Drug resistant tuberculosis in adults and its treatment

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Mycobacterium tuberculosis (MTB), the bacterium that causes tuberculosis (TB), is estimated to have infected almost one-third of the world's population, producing eight million new clinical cases each year and leading to almost three million deaths. Over 95% of the cases occur in the developing world.

Drug resistance

Drug resistance develops spontaneously in bacteria. Combinations of drugs are used to make clinically significant resistance, and thus treatment failure, unlikely. Non-adherence to therapy, inappropriate prescribing, malabsorption of drugs, and deterioration of the clinical and public health infrastructure necessary for adequate supervision of treatment are all associated with the selection of drug resistant strains and treatment failure. Overall trends in drug resistance are also a crude indicator of the effectiveness of a national TB programme. Rates of multiple drug resistant TB (MDRTB) - that is, resistant at least to isoniazid and rifampicin, two of the major first line drugs - are indicative of poorly functioning programmes. Recent outbreaks of MDRTB in the USA and Europe, particularly in HIV-infected patients, have focused attention on the emergence of drug resistance.

The worldwide level of drug resistance in TB is not known, and methodological problems in many studies have prevented the development of a clear global picture. These include:

- the selection bias of many surveys
- the absence of high quality culture facilities.

In 1994, the World Health Organisation (WHO) and the International Union Against Tuberculosis and Lung Disease began the Global Project on Anti-tuberculosis Drug Resistance Surveillance. The recently published results of surveys and surveillance programmes from 35 countries report drug resistance in all countries. MDRTB was found to be widespread, with one-third of the countries surveyed having levels above 2% in new patients (median prevalence 1–4%; range 0–14%). High rates were found in former countries of the USSR, the Baltic Republics, Argentina, India and China. In general, countries with poor NTPs had a higher prevalence of drug resistance, especially MDRTB.

A laboratory-based surveillance programme, MYCOBNET, was created in the UK in 1994 to monitor drug resistance in TB. Preliminary trend analysis published for the period 1993–1996 showed that in initial isolates, resistance to isoniazid over this period rose from 4.6% to 6.1%, monoresistance to rifampicin from 0.6% to 1.8%, and multidrug resistance from 0.6% to 1.6%. During the same period, the combined clinical prevalence of MDRTB (the total level of resistance occurring in a year) rose from 0.6% to 1.7%.

Treatment of tuberculosis

The principles underlying the treatment of TB have not changed since chemotherapy became possible in the 1940s: that is, combination chemotherapy in standardised regimens for the appropriate period of time.
Currently, rifampicin, isoniazid, pyrazinamide and ethambutol or streptomycin are given for the first two months. The fourth drug is either added until drug susceptibility data become available or omitted where drug resistance is unlikely. This is then followed by rifampicin and isoniazid for a further four months. Combination tablets should be used, and therapy can be given daily or two or three times weekly. Steroids may be of value, for example in TB meningitis or pericarditis. Extrapulmonary TB is treated using the same drugs for the same period of time, except that bone/joint TB and meningitis should be treated for 6–9 months and 12 months, respectively. The usual doses and side effects of TB drugs are given in Table 1.  

The WHO has emphasised the role of ‘directly observed treatment, short course’ (DOTS) as a key strategy in which each dose taken by the patient is monitored by a health care worker (see p312 for fuller discussion), but the development of new drugs and vaccines must also be a priority. In practice, DOTS is not necessary for all cases, but close, regular supervision involving a physician with access to TB nursing/contact tracing services is critical to success. Patients with fully drug sensitive isolates are usually (but not always) rendered non-infectious after two weeks of adequate combination chemotherapy. Although some groups such as alcoholic/homeless individuals often adhere poorly to therapy, prediction of compliance is difficult (doctors, for example, are arguably some of the least compliant individuals!). Supervising physicians must have a low threshold for placing patients on DOTS. Where a patient does not respond to treatment and MDR-TB is suspected, further advice may be sought from the PHLS Mycobacterium Reference Unit (tel: 0181 693 2830).  

Single drug resistance, with the exception of rifampicin, poses only limited problems therapeutically. Isoniazid resistance alone can be treated by either:

Table 1. Front-line anti-tuberculosis drug in adults. In general, daily or thrice weekly regimens are preferred to twice weekly dosing.

