National Tuberculosis Advisory Committee multi-drug resistant tuberculosis

Information Paper (October 2007)

Definition

Multi-drug resistant tuberculosis (MDRTB) is defined as a strain of *Mycobacterium tuberculosis* with resistance to at least isoniazid (H) and rifampicin (R), the two key drugs in TB treatment. Very recently, extensively drug-resistant tuberculosis (XDRTB) has gained notoriety and is defined as MDRTB with additional resistance to any fluoroquinolone, and to at least one of three injectable second-line anti-TB drugs (capreomycin, kanamycin, and amikacin) used in MDRTB treatment.

Geographic distribution

Drug resistance data have been collected from 90 countries since the launch of the Global Project on Anti-Tuberculosis Drug Resistance by the World Health Organization (WHO) and International Union Against Tuberculosis and Lung Disease in 1994. The estimated total number of MDRTB cases in 2004 was 424,203 (95% CI, 376,019–620,061), or 4.3% (95% CI, 3.8%–6.1%). High burden countries, such as India and China, have significant absolute numbers of MDRTB cases. Some other countries are recognised as 'hot spots' for MDRTB, including Kazakhstan, Uzbekistan and other former Soviet bloc countries. Unfortunately, drug resistance surveys are incomplete with greater than 100 countries (e.g. Indonesia, Nigeria) not included and only 1–2 provinces of large high-burden countries (such as India and China) screened.

Australia has a very low incidence of MDRTB. The Mycobacterium Reference Laboratory Network (MRLN) reports the susceptibility patterns for approximately 800 *M. tuberculosis* isolates obtained in Australia each year from the approximately 1,000 annual notified TB cases; the non-microbiologically-confirmed patients representing clinical, radiological and/or histological diagnoses. The annual incidence of MDRTB has varied between 0.3%–2.0% between 1995 and 2005 with no clear increasing or decreasing trend. Nearly 95% of patients with drug-resistant TB are overseas-born migrants. For example, 21 of 24 MDRTB cases in 2004–2005 were overseas-born migrants from India (n = 3), China (n = 3), Papua New Guinea (PNG, n = 6), Vietnam (n = 4), Eritrea, Sudan, Pakistan, South Africa and the Philippines. Preliminary data collected by the MRLN suggest an increase in the absolute number of MDRTB cases in 2006 (n = 23) compared with 2004 (n = 12) and 2005 (n = 12). The MRLN and NTAC are determining the migrant status of the MDRTB cases from 2006.

With the recent World Health Organization change to the XDRTB case definition, Australian authorities have reviewed previous Australian MDRTB cases and reclassified two as XDRTB over the last five years.

One region in Australia, Far North Queensland, is particularly impacted by the influx of people with TB (with a high proportion of multi-drug resistant cases). A treaty between Australia and PNG allows free movement of local inhabitants of the outer Torres Strait Islands of Australia and of selected coastal villages of the Western Province of PNG, for traditional cultural practices. Between 2001 and 2006, 15 of 57 (26%) bacteriologically-proven TB cases were MDR (Konstantinos A, Queensland TB Control Centre, personal communication).

Avoiding the production of multi-drug resistant tuberculosis

The estimated 4.3% prevalence of MDRTB has a corollary; the vast majority of TB is not multi-drug resistant and is treatable with standard short-course chemotherapy – H, R, ethambutol (E) and pyrazinamide (Z) for 2 months followed by H and R for 4 months (i.e. 2HRZE/4HR). Correctly applied, this multi-drug regimen produces cure rates greater than 97% and prevents the emergence of resistance. Unfortunately, *M. tuberculosis* can accumulate mutations as sub-populations of resistant organisms are selected by incomplete or inappropriate drug therapies.

Multi-drug resistant TB is therefore an iatrogenic disease produced by: prescribing errors, poor case supervision, drug malabsorption or unreliable drug supplies. The common prescribing errors are:

- addition of a single drug to a failing regimen;
- failure to identify drug resistance;
- provision of an initial regimen that was inadequate in content (i.e. only HR when resistance was likely) or duration; and

- failure to recognise or address patient non-compliance.

