The challenge of multidrug resistant tuberculosis

Multidrug resistant tuberculosis (MDRTB) is defined as resistance to the two principal drugs used to treat TB, isoniazid and rifampicin, whether there is resistance to other drugs or not. It is a relatively new phenomenon and poses one of the most difficult therapeutic problems in medicine because failure may not only mean death of the patient but infection and disease in others including healthcare staff.

Poor patient management, non-adherence to the prescribed regimen, a poor national programme or some combination of these three factors causes drug-resistant TB as patients are allowed to take a single drug resulting in resistance to that drug.

PREVALENCE

After a sudden upsurge in the UK from virtually no MDRTB cases in 1990 to about 50 cases a year in 1996, or about 1%, numbers have now declined slightly (Rose et al, 2001). In parts of Eastern Europe such as Latvia and Russia MDRTB cases form over 10% of all TB cases. Russian prisons pose a special problem (Raviglioni et al, 1997).

MDRTB is found much more frequently in previously treated patients. For example in Bombay a study found an incidence of under 10% in new patients but over 50% in those who had had previous treatment (Davies et al, 1998). MDRTB is not common in Africa, remaining below 5% in most countries, perhaps because most programmes could not afford rifampicin until relatively recently. Other risk factors include exposure to another patient with MDRTB, immigration from a country with a high incidence of MDRTB, substance including alcohol abuse and, in the setting of an outbreak of MDRTB, the presence of HIV infection or being a child.

Having HIV itself is not a risk factor for MDRTB. Because HIV increases the risk of infection leading to disease by 100-fold, co-infection with HIV and an MDR strain can be devastating. In the absence of effective treatment for both HIV and TB such patients have a very poor prognosis.

In the global village a case of MDRTB anywhere in the world is only an airplane flight away.

TREATMENT OF MDRTB

The treatment of MDRTB is difficult and should only be supervised by an expert centre. Second-line drugs are less effective and more likely to cause adverse effects. The older second-line drugs include cycloserine, ethionamide and prothionamide, amikacin, kanamycin and capreomycin, para-amino salicylic acid (PAS) and thiacetazone. By serendipity, not design, a number of newer drugs have been found to be active against TB. These include the quinolones, the macrolides, clofazimine and the combination of amoxycillin and clavulanic acid.

At least two and preferably three drugs should be given to which the bacterium is known to be susceptible on sensitivity testing. If these are not known at the time treatment is started the two principal first-line drugs isoniazid and rifampicin should be given, together with at least three second-line drugs which the patient has not been known to have had previously. These three drugs should include an injectable such as kanamycin, and two orals such as ethionamide and ciprofloxacin (Iseman, 1993). Treatment should be continued for 12–18 months after the patient has become culture negative. Cure rates vary widely from centre to centre. A success rate of 65% (compared with 95% for fully susceptible disease) may be regarded as acceptable.

FUTURE TREATMENTS

The sequencing of the genome of *Mycobacterium tuberculosis* now provides us with perhaps the most important single piece of information to find new drugs, vaccines and diagnostic methods (Young, 1998). The isolation of the genes providing templates for the enzymes responsible for the unique bacterial wall structure of *M. tuberculosis* should enable specially targeted drugs to be designed to inhibit these enzymes and so prevent the bacteria forming the walls. Synergistic mechanisms between new drugs and vaccines may provide a way of both treating disease and giving preventive therapy to latent infection. It is estimated that 5–10 years will pass before these developments take place.

A more rational approach to managing the drugs currently used would be valuable until new drugs are available. The practice of directly observed therapy (DOT) or supervised swallowing is now insisted upon by the World Health Organization (WHO). This should not only result in the cure of the patient but the prevention of the development of drug-resistant disease as the patient will have no opportunity to give him or herself monotherapy. But WHO insist that DOT is only one part of a five-part strategy, comprising:

1. Government commitment to provide resources
2. Use of drugs with proven bioavailability given by observation
3. Immaculate record keeping
4. Fully reliable microscopy smear services
5. Adequate funding.

