

Treating drug-resistant tuberculosis

June Minton, Yogini Jani and Anthony Grosso look at the prevention of tuberculosis and the treatment of drug-resistant strains

Resistance in all micro-organisms is a growing problem across the world. Drug-resistant tuberculosis (TB) has been recognised since the 1940s, with the rapid emergence of streptomycin resistance unless a combination of drugs was used.

Drug-resistant tuberculosis

Drug-resistant TB can be said to exist when treatment with a drug suppresses the growth of some bacilli (susceptible to that drug) but permits multiplication of pre-existing drug-resistant organisms. "Multidrug-resistant TB" (MDRTB) is resistant to both isoniazid and rifampicin. TB that is resistant to isoniazid, rifampicin and at least one second-line drug (see later for examples) is referred to as "super resistant" or "highly resistant". Second-line drugs are reserved for drug-resistant bacilli or when standard first-line drugs cause adverse effects. (See *PJ*, 18 September, p386 for a discussion of first-line drugs for TB.)

Drug resistance can be further classified as being "acquired" or "primary". Acquired drug resistance occurs in patients who have been treated for some time and for various reasons (eg, incomplete, erratic or inadequate treatment and poor quality of standard first-line anti-TB drugs) the bacilli become resistant to treatment. Primary drug resistance refers to tuberculosis that is drug-resistant from the outset — the patient contracts strains that are already drug-resistant (see Figure 1).

Major pathways to drug resistance The emergence of resistance is more likely where the bacterial load is high, such as in extensive or cavitary pulmonary disease.¹ Data collated

by the World Health Organization show that 85 per cent of all drug-resistant TB cases are made up of strains that are:

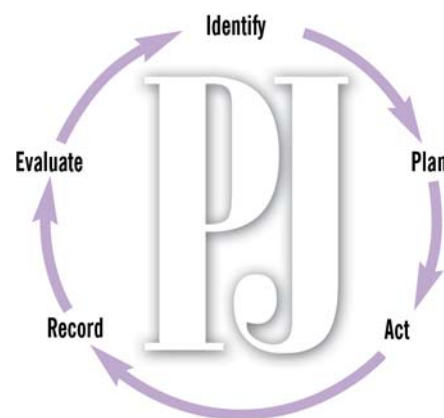
- Resistant to isoniazid or streptomycin (monoresistant)
- Resistant to isoniazid and streptomycin (double resistant)
- Resistant to isoniazid, streptomycin and rifampicin (triple resistant)
- Resistant to isoniazid, streptomycin, rifampicin and ethambutol (quadruple resistant)

Mono-resistance to isoniazid or streptomycin is thought to be the foundation for the acquisition of additional drug resistance. If mono-resistance to isoniazid is suspected, ethambutol should be included in initial standard first-line regimen (see *PJ*, 18 September p387). Streptomycin mono-resistance is considered less clinically important because the drug is rarely used — the efficacy of the regimen recommended for both respiratory and non-respiratory TB is not affected.

Trends in drug resistance In recent years, the spread of resistance has been accelerated by the increasing number of patients infected with human immunodeficiency virus, as highlighted in a recent WHO report.² Points from this report are summarised in Panel 1. Incidence of drug-resistant TB is on the increase in the UK (see Table 1). The proportion of resistant cases is significantly higher in groups with previous history of TB and among foreign-born patients. London, which has the highest incidence of TB in the UK because of the high homeless, migrant and substance misuser population, had the highest number of isoniazid-resistant cases in the outbreak recognised in 2000.

Treatment of MDRTB

Treatment failure during therapy or relapse after treatment in patients prescribed the standard British Thoracic Society (and WHO) first-line regimen is most likely to be caused by poor compliance, which may have caused drug resistance. The WHO strategy of



Identify knowledge gaps

1. What is the definition of multi-drug resistant tuberculosis?
2. What is DOTS- plus?
3. What are the UK recommendations for BCG vaccination?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: www.rpsgb.org/education). This article relates to "common disease states and their drug therapies" (see appendix 4 of "Plan and record").

using short course, directly-observed treatment (DOTS) has slowed the progress of drug-resistant TB, but not MDRTB, for which second-line reserve drugs (which are

Table 1: UK drug resistance surveillance (excluding Scotland)