Detection of multi-drug resistant tuberculosis

The early recognition of TB and MDRTB patients is becoming more problematic in Australia where the incidence of TB is very low (i.e. about 5 cases per 100,000 population) and a generation of doctors is now unfamiliar with the disease. Tuberculosis must be considered in the differential diagnosis of any patient with a cough lasting more than three weeks with associated risk factors. Groups at high risk of TB in Australia include migrants, the elderly, indigenous populations and other disadvantaged groups.

The key predictor of MDRTB is a history of previous treatment for TB especially in those with cavitary pulmonary disease. However, diagnosing MDRTB on the basis of clinical prediction alone risks misdiagnosis and unnecessary use of less effective, more toxic and prolonged treatment. In new TB cases treated with a well supervised standard regimen, treatment failure most commonly reflects insufficient treatment rather than the presence of drug resistance.

Culture and drug susceptibility testing (DST) is the principal method of detecting MDRTB. Positive culture and drug susceptibility results should be available within 30 days of specimen receipt using modern broth-based culture methods, which are now the 'standard of practice' in Australian mycobacteriology laboratories. Drug susceptibility tests must be performed in the following circumstances:

- all initial isolates of *M. tuberculosis;*
- isolates from patients who remain culture-positive after 3 months of treatment;
- isolates from patients who are clinically failing treatment; or
- an initial isolate from a patient relapsing after previously successful TB treatment.

Some laboratories may also offer direct molecular detection of R resistance on polymerase chain reaction-positive specimens from patients strongly suspected of having MDRTB. These molecular methods may be 'in-house' amplification and sequencing of the *rpoB* gene or a commercial reverse-hybridisation assay. The rationale for these molecular tests is that about 95% of R-resistant isolates contain mutations in an 81-bp segment of the *rpoB* gene, and R resistance is a marker for MDRTB. Risk factors that might prompt a molecular test for R resistance are:

- contact with a known MDRTB case;
- previous treatment for tuberculosis;
- migration from or residence in a country with a high prevalence of MDRTB; and/or
- HIV infection.

Approaches to treatment

There is limited clinical data to define precisely the best approach to the management of a MDRTB case in terms of the most appropriate drug combination and the duration of therapy. However, various guidelines have been developed based on expert opinion and, although differences exist, it is recommended that a MDRTB treatment regimen should be individually tailored based on the results of DST (providing that the results are timely) and, where previous treatment has occurred, a thorough history of previous drug usage.

With the loss of H and R, drug options are limited. WHO have classified anti-tuberculous agents into five categories to guide the selection process (Table). 'Second line' agents are invariably less effective and potentially more toxic. The initial regimen should include at least four new agents based on drug susceptibility testing but, depending on the severity of disease and level of resistance, more agents may be required. The best outcomes appear to be in patients with limited disease and where the organism is susceptible to an injectable agent and a quinolone (which are the key agents in treating MDRTB).

The duration of the initial phase (that includes an injectable agent) is usually decided by when culture conversion occurs. Recommendations vary from a minimum of 6 months use of the injectable agent to 4–6 months beyond the time of sputum conversion. Ultimately the decision will depend on the effectiveness of other drugs used, the sputum status of the patient, and treatment tolerance.

Again, recommendations vary regarding the total duration of therapy. The minimum standard suggested by the WHO is 18 months after culture conversion extending to 24 months in those with more extensive disease.

Surgery as an adjunct should be considered in those with a significant risk of failing medical treatment based on the level of drug resistance and disease severity. Suitability for surgery depends on disease being localised, adequacy of lung function and a sufficient period of completed treatment to reduce the bacillary burden as much as possible.

