Drugs 1999 Oct; 58 (4): 633-661
0012-6667/99/0010-0633/$29.00/0

Treatment and Prevention of Multidrug-Resistant Tuberculosis

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Abstract

Multidrug-resistant tuberculosis (MDRTB), which is defined as combined resistance to isoniazid and rifampicin, is a 'man-made' disease that is caused by improper treatment, inadequate drug supplies or poor patient supervision. Patients with MDRTB face chronic disability and death, and represent an infectious hazard for the community. Cure rates of 96% have been achieved but require prompt recognition of the disease, rapid accurate susceptibility results, and early administration of an individualised re-treatment regimen. Such regimens are usually based on a quinolone and an injectable agent (i.e. an aminoglycoside or capreomycin) supplemented by other 'second-line' drugs. This therapy is prolonged (e.g. 24 months), expensive, and has multiple adverse effects.

Prevention of MDRTB is therefore of paramount importance. The World Health Organization (WHO) has recommended a multifaceted programme, known by the acronym DOTS (directly observed therapy, short-course), that promotes effective treatment of drug-susceptible TB as the prime method of limiting drug resistance. DOTS was part of a successful MDRTB control programme in New York City, which also included treatment of prevalent MDRTB cases, streamlined laboratory testing, effective infection control procedures and wider application of screening and preventive therapy (although the optimal chemotherapy for MDRTB infection remains undefined).

Industrialised countries have the resources to treat patients with MDRTB and to mount these extensive control programmes. Unfortunately, MDRTB is also prevalent in Asia, South America and the former Soviet Union. First world countries have a vested interest, as well as a moral responsibility, to assist in controlling MDRTB in these 'hot spots'.

Tuberculosis (TB) was declared a global emergency by the World Health Organization (WHO) in 1993. Approximately 1.7 billion people (i.e. one third of the world's population) are infected with *Mycobacterium tuberculosis* and, despite the availability of effective chemotherapy during the latter half of this century, 10.2 million new TB cases and 3.5 million TB deaths are still expected in the year 2000.[1,2] More than 99% of these deaths will occur in developing countries, where TB accounts for 6.7% of all deaths.[1,3] In addition to this human cost, TB also represents a significant economic burden for the developing world because 80% of the TB morbidity in these countries affects adults aged 15 to 59 years, the care-givers and economically productive individuals in society.[1,3]

While the large majority of TB morbidity and mortality occurs in resource-poor countries, there has also been a recent highly publicised resurgence in TB in industrialised countries. For example, the US experienced a 20% increase in the annual incidence of TB from 22 201 cases in 1985 to 26 673 cases in 1992.[4] Similar upward trends in TB incidence were reported from the UK, the former Soviet states and some other European countries.[5-7]

The global problem of TB has been further complicated by a substantial increase in multidrug-resistant tuberculosis (MDRTB), which is defined here as resistance to at least isoniazid and rifampicin.[8-10] This increase in TB and MDRTB in developed and developing countries has been produced by the interaction of numerous factors: deteriorating public health infrastructures; reduced funding for TB control; increasing poverty and homelessness due to reductions in social services in industrialised countries, or to famine, war, natural disaster and urbanisation in resource-poor countries; immigration from endemic areas; physician mismanagement; patient noncompliance; the HIV epidemic; and demographic changes such as population growth.[2,6,11-18]

MDRTB is particularly problematic because it threatens both the individual and the community. For the individual, drug resistant disease often re-

sults in treatment failure, progressive disability and death, particularly in resource-poor countries unable to provide the expensive complicated 'second-line' treatments.[19,20] For the community, the patient with chronic MDRTB disease represents an infectious reservoir of resistant tubercle bacilli.[21-25] While this article will concentrate on the chemotherapy and chemoprophylaxis of MDRTB, the initial sections will highlight the epidemiology, evolution and prevention of MDRTB. The article will also review some novel therapeutic interventions which have been trialed or suggested for MDRTB.

1. Epidemiology of Multidrug-Resistant Tuberculosis (MDRTB)

1.1 Experience in the US

Before 1990, most US cases of MDRTB occurred sporadically in patients who acquired resistance while receiving prolonged inappropriate treatment.[16,26] Only occasional outbreaks of MDRTB were reported (or recognised) in which drug-resistant bacilli were transmitted to contacts (i.e. primary resistance).[24,25] Several outbreaks of MDRTB were then documented in the early 1990s in various institutions, particularly hospitals in New York and Miami.[10,22,23,27,28] More than 90% of outbreak patients were HIV-positive and their mortality rate was as high as 70 to 90% with a median interval from TB diagnosis until death of only 4 to 16 weeks.

In response to these epidemics, a nationwide survey of drug-resistant TB was conducted in 1991.[10] Nearly 10% of patients were found to be resistant to isoniazid and/or rifampicin, and resistance to isoniazid and rifampicin (i.e. MDRTB) was detected in 3.5% of patients. New York City accounted for 61.4% of US patients with MDRTB during the study period. Multiple interventions commenced, particularly in New York City, including directly-observed treatment programmes, better infection control procedures in hospitals, down-sizing of shelters for homeless people, and improved TB screening and isolation facilities in prisons.[29] A subsequent survey between 1993 to 1996 has found a relatively constant level of isoniazid resistance (i.e. 7.9 to 8.9%) but a significant reduction in patients with MDRTB from 2.8% in 1993 to 1.6% in 1996.[30] The decreased rate of MDRTB in the US was largely attributable to a dramatic reduction in MDRTB in New York.[29,30]

1.2 Global Experience

Nosocomial outbreaks of MDRTB have also been reported in Europe and South America[31-33] but the true global distribution of MDRTB is not well defined. Cohn et al.[8] reviewed all reports of *M. tuberculosis* antibiotic susceptibility surveys published between 1985 and 1994. The highest rates of acquired MDRTB were reported from Nepal (i.e. 48.0%), Gujarat State in India (33.8%), New York City (30.1%), Bolivia (15.3%) and Korea (14.5%). However, the authors noted several limitations in this literature. There were few laboratories for culturing *M. tuberculosis* and performing antibiotic susceptibility tests in developing countries, and those surveys that had been performed had often used nonstandardised laboratory techniques or had sampled small nonrepresentative groups of patients.

These problems were addressed by the Global Tuberculosis Program of the WHO and the International Union against Tuberculosis and Lung Disease (IUATLD) in the Global Project on Anti-Tuberculosis Drug Resistance Surveillance.[9] Between 1994 and 1997, this project surveyed 35 countries and found the median prevalences of primary and acquired MDRTB were 1.4% (range, 0 to 14.4%) and 13.0% (range, 0 to 54.4%), respectively. In general, the rates of MDRTB remain low in poor nations, particularly in Africa, where rifampicin is not widely available.[9,21] However, high rates of MDRTB were found in countries where antituberculosis drugs are widely available but where there are inadequate tuberculosis control programmes (e.g. the former Soviet Union, the Dominican Republic, Argentina, the Delhi region in India, Vietnam and Thailand).[9,21]

Surveys at the regional level demonstrate the immense problem that MDRTB poses for local TB control programmes. For example, Coninx et al.[34] studied patients with TB in Azerbaijan prisons. Of the 38 patients with newly diagnosed TB, 9 (24%) had MDRTB, as did 25 (89%) of 28 prisoners with previously-diagnosed TB not responding to a fully supervised WHO treatment regimen. Local TB control programmes cannot provide adequate therapy for these patients with MDRTB and former prisoners may transmit MDRTB to the general community. The adage 'prevention is better than cure' is therefore most aptly applied to the problem of MDRTB.[35]

2. Preventing the Evolution of Drug Resistance

An article on the chemotherapy of MDRTB must therefore highlight that the prevention, not the management, of MDRTB is most important.[20,36] To avoid producing MDRTB, a clinician must: (i) understand the mechanisms leading to drug resistance (ii) be aware of the recommended treatment regimens for drug susceptible TB and the associated supervision strategies and (iii) recognise the common treatment errors that produce this iatrogenic disease.

2.1 Use of Multiple Drugs to Prevent Resistance

Acquired resistance to streptomycin was detected even during the early treatment trials with this drug over 50 years ago.[37] Resistance to a single antituberculosis drug is produced by a spontaneous unlinked chromosomal mutation. The rate at which these mutations occur varies between drugs so that in an unselected population of tubercle bacilli approximately 10^{-6} organisms will be resistant to streptomycin, 10^{-6} organisms will be resistant to isoniazid, and 10^{-8} organisms will be resistant to rifampicin.[38] The probability of an organism spontaneously developing resistance to isoniazid and rifampicin is therefore 10^{-14} (i e. $10^{-6} \times 10^{-8}$ and is highly unlikely even in patients with extensive cavitary disease containing 10^{9} organisms.[26] However, *M. tuberculosis* can accumulate mutations as populations of resistant bacilli are selected by incomplete or inappropriate drug therapies.[16,39] Modern antituberculosis regimens therefore aim to prevent the emergence of resistance by prescribing multiple antibiotics that are active against the infecting tubercle bacilli.