| Drug            | Route* | Daily dose** | Intermittent twice weekly | Thrice weekly | Major side effects† | Monitoring‡ |
|-----------------|--------|--------------|--------------------------|---------------|---------------------|-------------|
| Isoniazid       | PO     | 300 mg       | 15 mg/kg max: 900 mg     | 15 mg/kg max: 900 mg | Peripheral neuropathy; hepatitis; CNS effects; increased phenytoin levels; interaction with drugs; hepatic enzyme elevation | LFT; levels of interacting drugs** |
|                 | IM     | 5 mg/kg      |                          |               |                     |             |
|                 | IV     |              |                          |               |                     |             |
| Rifampicin      | PO     | 600 mg       | 10 mg/kg max: 600 mg     | 10 mg/kg max: 600 mg | GI upset; hepatitis; rash; bleeding problems; contact lens and body fluids coloured orange/pink; decreased serum levels of warfarin, methadone, contraceptive hormone, dapsone, ketocanazole, theophylline; flu-like syndrome | LFT; levels of interacting drugs |
|                 | IV     | 10 mg/kg     |                          |               |                     |             |
| Pyrazinamide    | PO     | 1.5–2.5 g    | 2.5–3.5 g 50–70 mg/kg    | 2–3 g 50–70 mg/kg | GI upset; increase in hepatic enzyme levels; rash; joint pain; hyperuricaemia (gout rarely); may complicate control of diabetes mellitus | LFT; uric acid (if needed) |
|                 |        | 15–30 mg/kg  |                          |               |                     |             |
| Ethambutol      | PO     | 2.5 g (max)  | 50 mg/kg                 | 30 mg/kg      | Red/green colour blindness; optic neuritis; decreased visual activity; rash | Colour vision; visual acuity |
|                 |        | 15–25 mg/kg  |                          |               |                     |             |
| Streptomycin†   | IM     | 15 mg/kg     | 25–30 mg/kg              | 25 mg/kg      | Nephrotoxicity; ototoxicity; hypokalaemia; hypomagnesaemia | Blood chemistry renal function; audiometry |
|                 | IV     |              |                          |               |                     |             |

* Possible routes of administration; in practice, all drugs are given orally wherever possible.
** The daily dose is quoted for a man of average weight; all doses are adjusted in accordance with a patient’s weight.
† Isoniazid causes increased elimination of pyridoxine, leading to peripheral neuropathy particularly in alcoholics, the malnourished and in pregnancy. Daily doses of 10 mg of pyridoxine per day are sufficient to compensate for this loss.
‡ Liver function tests (LFT); specific monitoring points are given. At appropriate intervals, the patient should be monitored clinically, radiologically and bacteriologically. A full blood count (including platelets) should be performed if there is any bleeding tendency.
+ Streptomycin in patients over 60 years of age is more likely to lead to side effects; daily doses should be limited to 10 mg/kg, with a maximum dose of 750 mg. Closer observation of hearing loss and renal function may be necessary in this age group.
++ Aluminum-based antacids reduce absorption.

CNS = central nervous system; GI = gastrointestinal; IM = intramuscular; IV = intravenous; PO = per os
• rifampicin, pyrazinamide and ethambutol/streptomycin for 6–9 months, or
• rifampicin and ethambutol for 12 months.

Isolated streptomycin resistance poses no problems and requires no adjustment of regimen. Successful treatment of MDRTB, however, requires individualised therapy for prolonged periods with second- and third-line drugs. MDRTB carries a high mortality, particularly in the immunocompromised, but an improved outcome is associated with treatment using at least three drugs to which the organism is susceptible on in vitro testing (reviewed in Ref 3). Treatment should be planned with regard to the guidelines shown in the key points. The dosages, side effects and therapeutic monitoring requirements for second- and third-line agents are given in Table 2. Surgery (eg lobectomy, pneumonectomy) may also be a useful adjunct to medical treatment of localised pulmonary MDRTB and in the management of complications.

The rapid diagnosis of drug resistance is essential in order to institute correct therapy. Culture-based techniques (phenotypic methods) remain the basis of drug susceptibility testing, but novel automated rapid culture systems can reduce the time considerably. Molecular detection of drug resistance (genotypic methods) has been facilitated by the identification and sequencing of key genes and those regions associated with drug resistance.

### New drug therapies

The development of new therapeutic strategies for MDRTB remains slow. There has, however, been some progress in the development of novel agents within established drug groups.

### Table 2. Second-line anti-tuberculosis drugs in adults.

In general when commencing drugs at lower doses, the normal daily dose should be established as quickly as possible.

| Drug          | Route* | Daily dose                  | Major side effects                                                                 | Notes                                      |
|---------------|--------|-----------------------------|-----------------------------------------------------------------------------------|--------------------------------------------|
| Ciprofloxacin | PO     | 500–1,000 mg (max: 1,500 mg) (2 doses) | GI upset; abdominal cramps; photosensitivity; headache; insomnia; interacts with warfarin and theophylline; hypersensitivity | Antacids; iron supplements and sucralfate reduce gastrointestinal absorption. |
| Ofloxacin     | PO     | 600–800 mg                  | As above                                                                         | Monitor auditory and renal function; blood chemistry. |
| Amikacin†     | IM IV  | 15 mg/kg (max: 1 g)         | Otootisity; renal toxicity; occasional vestibular toxicity; hypokalaemia; hypomagnesaemia | Monitor LFT. Start with 250 mg daily dose and increase as tolerated. Increase to bd quickly. |
| Prothionamide | PO     | 0.5–1 g PO (in 1–2 doses)   | GI upset; raised hepatic enzymes; metallic taste; hypothyroidism (more likely if PAS given concurrently). (Antacids/emetics may help but watch other drug interactions) | Start with 250 mg daily and increase. Pyridoxine (50 mg) with each 250 mg may reduce CNS effect. |
| Cycloserine   | PO     | 0.5–1 g PO (in 1–2 doses)   | Rash; psychosis; depression; seizures; headache; increases phenytoin levels. Avoid if underlying CNS problems or depression | Monitor auditory and renal function; blood chemistry. |
| Capreomycin   | IM     | 15 mg/kg (max: 1 g)         | Otootisity; renal toxicity; vestibular toxicity; hypokalaemia; hypomagnesaemia; eosinophilia | Commence 1–2 g tds and increase as tolerated by patient. Tablets create a high sodium load – monitor volume and electrolytes in cardiac and renal patients. |
| PAS           | PO     | 8–12 g (divided doses)      | GI upset; increased hepatic enzymes; decreased digoxin levels; increased phenytoin levels; haemolytic anaemia in glucose-6-phosphate dehydrogenase deficiency | Only modest activity against TB; used principally to prevent emergence of drug resistance. |
| Clarithromycin| PO IV  | 500 mg PO (2 doses)         | GI upset; jaundice; hepatitis; interaction with many drugs including anticoagulants, antiepileptics, digoxin, rifabutin, usually by reducing liver enzyme activity | Avoid sunlight; dosing at mealtime may be helpful. |
| Clofazimine   | PO     | 100–300 mg                  | GI upset; causes skin darkening; abdominal pain; rare organ damage if drug crystal deposits occur |                                           |

