuberculosis

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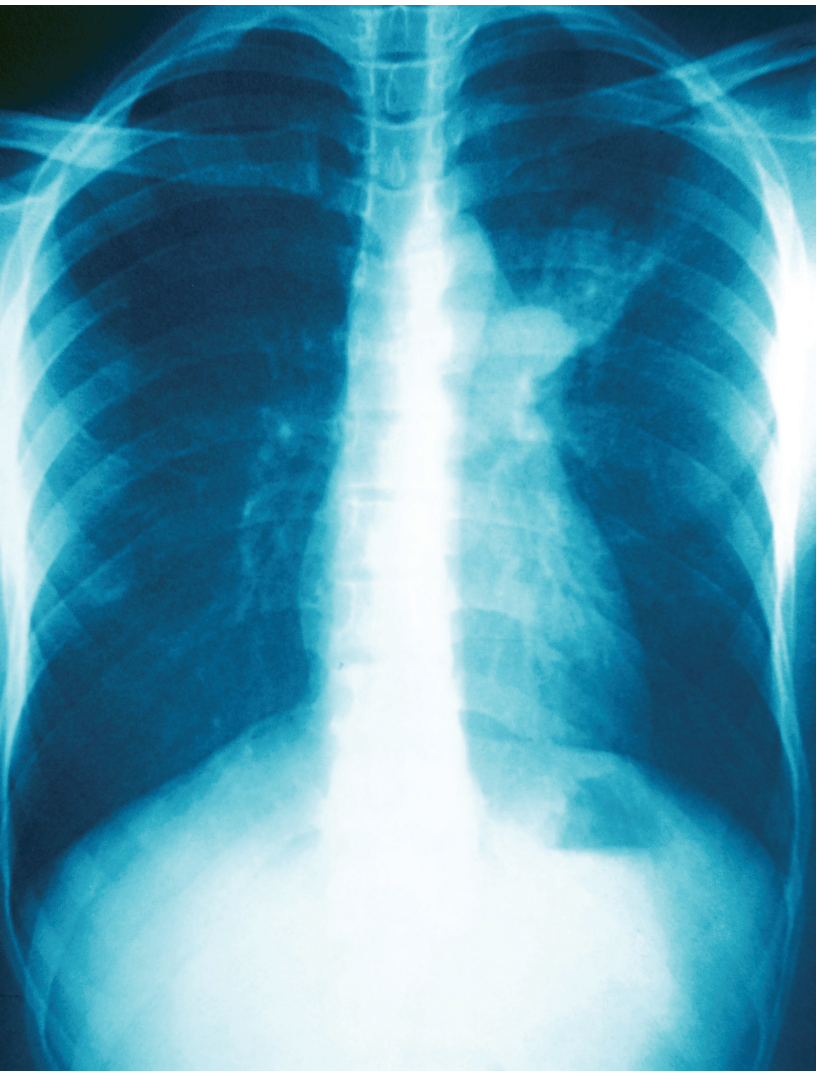

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Despite reductions in overall case numbers both globally and in the UK, tuberculosis (TB) remains a major health problem. Here, the authors discuss the pathogenesis of TB and important aspects of management, alongside recent developments in epidemiology, diagnostics and treatment.

Tuberculosis (TB) has recently been described as a neglected epidemic.[1] Despite significant resource investment, it is now the leading worldwide cause of death from a single infectious agent, although overall cases are falling both globally and in the UK.[2,3] However, in 2017 there were still an estimated 10 million incident cases globally, 1.3 million deaths in HIV-negative people and a further 300,000 deaths in those with HIV co-infection.[3]

In England in 2017, there were 5102 new reported cases of TB (incidence rate 9.2 per 100,000).[2] Although the lowest number of recorded cases since 1990, England continues to have one of the highest rates of TB in Western Europe. To address this, the Collaborative Tuberculosis Strategy for England 2015 to 2020 (a joint venture by NHS England and Public Health England [PHE]) aims to deliver continued decreases in TB incidence.

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% of cases involving the lungs (see Table 1).[2] Transmission is by spread of aerosolised respiratory droplets that establish primary 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.

Reactivation of latent tuberculosis infection (LTBI) may follow weakening of the immune system and is known as post-primary disease, which 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, which is likely to be multifactorial. The patients who are most

Site	Proportion
Lung	54.4%
Lymph nodes	33.1%
Pleura	8.6%
Bone	6.0%
Gastrointestinal tract	4.6%
CNS	4.3%
Miliary (disseminated)	2.7%
Genitourinary	1.5%

Table 1. Distribution of tuberculosis cases in England by disease site[2]

infective are those with cavitating lung disease, a productive cough and who have acid-fast bacilli (AFB) on sputum smear microscopy.[4]

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.[5] 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.[6] Overcrowding, poverty, malnutrition and marginalisation leading to 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.