Type of resistance	% of cases in 1996 ¹	% of cases in 2001 ²
Isoniazid	6.1	7.9
Rifampicin	1.8	3.1
Multidrug resistance	1.6	2.4
Ethambutol	—	2.6

Panel 1: Points from the third WHO report on anti-TB drug resistance²

- It is estimated that there are 300,000 cases of MDRTB in the world and most exist where HIV is spreading most rapidly
- 79 per cent of MDRTBs are super strains (ie, resistant to three or four first-line drugs)
- TB patients in Eastern Europe and the former Soviet Union are 10 times more likely to have MDRTB

June Minton, BPharm, MRPharmS, is a HIV/GUM and infectious diseases pharmacist, Yogini Jani, MSc, MRPharmS, is a senior clinical pharmacist and Anthony Grosso, BSc, MRPharmS, is principal pharmacist, formulary and medicines management. They are all at University College London Hospitals NHS Foundation Trust

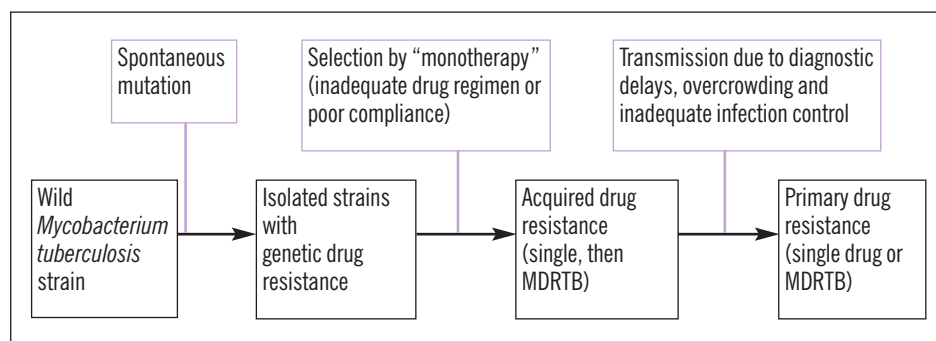


Figure 1: The development and spread of drug-resistant and MDRTB

less effective, more expensive and more toxic) have to be used. In such cases, treatment is usually managed by specialised units, which have the services of a laboratory able to carry out reliable drug sensitivity testing.

MDRTB drug regimens are tailored to sensitivity test results and previous treatment history. The five different drug types used for the treatment of MDRTB usually include⁴:

- A first-line oral agent to which the isolate is sensitive
- An injectable second-line drug (usually an aminoglycoside)
- A quinolone
- Other second-line bacteriostatic drugs needed to make up the five-drug regimen (two second-line drugs can be used or, in patients where it is possible to reuse pyrazinamide or ethambutol, one second line drug can be used depending on sensitivity results)

Andy Crump, TDR, WHO/SPL

Again, treatment is directly observed. This approach has been referred to as "DOTS-plus". More than five drugs can be used if sensitivities are unclear. After sputum conversion, treatment is continued with two drugs (or three, if strains are super-resistant) for at least 18 months to prevent relapse.

All doses and routes of administration mentioned below are based on the BTS and WHO dosing guidelines and local practice at University College London Hospitals NHS Foundation Trust. Some drugs, doses and indication for use in TB are unlicensed in the UK.

Aminoglycosides Aminoglycosides (eg, streptomycin, kanamycin, amikacin and capreomycin) have bactericidal activity against actively multiplying organisms. They inhibit protein synthesis and cause misreading of mRNA so that non-functional proteins are synthesised.

The usual dose is 15mg/kg/day (maximum 1g), given by injection. Amino-

Genetically modified tuberculosis bacteria are used for vaccine research

glycosides have a narrow therapeutic index and most side effects are dose-related. Therefore, therapeutic drug monitoring should be carried out, particularly in patients with renal impairment or in those on other nephrotoxic drugs. The main side effects are nephrotoxicity, ototoxicity, ataxia and vertigo.

Thioamides Ethionamide and prothionamide are two different presentations of the same active substance — they are related nicotinic acid derivatives. Thioamides are bacteriostatic at therapeutic concentrations, but can be bactericidal at higher doses. The mode of action is thought to be inhibition of mycolic acid biosynthesis in *Mycobacterium tuberculosis*. The usual dose range is 10–20mg/kg/day (maximum 1g/day) in one dose or two divided doses.