2.2 Current Short-Course Regimens for Drug-Susceptible Tuberculosis

While preventing the emergence of drug resistance, antituberculosis treatment regimens must also aim to provide a well tolerated, effective cure in the shortest possible time. To determine the optimal regimen, treatment trials over the last 5 decades have tried several drugs, administered either daily or intermittently, in various combinations for different durations.[40]

Ultimately, for patients with pulmonary disease caused by fully-susceptible organisms, a combination of isoniazid (H), rifampicin (R), and pyrazinamide (Z) given for 2 months followed by isoniazid and rifampicin for 4 months (i.e. 2HRZ/4HR) proved the shortest, most well tolerated and most effective regimen (i.e. producing cure rates >97%).[41,42] The American Thoracic Society (ATS), the Centres for Disease Control (CDC), and WHO all recommend this short-course regimen but with the addition of a 4th drug in the initial phase, either ethambutol (E) or streptomycin (S), pending the results of susceptibility tests (i.e. $2^{E}/_{S}$HRZ/4HR).[43-45] The US authorities would dispense with the 4th drug only if the local rate of primary isoniazid resistance was less than 4%, and the patient had no risk factors for MDRTB.[43,44]

2.3 Directly Observed Therapy, Short-Course (DOTS)

Short-course chemotherapy is not the only element in successful TB treatment and control.[43] A multi-disciplinary approach is necessary to meet the medical and social needs of patients and their contacts.[29,43,46] Patient adherence to the drug regimen must be promoted and monitored, preferably by having a healthcare worker or other respon-

sible individual go to the patient and observe the ingestion of all antituberculosis medications.

The ground-breaking British Medical Research Council studies and the subsequent IUATLD field trials emphasised the importance of directly observed therapy (DOT).[47] The ATS and CDC now suggest that DOT should be considered for all patients.[43,44] DOT has been shown repeatedly to improve treatment completion rates and to reduce rates of primary and acquired drug resistance.[46,48,49]

Treatment completion rates exceeding 90% are likely to be achieved using DOT, particularly when this patient-centred approach is supplemented by enablers (e.g. intermittent regimens, outreach programmes, transportation) and incentives (e.g. housing assistance, substance abuse therapy).[49] Less intensive programmes without appropriate enablers and incentives are not as effective, producing treatment completion rates of 78.6% to 87.6%.[49]

The alternative approach of using DOT only for noncompliers is essentially flawed. Clinicians cannot reliably identify adherent patients although some demographic characteristics may predict non-adherence (e.g. homelessness and substance abuse).[18] For example, in a study of patients with TB, physicians did not identify 68% of non-adherent patients but misclassified only 8% of adherent patients as non-adherent.[50] While the need for universal supervised therapy is debated, particularly in TB control programmes already achieving treatment completion rates greater than 90%,[51] DOT must be recognised as optimum treatment and it is the fault of the physician, not the patient, if DOT is not employed and the patient proves to be non-adherent.

A multi-disciplinary approach, that incorporates short-course regimens and DOT, has been enshrined in the WHO policy.[52] This policy, known as DOTS, has 5 key elements: (i) government commitment to TB control (ii) patient detection, generally by passive patient finding and sputum microscopy (iii) fully supervised treatment with a standardised short-course regimen (iv) reliable provision of drug supplies and (v) effective monitoring of TB control programmes. The DOTS policy has been successfully implemented in several developing countries, including Tanzania, Malawi, Peru and China, and has been associated with reductions in drug resistance.[53-55] Unfortunately, political, economical, social and medical factors have conspired so that only 23% of the world's population has access to short-course treatment and DOTS programmes.[55]

2.4 Physician Errors

MDRTB can flourish outside of DOTS programmes because therapy is often inadequate because of: (i) medical errors in prescribing chemotherapy, (ii) unreliable drug supplies and (iii) poor case supervision.[20,56] The prescribing errors that produce MDRTB must be emphasised. Mahmoudi and Iseman[16] reviewed the management of 35 patients admitted with MDRTB to the National Jewish Centre for Immunology and Respiratory Medicine in Denver between 1989 and 1990. An average of 3.9 errors per patient had been made by the previous treating physicians. The errors included: addition of a single drug to a failing regimen, failure to identify drug resistance, prescription of an initial regimen that was inadequate in content (e.g. administration of only 2 drugs when there was a high probability of initial resistance) or duration (e.g. less than 6 months' treatment with a regimen containing isoniazid, rifampicin and pyrazinamide in a smear-positive case), and failure to recognise or address patient noncompliance.

Disturbingly, an earlier publication by Byrd et al.[57] reported similar errors being made in 1977, and a very recent paper by Liu et al.[17] found that almost half of the patients with TB in New Jersey treated outside of a TB control programme by private practitioners and respiratory physicians received initial regimens that were contrary to CDC/ATS guidelines (i.e. less than 4 drugs despite a local level of isoniazid resistance above 4%).

To limit the number of new cases of acquired MDRTB, treating physicians must be educated about the local levels of drug resistance and current

treatment guidelines. TB control programmes must also be able to monitor patients treated privately. Such monitoring seems to have been achieved amicably and unobtrusively in Baltimore through TB clinic nurses and a pharmacy surveillance system.[46] A city ordinance requires that pharmacies report when antituberculosis drug prescriptions are filled. TB control staff can then review these reports to determine whether each patient's treatment is adequate, and whether the patient is compliant.

Physicians and other healthcare professionals also have a central role in preventing transmission of MDRTB.[58] Outbreaks of MDRTB in hospitals have been caused by delays in diagnosis, delays in obtaining drug susceptibility results, delays in initiating treatment, and inadequate patient isolation procedures.[59,60] To prevent transmission of TB and MDRTB, physicians must: identify patients who may have TB, isolate these patients in suitably ventilated rooms, collect adequate specimens, order drug susceptibility tests, begin treatment with enough drugs to prevent the emergence of resistance, and ensure that this initial regimen is adequate when the susceptibility results become available.[59-61]

3. Treatment of Patients with MDRTB

3.1 Recognition of Patients with MDRTB

TB must be considered in the differential diagnosis of any patient with a persistent cough lasting longer than 3 weeks.[60] Other features of TB include: haemoptysis, fever, night sweats, weight loss and anorexia. The likelihood that these symptoms and signs represent TB will depend on the prevalence of the disease in the local population. TB can be easily misdiagnosed in HIV-positive patients who may have atypical clinical and radiological presentations, or other concomitant infections such as *Pneumocystis carinii* or *Mycobacterium avium* complex (MAC).[60] Mandatory isolation is required for all patients in whom TB is considered and for any HIV-positive patient with an abnormal chest radiograph. These expanded isolation policies facilitate early recognition and treatment of patients with TB, and successfully prevent nosocomial transmission.[59,61]

Among those patients with TB, certain risk factors have been associated with the presence of drug resistance. In the US, MDRTB is more common in patients: who have had previous treatment for TB, who were born in a high-incidence area (e.g. South East Asia), who have had known contact with MDRTB, or who have cavitary lung disease.[62-65] However, 32 to 60% of drug-resistant cases have no apparent risk factors.[10,65] This poor sensitivity for predicting the presence of drug resistance confirms the need for using an initial 4 drug regimen until susceptibility results become available.

More recently, HIV-positive status and younger age have also been associated with MDRTB.[30,66] HIV-positive patients are not more prone to MDRTB than to drug susceptible TB. Rather, the epidemiological association of HIV-positive status and MDRTB reflects nosocomial transmission of TB (some being MDRTB) and the propensity of HIV-positive patients to progress rapidly to active disease.[67,68]

Some researchers have also suggested that particular clinical presentations (e.g. presence of interstitial infiltrates, hilar or mediastinal lymphadenopathy, cavitation on chest radiographs) are more typical of drug-resistant than drug-susceptible disease in HIV-positive patients.[28,66,69,70] However, there is no convincing evidence for these assertions. For example, Fischl et al.[28] found a higher rate of cavitation among HIV-positive patients with MDRTB, but 2 other studies have actually documented fewer cavitary lesions in such patients.[69,70]

The presence of drug resistance may also be indicated by a poor response to treatment. Two studies have found that failure to defervesce after 2 weeks of treatment with a standard 4-drug regimen is an independent marker of MDRTB.[66,70] In areas with a high prevalence of MDRTB, broader empirical treatment may be indicated for patients who fail to defervesce.[66] However, this approach has several limitations. For example, not all patients with TB present with fever. Secondly, persistent

fever can also be caused by severe miliary disease or another concomitant infection, and is therefore not a specific sign of MDRTB.