Host factors

Male gender, old age and certain chronic diseases such as diabetes mellitus and occupational lung disease result in increased risk of TB. Modifiable risk factors, such as homelessness, smoking tobacco and substance abuse including alcohol continue to pose a significant predisposition and are often linked with associated socioeconomic factors.[5]

Increasing numbers of immunocompromised and elderly people will also increase the burden of potential TB cases. The worldwide burden of HIV continues to play a significant role in the ongoing TB epidemic, with 9% of new cases in 2017 occurring in HIV-positive individuals and mortality three-fold higher in this group.[3] The risk is strongly influenced by the level of immunosuppression, but even patients who have achieved viral suppression and $CD4^+$ count restoration are still at greater risk of developing TB.[7] The clinical presentation of TB is also affected by HIV co-infection, with patients possibly presenting without cough and with atypical features on chest X-ray, such as lower lobe infiltrates instead of classical upper lobe lesions, or no abnormality at all.[8]

First- and second-line treatment options

The NICE guideline was updated in 2016 and this informs the current UK management of TB.[9] The backbone of treatment for active TB remains a multi-drug regimen for a minimum of six months' duration, with a two-month initial phase followed by a four-month continuation phase. A 12-month regimen is recommended for disease affecting the CNS. In high-risk patients, treatment should not be deferred until microbiological confirmation if clinical, radiological and/or histological features are consistent with TB. Specialist multidisciplinary teams including doctors, health visitors and TB specialist nurses should manage all patients.

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 2) 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. Rifampicin inhibits bacterial DNA-dependant RNA polymerase, isoniazid and ethambutol interfere with cell wall formation and pyrazinamide inhibits protein synthesis.

Combination agents Rifater (RHZ) and Voractiv (RHEZ) may be used to reduce tablet burden during the induction phase of treatment. 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.[9]

All patients should be counselled about the importance of adherence and adverse effects (see Table 2). Visual acuity plus liver and renal function should be documented before treatment. 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 – are suitable alternatives to ethambutol. Liver function should be carefully monitored in patients with non-severe liver disease, those with abnormal liver function pre-treatment and in those who misuse alcohol or drugs. Streptomycin is still rarely used, except in cases of hepatotoxicity or cutaneous drug reaction on standard therapy.[9]

Directly observed therapy (DOT) is advised on a daily or thrice-weekly basis for patients felt to be unlikely to comply with unsupervised 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.[10] With advances in smartphone technology, some centres have trialled video observed therapy, although its use is not widespread.

Drug-resistant tuberculosis

Resistance to first-line anti-tuberculosis treatment is an evolving concern. Multi-drug resistant TB (MDR-TB) is defined as laboratory-confirmed resistance to two first-line therapies, isoniazid and rifampicin, while extensively drug-resistant TB (XDR-TB) exhibits resistance to isoniazid, rifampicin and at least one fluoroquinolone and one injectable agent, *eg* amikacin or capreomycin.[11] Current data for England reveals minor recent decreases in confirmed or suspected drug resistance, with 55 cases treated for MDR-TB and three cases treated for XDR-TB in 2017.[2]

Though drug-resistant TB can occur in anyone, resistance is more likely in those with a previous history of TB and in those with social risk factors, particularly drug misuse or imprisonment. Drug resistance is also more common in non-UK born people compared with those born in the UK, with the highest number of cases in those born in India or Lithuania. The greatest proportion of TB cases that exhibit drug resistance is seen in those born in eastern Europe, particularly Lithuania.[2,9]

Since 2014, the novel class agents bedaquiline and delamanid have been approved for use in the UK as part of combination therapy for MDR-TB. Both have been shown to increase sputum culture conversion from positive to negative. The most significant adverse effect, particularly with bedaquiline, is prolongation of the QT interval and close monitoring is required. Other agents that have been repurposed for use in MDR-TB treatment include linezolid, meropenem and clofazimine.[10]

A specialist team should manage drug-resistant TB with at least five second-line drugs including an injectable agent. Treatment should be undertaken ideally at an MDR-TB centre and discussion held with the British Thoracic Society UK MDR-TB Clinical Advice Service. The initial phase is recommended to last for at least nine months, with a total treatment duration of up to 20 months, or longer if required. More recently, the WHO has advocated a shorter 9–12 month regimen with seven drugs that can be used in selected patients who have not been previously treated with second-line drugs for more than one month, and in whom resistance to fluoroquinolones and second-line injectable agents has been excluded.[12]

There is also evidence emerging in favour of oral-only regimens, which would greatly reduce the degree of inconvenience of treatment for the patient concerned.