No DOTS programme can be complete without all five components.

In the resource-rich west MDRTB patients should be nursed in an isolation room under negative pressure and staff should wear special sealant face masks. Patients suspected of having MDRTB should be cared for under these conditions until proved not to have MDRTB (Joint Tuberculosis Committee of the British Thoracic Society, 2000).

In the presence of HIV infection MDRTB has a very high mortality. Special precautions should be taken in the hospital setting to ensure that cross infection does not occur.

The drug costs of first-line treatment can be as little as $10 for a 6-month course. In the developed world second-line treatment may cost tens of thousands of dollars. This is clearly beyond the scope of most countries. The proponents of 'DOTS plus' (using second-line as well as first-line drugs) point out that unless we treat and hopefully cure MDRTB patients wherever they are, we may be storing up an insurmountable MDRTB mountain for the future. They also point out that the cost of second-line drugs has come down by 90% in some cases. More pressure on the pharmaceutical companies may force prices down even more. After all they argue, these drugs have been off patent for decades. On the other hand some say that second-line drugs will always be too expensive for the poorest countries where TB is endemic and in any case treatment of MDRTB carries a low success rate even in the best hands.

POVERTY AND TUBERCULOSIS

TB is a disease of poverty, and world poverty is worsening both in terms of increasing inequality of wealth distribution and the numbers in absolute poverty. There is a moral duty on world and corporate leaders to reverse the continuation of world poverty. Whether by omission or commission, those of us in the developed world bear a responsibility to the resource-poor nations.

As John Le Carré put it in his most recent novel *The Constant Gardener*, giving an account of a trial for a new TB drug in East Africa, 'the problem with the poor is always the same. They are not rich enough to buy expensive medicines.' More prophetically he adds, '[The plan] is to test the pill in Africa for two or three years, by which time KVH [the pharmaceutical company] calculate that TB will have become a big problem in the West.' (Le Carré, 2000). For 2–3 years read 20–30 years. We have been warned. HM

PDO Davies
Consultant Physician
Tuberculosis Research Unit
Cardiothoracic Centre
Liverpool L14 3PE

KEY POINTS

- Multidrug resistant tuberculosis is resistance to isoniazid and rifampicin, whether there is resistance to other drugs or not.
- Risk factors are previously prolonged therapy for tuberculosis, contact with a patient with multidrug resistant disease and immigration from a country with a high prevalence of multidrug resistant disease.
- Eastern Europe, countries of the former Russian republic , the Middle East, and South and South-East Asia are areas of the world with a high incidence of multidrug resistant tuberculosis.
- Second-line drugs used to treat multidrug resistant tuberculosis are less effective than first-line drugs.

Davies PDO, Udwadia ZF, Hakimiyan A, Rodrigues C, Jillisgar T, Mehta A (1998) Drug resistant tuberculosis in Mumbai, India. *Thorax* **53** (Suppl 4): A32

Iseman M (1993) Treatment of multi-drug resistant tuberculosis. *N Engl J Med* **329:** 784–91

Joint Tuberculosis Committee of the British Thoracic Society (2000) Control and prevention of tuberculosis in the United Kingdom: code of practice 2000. *Thorax* **55:** 887–901

Le Carré J (2000) *The Constant Gardener.* Hodder & Stoughton, London: 508

Raviglioni MC, Dye C, Schmidt S, Kreshi A (1997) The WHO Global Surveillance and Monitoring Project assessment of worldwide tuberculosis control. *Lancet* **350:** 625–9

Rose AMC, Watson JM, Graham C et al (2001) Tuberculosis at the end of the 20th century in England and Wales: results of a national survey in 1998. *Thorax* **56:** 171–9

Young DB (1998) Blueprint for the White Plague. *Nature* **393:** 537–44