After 2 months of treatment with a regimen containing isoniazid and rifampicin, 80 to 90% of patients with TB with positive pre-treatment sputum cultures should have converted to negative, and nearly 100% should have negative cultures within 5 to 6 months.[42,44,71] Slower sputum culture conversion rates are seen in patients who are initially smear-positive, have advanced cavitary disease, or are infected with drug-resistant organisms.[71] Hence, patients with positive sputum cultures after 2 months of treatment must be re-evaluated, susceptibility tests repeated, and adherence with treatment assured by direct observation.[44] Patients with positive sputum cultures after 5 to 6 months must be considered treatment failures, fresh drug susceptibility results obtained, and their treatment adjusted accordingly.[44]

Drug susceptibility testing is, of course, the cornerstone for detecting and managing MDRTB. After their outbreaks of MDRTB, the US authorities have reversed earlier statements and now recommend that susceptibility tests be performed on initial isolates from all patients with TB.[43,44] Laboratory delays in both the identification of *M. tuberculosis* and the recognition of drug resistance (e.g. 2 to 9 months after specimen collection) contributed to the MDRTB outbreaks.[22,27,59,72,73] Demanding goals have therefore been set for mycobacteriology laboratories in the US and similar standards are increasingly expected of laboratories in other industrialised countries. Sputum smear results are expected within 24 hours of specimen collection, culture identification of *M. tuberculosis* within 10 to 14 days, and drug susceptibility results within 15 to 30 days.[72]

Traditional mycobacteriological methods involve inoculation of solid media (e.g. Löwenstein-Jensen), incubation at 35 to 37°C in 10% CO_2, and biochemical identification of growth as *M. tuberculosis* (using tests for catalase, niacin and nitrate reduction). Susceptibility testing is then performed using the proportion method in which standard inocula are grown on drug-free and drug-containing media. A pre-determined 'critical concentration' of each antibiotic is used in the drug-containing media so that, when the colonies are counted after 3 weeks incubation, an isolate can be defined as resistant if growth on the drug-containing medium exceeds 1% of that on the control medium.[74] Using these conventional methods, the average time from specimen collection to reporting of identification and susceptibility results is over 6 weeks.[73]

However, modern methods can produce faster turnaround times. For example, the BACTEC® (Becton Dickinson Diagnostic Instrument Systems, Maryland, USA) radiometric system, which involves detection of growth in a liquid medium by the release of $^{14}CO_2$ from a radiolabelled substrate, combined with the use of nucleic acid probes or high performance liquid chromatography (HPLC) for *M. tuberculosis* identification, can reduce the time to reporting to about 3 weeks.[73-75] Susceptibility testing can also be performed in the BACTEC® system using a variation of the proportion method with results available within 10 days.[74] A combination of these modern techniques can therefore provide identification and susceptibility results within 4 to 5 weeks, thereby meeting the demanding goals set by the CDC.[72,73] Novel techniques employing molecular methods, oxidation-reduction dyes, flow cytometry, or HPLC quantification of mycolic acids are being developed to provide even faster drug susceptibility results for *M. tuberculosis*.[74,76,77]

Unfortunately, none of these technologies are available in many of the countries with high rates of MDRTB.[8,9,20] Clinicians must gauge progress based on the patient's clinical response and the results of sputum microscopy. Of the patients who are initially smear-positive, 75% will become smear-negative after 2 months of treatment with a regimen containing isoniazid and rifampicin, and over 95% will have converted by 5 to 6 months.[45,78] Smear positivity at 2 months may be caused by non-adherence with treatment, cavitation and heavy initial bacillary load, or the presence of drug resistance.[45,78]

The presence of dead bacilli can also produce 'false-positive' smear results early in treatment. For example, Kim et al.[71] found that 20.4% of 727 patients who were initially smear- and culture-positive had 'culture conversions' but continued to have positive smears 4 to 20 weeks after commencing treatment. This smear-positive/culture-negative reaction was more common among patients with cavitary disease and also in those treated with rifampicin-containing regimens. WHO recommends extending the intensive 4 drug treatment phase for a further month in patients with positive smears at 2 months.[45] However, drug treatment is only changed if smears remain positive at 5 months. The patient is then classified as a treatment failure and begins a retreatment regimen.

The drug susceptibility patterns among these treatment failures varies between programmes and between countries. Among TB patients who have had previous treatment, Pablos-Mendez et al.[9] found that the median prevalence of patients with fully-susceptible bacilli was 64.0%, for patients with bacilli resistant to at least 1 drug it was 36.0%, and for patients with MDRTB it was 13.0%. Hence, the WHO retreatment regimen (i.e. 2SHRZE/1HRZE/5HRE) given under strict supervision can still cure the majority of these treatment failures.[9,20,45] Unfortunately, over half of the patients who have failed 2 treatment courses (the second being this fully supervised retreatment regimen), will have MDRTB and will require the care of specialised units.[20,79]

3.2 Assessment of Patients with MDRTB

Planning drug therapy for a patient with MDRTB requires experience, skill and time.[19,20,80,81] The treatment history of the patient must be thoroughly chronicled listing the previous treatments (including preparations that might have been obtained privately from shopkeepers and pharmacists), the patient's adherence with these regimens, and the bacteriological response. Clinical and radiological changes should also be recorded, but can be affected by intercurrent conditions (e.g. pneumonia, embolism) and are therefore less reliable parameters of progress. Every effort must be made to obtain this information from the patient's files, old prescriptions and TB control programme records.

The patient's previous drug susceptibility results should also be reviewed, including those performed at other hospitals. Discrepancies in susceptibility patterns may occur because of the sampling of different populations of bacilli, variations in laboratory techniques, or laboratory error. More weight may be placed on the results obtained from a high quality laboratory but the conservative approach is to assume that any drug resistance that has been reported is real, irrespective of the reputation of the testing laboratory. These susceptibility results must also be correlated with the patient's response to each successive regimen. For example, a patient who has persistently positive smears despite treatment with a regimen that appears appropriate based on *in vitro* susceptibility results requires re-evaluation and confirmation of their adherence with treatment.

Susceptibility results other than those for the individual may also be useful. For example, if the patient is a known contact of another patient with MDRTB, then treatment should be based on the susceptibility patterns of the index patient. Similarly, susceptibility patterns in the local community may provide some (imperfect) guidance if no previous results are available for the patient.

Access to reliable susceptibility results is mandatory for the successful management of MDRTB. WHO have emphasised this fact by stipulating that specialised units wishing to treat patients with MDRTB must have access to a reliable laboratory that participates in a quality assurance programme.[8,20] However, previous therapy with a drug has been associated with a reduced clinical response to that drug despite apparent 'susceptibility' in *in vitro* laboratory tests.[26] The clinician treating an individual with MDRTB must therefore have the patient's past treatment history and *in vitro* susceptibility results.

3.3 Initial Retreatment Regimen

Having gathered all of this information, the likely resistance pattern can be inferred from the patient's history and previous susceptibility results. A patient, who had drug-susceptible TB and adhered to a satisfactory treatment regimen, presenting with a relapse years later is likely to have drug-susceptible disease and will respond to the WHO retreatment regimen.[45,80] In contrast, a patient who has failed therapy with multiple inadequate regimens is likely to have drug-resistant disease. In this circumstance, a retreatment regimen comprising a minimum of 3 or 4 agents must be prescribed while awaiting the current susceptibility results.[20,26,80,81] This regimen should contain drugs which the patient has not received previously (as the bacilli are unlikely to be resistant to these 'second-line' drugs). A 'first-line' drug that the patient has received previously may be added to this regimen if resistance appears unlikely based on the patient's previous treatment history. However, such additional drugs must not be relied upon until the results of new susceptibility tests become available.

Acceptable regimens for treating various drug resistance patterns are listed in tables I and II. A

Table I. Acceptable regimens for treating patients with drug-resistant tuberculosis (adapted from references[20,26,44,68,80,81])

Resistance profile	Initial phase[a]		Continuation phase[a]		Comments
	drugs	months	drugs	months	
Before/without susceptibility results	Aminoglycoside Ethionamide Pyrazinamide Quinolone[b]	≥3-4	Quinolone[b] Ethionamide	18[c]	The injectable agent could be KAN, AMI, or CAP.[d] CYC may be used if a quinolone is not available
Isoniazid ± streptomycin ± thiacetazone	Rifampicin Aminoglycoside Pyrazinamide Ethambutol	2-3	Rifampicin Ethambutol ± pyrazinamide	6	SM given if still effective, otherwise the injectable agent must be KAN, AMI, or CAP[d] PYZ in the continuation phase may add little to response rate Expect 100% response rate
Isoniazid + ethambutol ± streptomycin	Rifampicin Aminoglycoside Pyrazinamide Quinolone[b]	3	Rifampicin Quinolone[b] ± pyrazinamide	≥ 6	SM given if still effective, otherwise the injectable agent must be KAN, AMI, or CAP[d] PYZ in the continuation phase may add little to response rate ENA could substitute for the quinolone
Rifampicin	Isoniazid Aminoglycoside Ethambutol Pyrazinamide	2-3	Isoniazid Ethambutol ± pyrazinamide	15[e]	Isolated RIF resistance rare but increasing SM given if still effective, otherwise the injectable agent must be KAN, AMI, or CAP[d] PYZ in the continuation phase may add little to response rate

a Following sputum conversion, which generally occurs after 3 to 4 months in responders, the continuation phase must employ at least 2 drugs which are active and well tolerated; some experts would continue with the initial regimen for longer aiming for improved cure rates (see text).

b For example, ofloxacin.

c When susceptibility results are unavailable, Crofton et al.[20] recommended this 2-drug regimen; other clinicians may not consider this regimen adequate or would argue that no rational continuation regimen can be designed without susceptibility results.

d Because of cross-resistance between kanamycin and amikacin, the polypeptide antibiotic, capreomycin must be given if resistance is demonstrated to either of the 'second-line' aminoglycosides.

e If the patient can tolerate prolonged aminoglycoside treatment, Centres for Disease Control have recently recommended a 7-month continuation phase of isoniazid, pyrazinamide and an injectable agent (based on British Medical Research Council studies).[68]

AMI = amikacin; **CAP** = capreomycin; **CYC** = cycloserine; **ENA** = ethionamide; **KAN** = kanamycin; **PAS** = para-aminosalicylic acid; **PYZ** = pyrazinamide; **RIF** = rifampicin; **SM** = streptomycin.