The most common side effects are gastrointestinal (eg, nausea, vomiting, diarrhoea and metallic taste). Rare effects include optic neuritis and diplopia, elevated liver function tests (LFTs), altered thyroid function tests (TFTs) and hypoglycaemia. Monitoring should, therefore, include ophthalmic examinations, periodic LFTs and TFTs and, in diabetic patients, blood glucose tests.

Fluoroquinolones The quinolone antibiotics (eg, ofloxacin, ciprofloxacin, moxifloxacin) are bactericidal. They act by inhibiting bacterial DNA replication by blocking DNA topoisomerases, DNA gyrase in particular.

Examples of typical doses are:

- Ofloxacin 600–800mg/day in divided doses
- Ciprofloxacin 500–750mg *bd*
- Moxifloxacin 400mg *od*

Side effects include gastrointestinal upset, raised LFTs, jaundice, tendon rupture, fits and,

rarely, photosensitivity. Monitoring should include renal function and LFTs. Dose reductions can be required in moderate to severe renal impairment.

Macrolides Macrolides are predominantly bacteriostatic but can have some bactericidal activity. They bind to the 50s ribosomal sub-unit of susceptible bacteria and suppress protein synthesis. Examples of typical doses used in TB are clarithromycin 500mg *bd* and azithromycin 500mg *od*.

The main side effects of the macrolides are gastrointestinal upset, taste disturbances (with clarithromycin), raised LFTs and jaundice.

Cycloserine Cycloserine competes with D-alanine for incorporation into the cell wall and, therefore, interferes with bacterial wall synthesis. The usual dose is 500mg–1g daily, in divided doses. It is suggested that an initial dose of 250mg twice a day should be used for the first two weeks.

Most frequent side effects involve the central nervous system and include anxiety, headache, dizziness, vertigo, fits, psychoses (possibly with suicidal tendencies), depression and paranoia. Patients should be counselled about these potential effects before starting therapy. Hypersensitivity reactions (including rashes and photosensitivity) have been reported rarely.

Blood levels should be monitored, particularly in renal impairment. Neurological side effects are minimised if plasma concentrations do not exceed 30mg/L. Monitoring should also include full blood counts, folate and vitamin B₁₂ levels as well as renal function and LFTs.

TB prevention

Prevention strategies can be divided into two types: pharmacological and non-pharmacological.

Pharmacological interventions There are no data on what chemoprophylaxis regimen is effective in persons in contact with MDRTB. Therefore, current advice in the UK is long-term regular follow up of individual cases.

Global prevention Spread of TB can be prevented and has been part of the national immunisation schedule since 1953.⁵ All children between the ages of 10 and 14 years should be screened for immunity to TB by means of a Heaf test.

A patient with a grade 0 or 1 reaction or induration of up to 4mm should be vaccinated. Those with a grade 2 or above reaction

HIV co-infection

TB in patients with HIV can develop more rapidly and present in atypical ways compared with patients without HIV. It can generally be treated with standard TB treatment regimens but there is a potential for many complex drug interactions (particularly involving rifamycins with anti-retroviral agents). The British HIV Association has recently produced draft guidelines for treatment of co-infected patients which discusses these in depth (available at www.bhiva.org). The risk of adverse reactions to TB therapy appears to be increased in this group of patients.

Infection control should be more stringent in health care settings where patients with HIV are treated because of their increased susceptibility in contracting TB once exposed. At University College Hospital co-infected patients are treated in the chest clinic and do not attend the HIV clinic until their TB has been adequately treated.

Future treatments and vaccines

Faster and simpler therapy is essential to fighting TB's rapid spread, its deadly synergy with HIV and acquired immunodeficiency syndrome and its ability to mutate into drug-resistant strains. For the first time in 40 years, a robust portfolio of drugs is being assembled, managed and advanced toward clinical trials.

Advances in mycobacterial genetics and immunology over the past decade, including genome sequencing of *Mycobacterium tuberculosis* in 1998, have allowed the formulation of a wide range of new vaccine candidates. As explained in the main text, the current vaccine has an efficacy of only 70–80 per cent for at least 10 years so any improvement on this would be a huge advance against a disease that has growing incidence, resistance and mortality (if untreated) associated with it. One vaccine, developed in the UK, entered a Phase I safety trial this year. A usable new TB vaccine is probably a decade away.

are hypersensitive to tuberculin purified protein derivative (ie, they may have latent TB infection or previous exposure to TB) and should not be vaccinated. Those who have recently moved to the UK or have a history of contact with TB should be referred to a chest clinic for further screening.