* Drugs are given daily; orally wherever possible. Treatment of drug resistant TB should be performed by those experienced in its management.
† After bacteriological conversion, aminoglycosides can be given three times weekly.

CNS = central nervous system; GI = gastrointestinal; IM = intramuscular; IV = intravenous; PAS = para-aminosalicylic acid; PO = per os
for example, rifamycins (eg rifabutin, rifapentine), macrolides and fluoroquinolones (FQ), and also of immunomodulators and improved methods of delivering established agents.

**Rifabutin**

Rifabutin, a member of the rifamycin drug group, is as effective against MTB as rifampicin. It is also effective both against a small proportion of isolates that are resistant to rifampicin and as prophylaxis against *Mycobacterium avium intracellulare* (MAC). It is usually contraindicated with most protease inhibitors used in anti-retroviral therapy for HIV-positive patients. When used for MAC prophylaxis, it has been associated with acquired rifampicin monoresistance in subsequent TB and uveitis.

**Rifapentine**

A long half-life formulation, rifapentine, which permits weekly or twice-weekly dosing is being evaluated, but there were high relapse rates in a recent Hong Kong study using a Chinese manufactured drug due to the low bioavailability of the preparation. An improved formulation is undergoing trials in the USA and South Africa, but preliminary results in the former have also indicated a high rate of relapse with acquired rifampicin monoresistance.

**Benzoxazinorifamycin**

Benzoxazinorifamycin has a lower minimal inhibitory concentration in vitro than either rifampicin or rifabutin, but it exhibits cross resistance with rifampicin.

**Macrolides**

Novel macrolides such as azithromycin and clarithromycin show only modest activity against TB (approximately equivalent to thiacetazone). Their main use is to prevent the emergence of resistance to other drugs when used in combination with them.

**Fluoroquinolones**

Ciprofloxacin is a useful bactericidal second line agent for TB. Other FQs such as ofloxacin, levofloxacin and sparfloxacin which achieve higher serum levels have been developed, but there is no clear evidence that they are clinically more effective than ciprofloxacin.

**Delivery systems**

Novel delivery systems have a limited role at present, principally due to cost. For example, liposomally encapsulated amikacin in vitro and in experimental animals has better delivery and activity against MTB than the free agent because of increased macrophage uptake. Depot preparations may also circumvent compliance problems, and isoniazid preparations in rodents and rabbits have produced therapeutic levels for 60 days.

**Immunotherapies**

The use of *Mycobacterium vaccae* as an immunotherapeutic adjunct to chemotherapy is under evaluation in several locations in Europe, Asia and Africa. There are some recent encouraging results from Romania, but a randomised controlled trial in South Africa has recently reported disappointing results.

In vivo, different cytokines have been shown to inhibit or promote mycobacterial growth. Arguably the most studied has been gamma interferon (IFNγ), whose properties are indicated in Table 3. In mice, administration of IFNγ potentiates macrophage killing of MTB, and sublethal bacterial doses kill IFNγ gene knock out mice. Published data on the clinical use of immunomodulating cytokines in refractory TB are limited, but one recent open label study in which five MDRTB smear and culture positive patients were given chemotherapy and...
aerosolised IFNγ indicated that there was some clinical benefit, in that:
- body weight increased in all patients
- smears became negative
- the time taken to produce a positive culture decreased, reflecting a reduction in bacterial viability on treatment
- computed tomography showed a reduction in cavity size.

Thalidomide treatment, which antagonises the production of tumour necrosis factor, has been shown to produce weight gain and general well being. Animal studies with interleukin 12 have also shown some benefit (Table 3).

Conclusion

Effective supervised combination treatment is the key to successful therapy in drug sensitive or resistant TB. Nevertheless, if we are to address MDRTB seriously in cities like London with their significant social deprivation, higher numbers of homeless individuals and immigration from countries with considerable drug resistance problems, the development of model centres for treatment may need to be considered, together with the greater use of DOTS.

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