Table II. Acceptable regimens for treating patients with multidrug-resistant tuberculosis (adapted from references[20,26,80,81])

Resistance profile	Initial phase[a]		Continuation phase[a]		Comments
	drugs	months	drugs	months	
Isoniazid ± rifampicin ± streptomycin	Aminoglycoside Ethionamide Pyrazinamide Quinolone[b] Ethambutol	≥3-4	Ethionamide Quinolone[b] Ethambutol ± pyrazinamide	18-24	Aminoglycoside or CAP as injectable agent[c] EMB dose may be increased to 25 mg/kg with careful monitoring for retrobulbar neuritis. PYZ in the continuation phase may add little to response rate Consider surgery if no conversion after 6 months
Isoniazid + rifampicin + ethambutol ± streptomycin	Aminoglycoside Ethionamide Pyrazinamide Quinolone[b] Cycloserine	≥3-4	Ethionamide Quinolone[b] Cycloserine ±pyrazinamide	18-24	Aminoglycoside or CAP as injectable agent[c] PAS may be substituted for CYC. PYZ in the continuation phase may add little to response rate. Consider surgery if no conversion after 6 months
Isoniazid + rifampicin + pyrazinamide ± streptomycin	Aminoglycoside Ethionamide Ethambutol Quinolone[b] Cycloserine	≥3-4	Ethambutol Quinolcone[b] Ethionamide	18-24	Aminoglycoside or CAP as injectable agent[c] EMB dose may be increased to 25 mg/kg with careful monitoring for retrobulbar neuritis. PAS may be substituted for CYC. Consider surgery if no conversion after 6 months
Isoniazid + rifampicin + ethambutol + pyrazinamide ± streptomycin	Aminoglycoside Ethionamide Quinolone[b] Cycloserine PAS	≥3-4	Ethionamide Quinolone[b] Cycloserine	18-24	Aminoglycoside or CAP as injectable agent[c] PAS may be substituted for CYC in the continuation phase. Strongly consider surgery

a Following sputum conversion, which generally occurs after 3 to 4 months in responders, the continuation phase must employ at least 2 drugs which are active and well tolerated; some experts would continue with the initial regimen for longer aiming for improved cure rates (see text).

b For example, ofloxacin.

c Streptomycin given if still effective, otherwise the injectable agents must be kanamycin, amikacin or capreomycin; because of cross-resistance between kanamycin and amikacin, the polypeptide antibiotic, capreomycin must be given if resistance is demonstrated to either of the 'second-line' aminoglycosides.

CAP = capreomycin; **CYC** = cycloserine; **EMB** = ethambutol; **ENA** = ethionamide; **PAS** = para-aminosalicyclic acid; **PYZ** = pyrazinamide; **RIF** = rifampicin.

salvage regimen for a patient with MDRTB should ideally contain multiple drugs with bactericidal activity (i.e. an injectable agent, a quinolone, pyrazinamide, or ethionamide) with the bacteriostatic drugs [e.g. cycloserine, para-aminosalicylic acid (PAS)] added to prevent the development of further resistance (table III).[20,26,81] The importance of adherence with these 'last-chance' retreatment regimens must be emphasised to the patient and the family, and must be guaranteed by instituting DOT for all patients with drug-resistant disease.

3.4 'Second-Line' Drugs Used to Treat MDRTB

The pharmacology of the 'first-line' antituberculous drugs (i.e. isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin) has been well reviewed.[44,45,82] The following details are listed in table III for each of the 'second-line' drugs: the type of antimycobacterial activity, the usual daily dose, the peak serum concentration, the range of minimum inhibitory concentrations (MICs) for susceptible *M. tuberculosis* isolates, the critical concentrations for determining *in vitro* resistance, and the common adverse reactions.

3.4.1 Kanamycin, Amikacin and Capreomycin

Apart from streptomycin, the aminoglycosides with activity against mycobacteria at concentrations obtainable *in vivo* are kanamycin and amikacin. Kanamycin is a glycoside of 2-deoxystreptamine and amikacin is a derivative of kanamycin.[74] The aminoglycosides inhibit protein synthesis by irreversibly binding to the bacterial 30S ribo-

somal subunit and blocking the aminoacyl-tRNA. Cross-resistance occurs between kanamycin and amikacin because of their structural similarity, but cross-resistance between them and streptomycin is rare.[26] Capreomycin has a similar action and adverse effects to the aminoglycosides.[26] However, it is a basic polypeptide antibiotic and so cross-resistance with the aminoglycosides occurs only occasionally.[74,83] All of these injectable agents are bactericidal against actively replicating bacilli and have therefore become essential agents in retreatment regimens for MDRTB.

The usual daily dose of kanamycin and amikacin is 15 to 30 mg/kg given intramuscularly, with a maximal daily dose of 750mg to 1g.[44] These drugs can also be given by intravenous infusion through a central venous line.[26] Following parenteral administration, these drugs can be detected in body tissue and fluids. They cross the placenta but their penetration into the cerebrospinal fluid (CSF) is unreliable. Excretion is by glomerular filtration. With both agents, ototoxicity is more common than nephrotoxicity.[84] Monthly audiometry is therefore recommended while patients are on treatment.[44] Dosage adjustment and careful monitor-

Table III. Pharmacology of 'second-line' antituberculosis medications (adapted from references[20,26,74,81,83])

Drug	Type of activity	Average daily dose	Serum concentration[a] (mg/L)	Usual MIC[b] range (mg/L)	Critical concentration[c] (mg/L)		Adverse effects
					BACTEC®	7H11	
Kanamycin	Bactericidal[d]	15 mg/kg intramuscularly	14-29	1.5-3.0	5	6	Hearing loss, ataxia, nystagmus, nephrotoxicity, electrolyte abnormalities, contraindicated in pregnancy
Amikacin	Bactericidal[d]	15 mg/kg intramuscularly	16-38	0.5-1.0	1[e]	ND	As for kanamycin
Capreomycin	Bactericidal[d]	15 mg/kg intramuscularly	30	1.25-2.5	5	10	As for kanamycin
Ethionamide	Bactericidal	250mg bd or tds	2-20	0.3-1.2	5	10	Nausea, GI disorder, metallic taste, vomiting, psychoses, hepatitis, hypoglycaemia
Ciprofloaxacin	Weakly bactericidal	750mg bd	2-4	0.25-3	2[e]	ND	GI disorder, dizziness, headaches, psychoses, thrush, drug interactions (e.g. antacids), contraindicated in pregnancy and children
Ofloxacin	Weakly bactericidal	400mg bd	3-11	0.5-2.5	2[e]	ND	As for ciprofloxacin
Cycloserine	Bacteriostatic	250mg bd or tds	20-40	5-20	50	30	Dizziness, slurred speech, convulsions, headache, psychoses (particularly depression and suicide)
Para-aminosalicylic acid	Bacteriostatic	5-6g bd	7.5	1	4	8	GI disorder, diarrhoea, rash, hypersensitivity, hypokalaemia, oedema

a Serum concentration 1 to 4 hours after usual dosage.

b Minimum inhibitory concentration (MIC) of susceptible *Mycobacterium tuberculosis*.

c Recommended concentrations of antimycobacterial agents to test against *M. tuberculosis* in radiometric and proportion methods.

d Bactericidal against replicating bacilli.

e Tentative critical concentration.

bd = twice a day; **GI** = gastrointestinal; **ND** = no data; **tds** = 3 times per day.

ing of renal function are also required in patients with renal impairment. The aminoglycosides are contraindicated in pregnancy.