Although Bacillus Calmette-Guérin (BCG) vaccination is recommended for all people who have a negative Heaf test during screening, it has been shown to confer most immunity in children under the age of 16 years.⁶ Vaccination should, therefore, only be offered to older people if there are specific occupational, ethnic or travel risk factors that put them at high risk. The vaccine has an efficacy of 70–80 per cent for at least 10 to 15 years.

People who have an increased chance of contact with TB in an occupational setting are also recommended to have their immunity routinely assessed when starting work. This includes the following groups of staff:

- Health care workers
- Prison and police officers
- Veterinary workers

BCG should not be given to people who:⁷

- Have untreated malignant disease or altered immunity; this includes people receiving immunosuppressive treatment, radiotherapy or high dose steroids
- Are HIV-positive
- Have TB or a positive tuberculin skin test
- Are pregnant
- Have a generalised septic skin condition
- Have received another live vaccine less than three weeks earlier, although two live vaccines can be given at the same time (this three-week gap does not apply to oral polio vaccine)

Non-pharmacological interventions

Non-pharmacological interventions include isolation and contact tracing.

Isolation As a rule, people with suspected or confirmed TB should be considered potentially infectious until proved otherwise. These people should not mix with immunocompromised patients and should not be on the same ward as such patients unless they are nursed in a separate room with appropriate negative pressure isolation facilities.

Any patient with smear-positive pulmonary TB should, ideally, be nursed in a negative pressure isolation room until drug therapy has rendered him or her “non-infectious”. Infectiousness is assessed clinically, but usually requires a minimum of two week's administration of effective anti-tuberculous therapy. During this period, visitors should be limited to minimise the risk of disease transmission. If there are any concerns regarding drug resistance or poor response to therapy then patients should remain in isolation until three consecutive sputum samples (taken on different days) remain smear negative. For patients with MDRTB this last criteria is essential to minimise the risk of spread to other patients or staff.

The wearing of masks meeting the 1992 Personal Protection Equipment (EC Directive) Regulations has not been shown to reduce the development of TB in exposed health care workers, especially if the patient is nursed in a negative pressure isolation room. However, if someone has suspected or proved MDRTB then masks should be worn by all staff and visitors during patient contact, for the period during which the patient is considered infectious.

Contact tracing Contact tracing can identify additional people who might have been

Summary

- Monoresistance to isoniazid or streptomycin is thought to be the foundation for the acquisition of additional drug resistance
- Multidrug-resistant TB is usually treated with a five-drug regimen
- The Bacillus Calmette-Guérin vaccine has an efficacy of 70–80 per cent for at least 10 to 15 years
- Non-pharmacological interventions to prevent the spread of TB include isolation and contact tracing

infected by or be the source of infection for the index case (the earliest documented case of the disease). It also identifies who could benefit from chemoprophylaxis.

Active TB is diagnosed in approximately 1 per cent of contacts. Contact tracing should be undertaken rapidly to prevent the spread of disease and co-ordinated by a variety of members of the health care team including the consultant in communicable disease control, TB nurse specialist and chest clinic staff. Contact tracing is usually limited to close contacts of the index case. This is likely to include family, friends and colleagues who were in contact with the patient one month before he or she became symptomatic. All contacts should be screened according to British Thoracic Society guidelines (eg, Heaf test or x-ray or both).

Airport screening Most diagnoses of TB occur after entry into the UK. Individuals who have travelled from an area where the incidence of TB is high could be screened at airports by means of a chest x-ray, especially if they appear symptomatic. If there is a high level of suspicion of active disease the person can be referred to the local hospital for further tests.

Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Find out what the TB resistance pattern is in your area.
2. Investigate whether DOTS or DOTS-plus are used in your TB clinic.
3. Visit the TB antimicrobial acquisition and coordination facility (www.taacf.org) and find out about a global discovery programme for novel anti-TB drugs.

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities.

Answer the following questions:

What have you learnt?

How has it added value to your practice? (Have you applied this learning or had any feedback?)

What will you do now and how will this be achieved?

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