Molecular diagnostics for detection of mycobacteria

Advancements in molecular diagnostic techniques have led to reductions in the time to diagnosis and initiation of anti-tuberculosis therapy. Widely accessible nucleic amplification tests (Xpert/Xpert Ultra) have high positive predictive value for distinguishing between tuberculous and non-tuberculous mycobacteria in smear-positive specimens. The WHO End TB Strategy calls for the early diagnosis of TB and universal drug susceptibility testing (DST), and recommends the use of molecular line probe assays as a rapid diagnostic test for detection of rifampicin and isoniazid resistance.[13] However, these platforms do not replace traditional microbiological tests, including sputum smear for AFB, culture and sensitivity testing.

March 2017 saw the launch of routine whole genome sequencing (WGS) for mycobacterial infections undertaken by PHE. All mycobacterial positive cultures sent to the PHE reference laboratory undergo WGS, with reports returned to clinicians within five to seven days detailing mycobacterial species, and predicting drug susceptibility and genetic relatedness for the *Mycobacterium tuberculosis* complex.[14] It is anticipated that this will have profound impacts upon treatment and control of TB in the UK, including individually tailored anti-tuberculosis

Drug	Dosage	Adverse effects
Rifampicin	<50kg body weight: 450mg daily ≥50kg body weight: 600mg daily	Hepatotoxicity Liver enzyme induction Orange discoloration of urine and contact lenses
Isoniazid	300mg daily	Peripheral neuropathy Hepatitis Psychosis (rare)
Pyrazinamide	<50kg body weight: 1.5g daily ≥50kg body weight: 2g daily	Hepatotoxicity Gout/arthropathy
Ethambutol	15mg/kg daily	Loss of visual acuity Colour blindness Visual field defect
Rifater (rifampicin/isoniazid/pyrazinamide)	<40kg body weight: 3 tablets daily 40–49kg body weight: 4 tablets daily 50–64kg body weight: 5 tablets daily ≥65kg body weight: 6 tablets daily	As above for rifampicin, isoniazid and pyrazinamide
Rifinah (rifampicin/isoniazid)	<50kg: 3 tablets of 150mg/100mg ≥50kg: 2 tablets of 300mg/150mg	As above for rifampicin and isoniazid

Table 2. Dosing of first-line anti-tuberculosis drugs and their adverse effects

therapy according to the susceptibility of the specific mycobacterium causing infection.[15]

The GP's role in management

The primary care physician continues to play important roles 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, significant weight loss, unexplained fatigue or lymphadenopathy, especially cervical nodes, should trigger the suspicion of active TB. A cough lasting more than three weeks, chest pain or haemoptysis are common symptoms of pulmonary TB.

The new migrant LTBI systematic testing and treatment programme has been in existence since 2015. At present, no gold-standard test exists for screening LTBI; however, in the UK an interferon-gamma release assay (IGRA) is used for screening purposes, with a recommendation to also screen for HIV in individuals arriving from high-incidence countries.[16] Focus is placed upon migrants aged 16–35 years old arriving into the UK within the past five years.[17] A positive IGRA test result should prompt referral to a TB specialist and HIV screening, and a negative test should prompt education about the symptoms of TB.

BCG (*Bacillus Calmette-Guérin*) is a live attenuated TB vaccine and recommendations for eligible populations (see Table 3) and contraindications are outlined in *The Green Book*.[18]

- All infants (aged 0 to 12 months) living in areas of the UK where the annual incidence of tuberculosis (TB) is 40/100,000 or greater
- All infants (aged 0 to 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 one to five 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 between six and 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 close contacts of respiratory TB cases
- Previously unvaccinated, tuberculin-negative individuals under 16 years of age who were born in or who have lived for a prolonged period (at least three months) in a country with an annual TB incidence of 40/100,000 or greater

Table 3. Indications for BCG vaccination in the UK[18]

Conclusion

Despite reductions in overall case numbers, TB remains a major global health problem. Its continued association with HIV and poverty, alongside the increasing burden of MDR-TB, presents a particular challenge to controlling this disease. However, there is hope that recent advances in molecular diagnostics and new drug classes will have an important role to play. Early recognition of symptoms and screening of at-risk groups facilitate rapid diagnosis and treatment, which should involve a multidis-

ciplinary approach including primary care physicians, specialist doctors, health visitors and nurses.

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Recommended reading

TB Drug Monographs: A UK based resource to support the monitoring and safe use of anti-tuberculous drugs and second-line treatment of multi-drug resistant tuberculosis. Available from: www.tbdrugmonographs.co.uk

Declaration of interests

None to declare.

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