Capreomycin is given by intramuscular injection at the daily dose of 15 to 30 mg/kg, to a maximum dose of 1g.[44] The dosage should not exceed 20 mg/kg/day for more than 40 to 120 days because the risk of adverse effects increases thereafter.[20] If necessary, capreomycin can be continued but given only 2 to 3 times per week. Although recommended only for intramuscular injection, capreomycin can be given intravenously with good tolerability.[84] Capreomycin causes high frequency hearing loss in 3.2 to 9.4% of patients before vestibular dysfunction occurs.[44] Monthly audiometry is therefore recommended while patients are on treatment, with occasional examinations of vestibular function. Renal toxicity may also occur, especially in the elderly among whom the total daily dose should not exceed 750mg. Electrolyte disturbances (i.e. hypokalaemia, hypocalcaemia, hypomagnesaemia) possibly resulting from renal tubular damage are seen with capreomycin (and the aminoglycosides), particularly after 3 to 4 weeks of antituberculosis therapy.[20,44,84] Renal function and serum biochemistry must therefore be monitored. Cutaneous reactions and hepatitis have been reported rarely.[84] Capreomycin is contraindicated in pregnancy and should be avoided in children.[20]

3.4.2 Ethionamide

Like isoniazid, ethionamide (2-ethyl-pyridine-4-carbonic acid thioamide) is a derivative of isonicotinic acid and exerts a bactericidal effect by inhibiting mycolic acid synthesis.[74,85] However, isoniazid-resistant isolates of *M. tuberculosis* are susceptible to ethionamide suggesting different sites of action for these 2 drugs.[74] Ethionamide is also structurally related to thioacetazone. Isolates resistant to thioacetazone are usually sensitive to ethionamide but ethionamide resistance is almost always associated with thioacetazone resistance.[20]

Prothionamide is the N-propyl derivative of ethionamide and has similar activity, clinical efficacy and adverse effects.[85]

Ethionamide is absorbed from the gastrointestinal tract and distributed widely throughout the body, including the CSF.[85] The drug is extensively metabolised in the liver with less than 1% appearing unchanged in the urine. The usual daily dose is 15 to 20 mg/kg (i.e. 500 to 1000mg in divided doses), with a maximum daily dose of 1g.[44] The main adverse effect of ethionamide is gastrointestinal intolerance (i.e. nausea, metallic taste, epigastric discomfort, and diarrhoea). The drug should be introduced slowly in 250mg increments as tolerated, and can be given with milk or at bedtime with a sedative to avoid nausea.[20,84]

Hepatitis with jaundice occurs in 4.3% of patients and can present up to 5 months after commencing therapy.[85] Withdrawal of treatment usually results in resolution. Hepatic enzymes (i.e. AST, ALT) should therefore be monitored monthly.[44] Transient abnormalities may be detected but will usually normalise despite continued administration of the drug.[85] Hence, in the absence of symptoms or jaundice, ethionamide administration should only be stopped if there is a 5-fold elevation of AST or ALT.[44] Other reported adverse effects include psychotic reactions, convulsions, headache, dizziness, peripheral neuritis, hypoglycaemia (which is particularly important in patients with diabetes mellitus), hypothyroidism, gynaecomastia, acne, menstrual abnormalities, impotence and alopecia.[20,44,85] In view of this list of adverse effects, ethionamide should be used carefully in patients with diabetes mellitus, liver disease and psychiatric conditions. The drug is teratogenic in animals and so should not be used in pregnancy.[20,85]

3.4.3 Quinolones

Despite the lack of extensive clinical trials, the urgent need for well tolerated oral medications with activity against drug-resistant tuberculosis has seen the rapid introduction of quinolones into the treatment of MDRTB.[26] The newer broad spectrum compounds (i.e. sparfloxacin, levofloxacin, clinafloxacin, and moxifloxacin) exhibit greater *in vitro* activity against *M. tuberculosis* than the narrow spectrum fluoroquinolones (e.g. ciprofloxacin, ofloxacin).[86-88] Sparfloxacin and moxiflox-

acin (but not clinafloxacin) have also demonstrated *in vivo* bactericidal effects in a mouse model, and may have an important future role in MDRTB treatment.[86]

However, most clinical experience in tuberculosis treatment has been with ciprofloxacin and ofloxacin (reviewed in Alangaden and Lerner[89]). Ciprofloxacin has been shown to have an early bactericidal action but neither ciprofloxacin nor ofloxacin have enhanced the sterilising ability of long term regimens containing isoniazid and rifampicin.[89-91] In fact, Kennedy et al.[90] reported a slower bacteriological response and a higher relapse rate in patients, particularly those infected with HIV, receiving isoniazid, rifampicin and ciprofloxacin (4HRC/2HR) compared with a control regimen (i.e. 2HRZE/2HRZ/2HR). The current fluoroquinolones therefore should not be considered as 'first-line' agents but they do have a definite place in MDRTB treatment.[89] Bacteriological responses have been demonstrated in some patients with MDRTB when a quinolone has been used as monotherapy or added to a 'second-line' regimen.[92-94] For example, Yew et al.[93] gave patients with MDRTB either ofloxacin 300mg or 800mg daily in combination with a variety of other 'second-line' agents.[93] Culture conversions were obtained in 5 of 10 receiving the low dose, and in 8 of 10 receiving the higher dose.

The quinolones exert a mycobactericidal effect by binding to the DNA gyrase and inhibiting DNA synthesis.[74] There is no recognised cross-resistance with other antituberculous medications but there is complete cross-resistance within the fluoroquinolone group.[20,89] This fluoroquinolone resistance develops readily and rapidly, and has been associated with mutations in the DNA gyrase.[95,96] Among patients who failed to respond to quinolone treatment in the study by Yew et al.,[93] 2 patients receiving monotherapy and 3 others receiving companion drugs developed resistance to ofloxacin 4 to 9 months after starting therapy. Another study from New York described 16 patients who acquired quinolone resistance while on inadequate or inappropriate unsupervised treatment.[95] The number of known days of fluoroquinolone therapy in these 16 patients ranged from 23 to 271 days (median 64). These reports emphasise that the fluoroquinoiones must be used in combination with other effective drugs when treating MDRTB and that these regimens must be administered under direct observation.

The usual daily doses of ciprofloxacin and ofloxacin are listed in table III. These drugs are generally given twice a day but have also been given in single daily doses.[20,84] They are well absorbed orally with bioavailabilities ranging from 60% for ciprofloxacin to 95% for ofloxacin.[97] Their distribution is ideal for treating tuberculosis with concentrations in the lung and in macrophages being several times higher than serum concentrations.[97] These drugs also penetrate well into other tissues but not the CSF where levels can be variable. The quinolones are predominantly cleared by glomerular filtration so the dosage should be adjusted in renal failure.[44,97]

Adverse reactions are uncommon but gastrointestinal disturbance (anorexia, nausea, vomiting), neurological symptoms (dizziness, tremors, headaches, insomnia, mood changes, convulsions), hypersensitivity and crystalluria have been associated with quinolone therapy.[20,44,89] Although quinolones are usually used only for short periods to treat standard bacterial infections, they also appear to be well tolerated when used for 2 years or more in the long term treatment of mycobacterial infections.[98]

Animal studies have suggested that the quinolones may adversely affect growing cartilage. Hence, these drugs should only be used during pregnancy or in children after balancing the potential benefits against this theoretical risk.[44] Quinolones also increase serum theophylline concentrations and hence may increase the adverse effects of theophylline if given in combination.[44] Finally, the absorption of quinolones may be reduced by concomitant administration of antacid preparations.

3.4.4 Cycloserine

Cycloserine (4-amino-3-iso-oxazolidinone) is a structural analogue of D-alanine that competitively blocks enzymes involved in the synthesis of the dipeptide, D-alanly-D-alanine.[74,85] By inhibiting synthesis of this dipeptide, which is an essential component of the mycobacterial cell wall, cycloserine limits cell growth and hence has a bacteriostatic effect. This mode of action is unique so cycloserine shares no cross-resistance with other antituberculosis drugs.[20]

The drug is rapidly absorbed from the gastrointestinal tract and is widely distributed throughout the body, including the CSF.[74,85] Clearance is mainly by glomerular filtration.[84] Cycloserine administration is associated with significant neurological adverse effects (i.e. peripheral neuropathy, dizziness, tremor, headache, convulsions) and behavioural complications (i.e. confusion, hyperactivity, depression, psychoses, suicidal ideation).[20,44,85] Patients must, therefore, be closely observed for mood and personality changes. These complications are more common in alcoholics, patients with epilepsy, and patients with renal impairment or previous psychiatric illness.[44,85] Cycloserine also interferes with the elimination of phenytoin, further complicating its use in epilepsy.[44]

The drug is introduced slowly over several days (e.g. 250mg daily for a few days, then 250mg twice daily for a few days, and finally 750mg daily perhaps given as 500mg in the morning and 250mg in the evening).[84] Therapeutic drug monitoring has greatly improved the efficacy and tolerability of cycloserine treatment. Peak serum concentrations (i.e. 2 hours post dose) <10 mg/L may be less effective and concentrations >30 to 35 mg/L are associated with increased toxicity.[84] These concentrations should be checked 1 to 2 weeks after commencing therapy and should be measured following the larger dose if the 500mg/250mg regimen is used. Pyridoxine (50 to 100mg daily) has also been given with cycloserine in an attempt to reduce the neurological adverse effects, particularly when the drug is given with isoniazid.[26,44]

3.4.5 Para-Aminosalicylic Acid

PAS is a structural analogue of para-aminobenzoic acid (PABA) that has a bacteriostatic effect by competitively blocking the conversion of PABA into folic acid (an essential purine required for DNA synthesis).[74,85] PAS is readily absorbed from the gastrointestinal tract. It diffuses rapidly into caseous tuberculous lesions but does not cross uninflamed meninges. PAS is metabolised in the liver to acetylPAS, and both compounds are excreted in the urine.[84] Hence, PAS is generally avoided in renal failure.