Case management

Given the small number of cases of MDRTB in Australia and the complexities involved, management should be by a 'team approach' and coordinated by those with TB expertise. All treatment should

World Health Organization anti-tuberculosis drug classification

Group	Drugs
Group1 – First line (oral)	Isoniazid, Rifampicin, Ethambutol, Pyrazinamide
Group 2 – Injectable agents	Streptomycin, Kanamycin, Amikacin, Capreomycin
Group 3 – Quinolones	Ciprofloxacin, Ofloxacin, Moxifloxacin, Gatifloxacin
Group 4 – Other second line agents (bacteriostatic)	Ethionamide, Protionamide, Cycloserine, Para-aminosalicylic acid, Thioacetazone
Group 5 – Agents of uncertain efficacy (not routinely recommended)	Clofazimine, Amoxicillin-clavulanate, Clarithromycin, Linezolid

be administered by direct observation and patients isolated until sputum cultures have converted to negative. Patients should be reviewed for at least two years after successful completion of treatment. Longer follow-up may be indicated depending on the level of drug resistance and the complexity of the treatment course.

Management of contacts of the multi-drug-resistant tuberculosis case

The risk of infection in contacts of an infectious MDRTB case is not significantly different than for contacts of drug susceptible cases. However, unlike the high level of proven efficacy of preventive treatment in the individual recently infected with a drug susceptible organism, treatment of individuals likely infected with an MDRTB strain is problematic. Their management should therefore be undertaken by those with appropriate TB clinical expertise.

Assessment of the individual exposed to an MDRTB case should consider the probability of recent infection and the subsequent risk of progression to active disease. The US Centers for Disease Control and Prevention guidelines recommend that treatment should be considered in those with a high probability of infection and an added risk factor (such as HIV co-infection) predisposing to progression to active TB disease. In those with a lower probability of recent infection, an observation alone approach or treatment as for the contact of a drug susceptible case was advised.

When preventive treatment is indicated, the consensus is that at least two drugs be used daily for a 6–12 month period based on the drug susceptibility results of the source case. The combination most commonly recommended is pyrazinamide plus a quinolone.

Avoiding the transmission of tuberculosis and multi-drug-resistant tuberculosis

The problem of TB and MDRTB can be exacerbated by transmission of infection to other patients and staff. A TB infection control program contains three principal strategies:

- administrative measures;
- engineering controls (e.g. negative pressure ventilated rooms); and
- personal respiratory protection (PRP, e.g. N95 masks, powered air-purifying respirator).

Recommendations from the Centers for Disease Control and other publications listed at the end of this document fully describe these three strategies. Recognising there has been an emphasis on recruiting healthcare workers from high-prevalence TB and MDRTB countries who have a higher risk of infection and disease, it is important that infection control services in Australia provide appropriate screening and health services to assist these recruits and to protect Australian healthcare services.

Administrative measures are the most important and cost-effective interventions for TB control. These measures aim to facilitate the early recognition and treatment of TB, and hence to prevent subsequent nosocomial transmission. Engineering controls and PRPs, while important, are expensive interventions and cannot compensate for imperfect administrative controls.

The key administrative measure is the prompt recognition of TB patients. Various algorithms have been developed to identify patients requiring isolation and investigation for TB. These algorithms consider the patient's symptoms (e.g. chronic cough, fever ≥ 3 weeks, loss of $>$ 10% body weight) and epidemiological risk factors (e.g. contact with TB, migrant from a TB-endemic country). Hospitals and other health services must adapt these algorithms to their local circumstances, balancing the likelihood of TB in their patient populations, the availability of isolation rooms, and the 'costs' of TB transmission from undiagnosed patients.

Effective TB control in Australia is also dependent on what is happening in neighbouring countries; this is especially true for MDRTB. There is some evidence that movement of people from high risk areas, including the 'Torres Strait Protected Zone', represents a high risk for transmission of MDRTB to the Australian community.

Acknowledgement

We would like to thank the preparatory writers of this document, Rick Stapledon and Ivan Bastian and the current NTAC members.

Further reading

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Current status

- NTAC endorsed the MDRTB Position Paper via teleconference on 9 March 2007;
- CDNA endorsed the MDRTB Position Paper on 18 April 2007;
- AHPC endorsed the MDRTB Position Paper on 12 October 2007.

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