PAS may cause gastrointestinal disorders (i.e. anorexia, nausea, vomiting, diarrhoea) which can frequently lead to non-adherence with therapy. Other adverse effects include hypersensitivity (with rash and pruritus), hepatitis, lymphadenopathy, arthralgia, pulmonary infiltrates and eosinophilia.[20,44,85] PAS inhibits the uptake of iodine by the thyroid gland so prolonged administration of high doses can produce myxoedema.[20,85] The drug has also been reported to induce haemolysis in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency, and the heavy sodium load in the PAS salt has caused pulmonary oedema in predisposed individuals.[85]

PAS is introduced gradually over several days to a final dosage of about 10 to 12 g/day in 3 to 4 divided doses.[84] Gastrointestinal disorders may be minimised by giving the drug after food or with milk.[20] Few patients can tolerate the gastrointestinal adverse effects produced by combined administration of PAS and ethionamide.[26] PAS may also inhibit absorption of rifampicin.[20] Finally, PAS is an expensive drug because large quantities are prescribed (e.g. 12 g/day) and the drug is not widely available.

3.5 Monitoring Retreatment in MDRTB Patients

The most reliable marker of progress is the bacteriological response to treatment, so weekly then monthly sputum examinations by microscopy and culture are required.[20] In the largest treatment series of MDRTB patients, Goble et al.[19] reported

that culture conversions were obtained in 65% of patients with the interval from commencing therapy to a series of negative cultures being 1 to 8 months (median, 2 months). Once sputum conversion has been obtained, some authorities recommend withdrawing the weaker and more toxic drugs from the regimen.[20,44] The patient then completes another 18 to 24 months' treatment with the remaining 2 to 3 active, well tolerated drugs (see tables I and II). Other experts would persist with the initial treatment hoping to improve the cure rate.[26,81] For example, Iseman recommended using a parenteral agent for 4 to 6 months unless toxicity develops.[26] Whether the initial treatment is continued or altered, bacteriological examinations are performed quarterly until the completion of treatment.[20]

As table III shows, there is only a small 'safety margin' between the obtainable serum concentration and the MIC for some of the 'second-line' drugs. MDRTB treatment could, therefore, fail because of drug malabsorption, particularly in patients with AIDS who have multiple intestinal infections and enteropathies.[84,99] Hence, workers at the National Jewish Centre for Immunology and Respiratory Medicine have advocated that therapeutic drug monitoring should not only be used to avoid toxicity (e.g. cycloserine) but also to verify absorption of antituberculosis drugs in MDRTB patients.[26,84,99] However, the usefulness of therapeutic drug monitoring for verifying absorption and predicting response remains controversial.

3.6 Indications for Resectional Surgery

If retreatment is going to be successful in a patient with MDRTB, sputum conversion generally occurs within 4 months, although occasionally conversions can occur up to 8 months after commencing therapy.[19,26] Persistently-positive sputum examinations after 4 months treatment (or relapse) is therefore an ominous sign that presages the development of resistance to drugs in the current regimen. In these circumstances, resectional surgery is of benefit for selected patients.[100-102]

The National Jewish Centre for Immunology and Respiratory Medicine, Denver, has the greatest experience with surgical treatment of MDRTB.[100] Of 99 patients admitted with MDRTB between 1983 to 1988, 29 were selected for surgery after multiple investigations including computed tomography and radionuclide scans of the lungs, spirometry, arterial blood gas measurements, and weekly sputum examinations. The criteria for surgery were: (i) extensive drug resistance resulting in likely (or proven) failure of chemotherapy, (ii) presence of localised disease allowing successful de-bulking of abnormal lung without compromising respiratory function, and (iii) sufficient residual antibiotic activity to permit healing of the bronchial stump. After surgery, 23 (79%) of the 29 patients remained sputum-culture negative for 9 to 69 months (mean, 39 months). However, surgery was associated with some morbidity and mortality in this debilitated population: 2 post-operative deaths occurred, 1 patient relapsed and died, 1 patient developed pulmonary hypertension and another had respiratory insufficiency. Nonetheless, surgery did provide an improved outcome for this group of 29 selected patients.

A recent update on this surgery for MDRTB suggests that, with appropriate drug therapy, nutritional support, and certain operative techniques, cure rates over 90% can be achieved in properly selected patients.[102] The timing of surgery is also important.[81] Some clinical response to chemotherapy is desirable so that residual local disease can be successfully treated post-operatively and the development of a bronchopleural fistula prevented. However, surgery cannot be delayed indefinitely. Further resistance could develop or the disease could spread making surgery impossible.

4. Treatment Outcomes for MDRTB Patients

4.1 HIV-Negative Patients

Mitchison and Nunn[103] reviewed the treatment trials coordinated by the British Medical Research

Council. They found that short-course regimens that included rifampicin and companion drugs were effective in treating TB with initial isolated resistance. In the face of initial isoniazid and/or streptomycin resistance, 2- or 3-drug regimens (i.e. SH or SHZ) were associated with failure rates of 32 to 40% whereas the failure rate was only 2% with 4- or 5-drug regimens containing rifampicin for at least 6 months (e.g. HRZE). However, their review also found that the handful of patients with initial isoniazid and rifampicin resistance (i.e. MDRTB) had dismal outcomes. Only 8 patients in the review had MDRTB and of these 5 failed treatment and 2 relapsed.

The depressing outcomes for immunocompetent individuals with MDRTB were confirmed by the landmark study by Goble et al.[19] The authors reviewed the clinical courses of 171 patients with pulmonary MDRTB referred to the National Jewish Centre for Immunology and Respiratory Medicine in Denver between 1973 and 1983. Of 134 evaluable patients, 47 (35%) had no response to therapy (i.e. sputum cultures were persistently positive) and 12 initial responders relapsed. The overall response rate was therefore only 56% for a mean follow-up period of 51 months (range, 10 to 167). Hence, MDRTB had resulted in a failure rate of 44% (and a TB-associated mortality rate of 22%) despite the full application of modern medicine. The median hospital stay for these patients was more than 7 months; 9 had had surgery; the median number of drugs administered per patient was 4 (32 patients had received 6 or more drugs).

Fortunately, some later studies have reported better response rates in HIV-negative patients with MDRTB.[65,69] Telzak et al.[65] described their experience in New York City between March 1991 and September 1994 with 25 evaluable patients. 24 (96%) had clinical responses, and all 17 for whom data on microbiological response were available had documented culture conversions. The median follow-up period was 91 weeks (range, 41 to 225).

Goble et al.[19] and Telzak et al.[65] were probably treating different patient populations. The Denver group were treating a highly selected group of patients who had had TB for a median of 6 years, had damaged lungs, and had acquired resistance to a median of 6 drugs through previous inappropriate treatments with a median of 6 drugs. In contrast, the New York patients often had primary MDRTB, and those with acquired disease had TB for a shorter period (i.e. median, 2.5 years), had received fewer drugs before retreatment (i.e. median number of drugs, 3.5), and had access to quinolone treatment.[65,69,81]

4.2 HIV-Positive Patients

The outcomes of MDRTB in the initial studies of HIV-positive patients were even bleaker than those for immunocompetent individuals.[10,22,23,27,28] In the US epidemics of MDRTB among HIV-positive patients, the mortality rate was as high as 90% with a median interval from TB diagnosis until death of as little as 4 weeks.[27] Fischl et al.[28] compared the outcome of 62 HIV-positive patients with MDRTB with the progress of 55 HIV-positive patients with single drug-resistant or susceptible TB (i.e. controls). The median survival time for the MDRTB patients was 2.1 months compared with 14.6 months for the controls. Patients with AIDS and MDRTB had a significantly shorter survival time than patients without both AIDS and MDRTB. Importantly, Fischl et al.[28] noted that, after controlling for a diagnosis of AIDS in their analysis, patients who received 3 or more drugs to which their isolate was susceptible had a significantly greater survival time than patients receiving less than 3 effective drugs. This early study therefore recognised the importance of the early diagnosis of MDRTB and prompt initiation of appropriate therapy. Later studies have applied these principles and achieved marginal improvements in outcome for HIV-positive patients with MDRTB (i.e. median survival times ranging between 5.8 and 10 months have been obtained).[66,69,70]

Additional factors affecting survival were recognised by Frieden et al.[104] in an extensive analysis of a cohort of 267 patients infected with the MDRTB strain W which was prevalent in New

York between January 1990 and August 1993. 230 (86.1%) of these patients were known to be HIV-positive. Early diagnosis and treatment were again noted as being vitally important. The 30 HIV-positive patients who were started on at least 3 effective antibiotics within 60 days of submitting their first positive culture survived a median of 8.7 months. Thirteen of these patients were adequately followed-up; 10 (77%) had documented sputum culture conversions a median of 60 days after starting treatment. Furthermore, multivariate analyses showed that survival was prolonged in patients with CD4+ T lymphocyte counts above 200/μl, and in patients receiving capreomycin, and to a lesser extent, a fluoroquinolone and isoniazid.

4.3 Cost of Effective MDRTB Treatment

Based on the recent outcome studies in both HIV-negative and -positive patients,[65,66,69,70,104] Harkin and Harris[81] have argued that a patient with MDRTB who has not previously received a quinolone, who is infected with an organism which is susceptible to an injectable agent that the patient tolerates, and who has appropriate supervised therapy has 'a reasonably good chance of a cure'. This successful outcome requires prompt recognition of MDRTB, access to rapid accurate susceptibility results, and early institution of supervised treatment with toxic and/or expensive 'second-line' drugs (e.g. capreomycin and ciprofloxacin).

Industrialised countries such as the US may be able to provide these services and achieve these results, at a price. In 1989 to 1990, Mahmoudi and Iseman[16] estimated that the treatment of 28 patients with MDRTB caused by medical mismanagement cost $US4.8 million (i.e. 53% of the federal TB budget for 1990). Savings in hospitalisation costs and less intensive investigation may be possible in developing countries. However, the cost of treating a patient with MDRTB in Rwanda with ofloxacin, cycloserine, prothionamide, isoniazid and streptomycin for 2 to 4 months in hospital, followed by unsupervised treatment as an outpatient, was still estimated to be $US1350.[105] This amount corresponds to the cost of drugs for treating 40 to 47 patients with drug-susceptible TB. Hence, MDRTB patients living in resource-poor countries generally do not have access to such treatment and are subject to the natural history of TB (e.g. 55 to 65% of diseased immunocompetent individuals died within 5 years in the pre-chemotherapeutic era).

5. Chemoprophylaxis for Contacts of MDRTB

Prevention of MDRTB is of paramount importance because this disease costs money and lives. The CDC has produced detailed recommendations for preventing the transmission of *M. tuberculosis*.[60] Three levels of control are recognised: (i) the use of administrative measures to reduce the risk of exposure (e.g. early recognition of potential TB cases, prompt laboratory diagnosis, and immediate implementation of effective chemotherapy) (ii) the use of engineering controls to prevent the spread of TB bacilli (e.g. ventilated rooms, air filtration, and ultraviolet air disinfection) and (iii) the use of personal respiratory protective equipment such as high efficiency particulate air filter (HEPA) respirators.

Nosocomial outbreaks of MDRTB have been controlled after implementing effective administrative and isolation procedures (i.e. the first 2 levels of control recommended by the CDC).[61,106,107] The requirement for and the effectiveness of HEPA respirators, which are expensive and cumbersome, therefore remain unproven.[108]

5.1 Rationale of Preventive Treatment

If the above measures fail and infection occurs, chemoprophylaxis can be administered to prevent latent asymptomatic infection from progressing to clinical disease.[44,109-111] After exposure to drug-susceptible TB, isoniazid prophylaxis for 12 months has been demonstrated to be 93% effective in patients who adhere to treatment.[110] Six-month regimens are 69% effective but have higher compliance rates, less hepatotoxicity, and are more cost effective.[110,111] Preventative therapy is therefore recommended for tuberculin-negative individuals

recently exposed to TB, and for tuberculin reactors who are recent tuberculin converters, intravenous drug users, individuals who have abnormal chest radiographs but no bacteriological evidence of active infection, or individuals with medical conditions predisposing them to active TB disease.[44,109]

HIV-positive individuals are one group at markedly increased risk of active TB disease in whom preventative therapy is of great importance. However, the problems of instituting chemoprophylaxis among HIV-positive patients parallel the experience with preventative therapy in other groups and explain its limited application.[112] Physicians are apprehensive about the (rare) occurrences of isoniazid-related hepatotoxicity, and asymptomatic individuals have difficulty adhering to 6 to 12 months of preventative therapy. Operational problems have also been recognised in instituting isoniazid prophylaxis among HIV-positive patients, particularly in developing countries. In these settings, the costs and practicalities of identifying HIV-positive individuals, of excluding active TB disease, and then of ensuring safe administration of isoniazid for an adequate period, are prohibitive. The WHO and IUATLD have therefore stated that isoniazid prophylaxis may be indicated for an HIV-seropositive person with a positive tuberculin test but that there is insufficient information to recommend its implementation in TB control programmes.[113]

5.2 Preventive Treatment of Drug-Resistant TB

Drug resistance further exacerbates the problems of chemoprophylaxis. When the source patient has isoniazid-resistant organisms, US authorities recommend that contacts at increased risk of active TB disease should receive rifampicin with or without a second drug (e.g. ethambutol) for 6 to 9 months.[44] At the time of this recommendation, there were no data to justify the use of rifampicin prophylaxis but expert opinion and a decision analysis agreed that preventative regimens containing rifampicin were reasonable when there was a high probability of infection by isoniazid-resistant bacilli.[112,114] There has been some subsequent experience with rifampicin prophylaxis to justify this continued recommendation. Villarino et al.[115] reported the use of rifampicin prophylaxis for 157 high school students exposed to strains of *M. tuberculosis* resistant to isoniazid. The treatment was well tolerated and protective efficacy was at least 56% after 2 years of follow-up. Rifampicin-containing preventive therapy was also found to be effective in preventing disease among homeless men in Boston exposed to isoniazid- and streptomycin-resistant TB.[116]

Prophylaxis following exposure to MDRTB is however, far more problematic and controversial. The CDC has issued detailed guidelines for the management of individuals exposed to MDRTB.[117] Observation without preventive therapy was recommended for most individuals exposed to MDRTB. Preventive treatment was only recommended for contacts likely to have been infected with MDRTB who were at high risk of progressing to active disease (e.g. HIV-positive individuals). With no data on which to base treatment recommendations, only potential regimens were suggested such as pyrazinamide and ethambutol, or pyrazinamide and a quinolone, and the proposed duration of therapy was 6 to 12 months.[44,117]

A survey of expert opinions contradicted these recommendations.[118] The expert panel believed that prophylaxis was warranted for all exposed individuals but no decision was reached on an agreed regimen. Treatment with pyrazinamide 1500mg daily plus ciprofloxacin 750mg twice daily for 4 months did have some support. Similarly, a decision analysis suggested that pyrazinamide-ciprofloxacin was appropriate chemoprophylaxis for an HIV-negative healthcare worker exposed to MDRTB but the benefit was marginal when compared with the outcome of simple observation without prophylaxis.[119] Furthermore, the probability of cure (pCURE) of MDRTB disease used in the decision analysis was potentially unstable. The analysis used a value of 0.6490 for pCURE based on the experience of Goble et al.[19] However, as was explained in section 4.1, this group of

patients was highly selected and the study was performed before the wide use of quinolones in the treatment of MDRTB. The threshold value of 0.9054 for pCURE at which prophylaxis was no longer beneficial might approach the recent experience of treating MDRTB in HIV-negative patients.[65,81]

Patient preference and drug adverse effects become major factors if the benefit of MDRTB prophylaxis is small. A 6-month preventive regimen of pyrazinamide and ofloxacin was poorly tolerated by 16 healthcare workers exposed to MDRTB in a New York City hospital; 14 discontinued prophylaxis prematurely and the median duration of preventive treatment was only 3 months (range, 1 to 6 months).[120] The adverse effects reported included arthralgia, gastrointestinal disorders, hepatitis, pruritus, fatigue, rashes and insomnia.

The appropriate management of people exposed to MDRTB therefore remains a vexing problem. Trials of various preventive regimens for MDRTB are required but would need to be conducted in industrialised countries with the resources to follow-up large numbers of patients for prolonged periods. No such trials are in progress nor do such trials appear feasible in the near future.[121] Clinicians, and their informed patients who have been exposed to MDRTB, are therefore left in the unenviable position of deciding on the basis of inadequate data between simple observation and an unproven preventive regimen with appreciable adverse effects (e.g. pyrazinamide plus a quinolone).

5.3 Bacille Calmette-Guérin Vaccination

In view of the drug resistance problems confounding chemoprophylaxis, several authors have re-examined the use of bacille Calmette-Guérin (BCG) vaccination, particularly for healthcare workers.[122-124] A meta-analysis found that BCG vaccination provided approximately 50% protection and was even more effective in preventing TB meningitis and disseminated disease.[125] However, BCG vaccination may cause a false-positive tuberculin reaction and hence invalidates subsequent skin test results.[44] Vaccination also occasionally causes local reactions and adenitis, and rarely results in osteomyelitis and disseminated disease.[44,124]

The risks and benefits of BCG immunisation must therefore be balanced in the setting of possible exposure to MDRTB. A decision analysis compared the usefulness of BCG immunisation and post-infection prophylaxis with ciprofloxacin-pyrazinamide for a healthy HIV-negative healthcare worker exposed to MDRTB.[123] BCG vaccination proved to be marginally superior to screening and preventive treatment. Most variations in the probabilities used in the decision analysis tended to further favour the use of BCG vaccination. For example, BCG immunisation had to be only 26% effective to be favoured over post-infection prophylaxis. Despite this pressure for wider use of BCG immunisation, the current US recommendations are that BCG is only indicated for infants and children at continued risk of TB infection.[126] However, BCG vaccination may now be 'considered' for healthcare workers who remain exposed to MDRTB despite the institution of comprehensive infection control procedures.

6. Suggested Alternative Treatments for MDRTB

The incidence of TB in industrialised countries was falling until the mid-1980s. There was, therefore, little impetus for antituberculosis drug development by private pharmaceutical companies or for publicly funded treatment trials. Increased funding, re-establishment of the necessary infrastructures, and the full sequencing of the *M. tuberculosis* genome will hopefully result in the production of novel antituberculosis compounds in the next 5 to 10 years.[127] In the meantime, several 'established' drugs have been suggested or trialed for the treatment of MDRTB.

6.1 High Dose Isoniazid

Cessation of isoniazid administration is generally recommended in the presence of confirmed MDRTB.[20,44,81] Interestingly, multivariate analyses of the outcomes of patients infected with the

MDRTB strain W in New York in the early 1990s found that prolonged survival was not only associated with capreomycin treatment but also with administration of a fluoroquinolone or isoniazid.[104] Moulding reviewed the literature on the continued administration of isoniazid despite the presence of *in vitro* resistance.[128] There is some bacteriological justification for this practice. Strains of *M. tuberculosis* identified in the laboratory as isoniazid resistant often contain mixtures of susceptible and resistant organisms. In fact, Victor et al.[129] found that 48% of a cohort of South African patients with MDRTB had isolates resistant to levels just above the critical concentration for isoniazid (i.e. MICs of 0.2 to 5.0 mg/L). The use of high dose isoniazid, 16 to 20 mg/kg (i.e. 1 to 1.5 g/day), would eliminate susceptible organisms and those with low-level resistance. Despite apparent *in vitro* resistance, isoniazid also retained appreciable residual activity against a strain of MDRTB in a mouse model.[130]

Two studies have addressed the use of isoniazid in retreatment regimens (reviewed by Moulding[128]). An IUATLD study found no benefit in including isoniazid at a regular dosage (i.e. 300 mg/day) in a regimen with cycloserine, ethionamide, and/or pyrazinamide. In contrast, the second study found that 69% of patients receiving high dose isoniazid as well as the retreatment regimen (i.e. ethionamide and pyrazinamide) had sputum conversions without relapses compared with 21% of patients receiving the retreatment regimen alone ($p < 0.002$). High dose pyrazinamide is associated with hepatotoxicity, peripheral neuropathy (which is prevented by administering pyridoxine 6 mg/day), and convulsions (which may be prevented by giving higher doses of pyridoxine).

Moulding[128] concluded that conventional dosages of isoniazid are of no benefit in treating isoniazid-resistant TB and that high dose isoniazid treatment should not be considered if effective alternative therapies are available. However, high-dose isoniazid arguably has a place as an adjunctive drug in MDRTB retreatment regimens in developing countries unable to afford the expensive 'second-line' drugs. This approach requires further investigation.

6.2 Rifabutin

Rifabutin is a semisynthetic spiropiperidyl derivative of rifamycin S (ansamycin, LM-427) which may be more active than rifampicin (rifampin) against *M. tuberculosis*.[44,131] Rifabutin is rapidly absorbed from the gastrointestinal tract, has a serum half-life of 16 hours (which is longer than rifampicin), and achieves higher tissue concentrations than rifampicin. The drug is eliminated by the kidney and the liver. Adverse effects associated with rifabutin include gastrointestinal disorders, hypersensitivity, hepatotoxicity and haematological reactions.[44]

The critical concentration for rifabutin has been tentatively set at 0.5 mg/L.[132] The MICs of rifabutin for rifampicin-sensitive strains of *M. tuberculosis* are less than 0.06 mg/L whereas rifampicin-resistant strains have MICs ranging from 0.25 to 16.0 mg/L. There is obvious cross-resistance between these 2 drugs. Nonetheless, the wide range of rifabutin MICs among rifampicin-resistant isolates suggested that a few MDRTB strains could be effectively treated with rifabutin and that this possibility required clinical investigation.

While rifabutin has been demonstrated to be equivalent to rifampicin in the treatment of newly diagnosed drug-susceptible pulmonary tuberculosis in HIV-positive and -negative patients,[131,133-135] the clinical trials investigating whether rifabutin can contribute to MDRTB retreatment regimens have been either inconclusive or disappointing. Five uncontrolled open-label studies and 1 partially randomised dose-finding study provided preliminary data on the effectiveness of rifabutin in treating MDRTB.[131,135] A sustained bacteriological response was reported in 23 to 47% of the 270 patients in the uncontrolled studies. Rifabutin was well tolerated, and the outcome of therapy was supposedly 'independent of the concomitant medications and of resistance patterns'.[131,135] The partially randomised study involving 104 patients showed a dose-response effect with an 8% re-

sponse for the 150 mg/day dosage increasing to a 50% response for the 450 mg/day dosage, suggesting that rifabutin was having some effect. Unfortunately, these studies cannot be properly interpreted because they have only been published as abstracts or reviews, were uncontrolled, and provided little microbiological data.

A controlled study of rifabutin in the treatment of MDRTB was conducted in Hong Kong.[94] Eleven pairs of patients matched for the resistance patterns of their isolates received similar companion drugs plus one of the pair received rifampicin, the other rifabutin. No difference was demonstrated between those receiving rifampicin or rifabutin, and no patient had a sustained bacteriological response. A temporary response was seen in 2 rifabutin-treated patients who had strains that were initially susceptible to rifabutin. They subsequently relapsed and their isolates developed rifabutin resistance (arguing that rifabutin had contributed to their initial response). Nonetheless, the overall finding of this study was that rifabutin made little contribution to the treatment of MDRTB. Iseman[26] has also stated that rifabutin was used extensively for MDRTB at the National Jewish Centre for Immunology and Respiratory Medicine in the late 1980s with minimal clinical benefit.

In summary, the favourable pharmacokinetics and putatively superior activity of rifabutin implied that this drug could be effectively included in retreatment regimens for some MDRTB isolates. The preliminary trials were inconclusive and incomplete, and later clinical experience has suggested that rifabutin does not have a role in the treatment of MDRTB.

6.3 Clarithromycin

Clarithromycin is a macrolide antibiotic that is well absorbed orally, attains peak serum concentrations of 2 to 4 mg/L, and concentrates in tissues. A total of 30 to 40% is excreted unchanged or as an active metabolite via the kidneys; biliary excretion accounts for the remainder.[136] The most frequently reported adverse effects of clarithromycin have been nausea, diarrhoea and abdominal pain.

Clarithromycin, and the related antibiotic azithromycin, are now the cornerstones of treatment of many nontuberculous mycobacterial infections, including MAC. However, clarithromycin has not been used in MDRTB treatment because the drug has demonstrated poor *in vitro* activity against *M. tuberculosis*.[137-140] The MICS were generally above 16 mg/L and the MIC_{50} (i.e. the concentration at which 50% of tested strains were inhibited) was 64 mg/L. These levels are far higher than the achievable serum or tissue concentrations.

Nonetheless, there have been some other encouraging *in vitro* results. Cavalieri et al.[140] reported that addition of clarithromycin in combination tests resulted in 4- to 32-fold reductions in the MICs of isoniazid, ethambutol and rifampicin against 12 strains of MDRTB. Luna-Herrera et al.[138] could not confirm this synergistic activity in 4 other strains of *M. tuberculosis* but did show that clarithromycin was active *in vitro* against MDRTB strains within J774A.1 macrophages at concentrations attainable *in vivo* (i.e. 0.06 to 2.0 mg/L). Furthermore, in these *in vitro* macrophage experiments, clarithromycin potentiated the activity of rifampicin.

Murine models have also been used to investigate the antituberculous activity of clarithromycin, again with mixed results.[138-140] Clarithromycin reduced the mortality in mice given a lethal intravenous inoculum of drug-susceptible *M. tuberculosis* H37Rv but did not have significant bactericidal or bacteriostatic activity. In fact, clarithromycin had activity only 'slightly superior' to that of thioacetazone in the mouse model.[138] The usefulness of clarithromycin as a 'second-line' drug in the treatment of MDRTB remains to be defined but the inconclusive *in vitro* and *in vivo* data suggest that it will be of minimal value.

6.4 Clofazimine

Clofazimine (B-663) is a riminophenazine compound that was originally developed as a potential antituberculosis drug but showed poor activity in

certain animal models. The drug was subsequently found to have *in vitro* and *in vivo* activity against *Mycobacterium leprae* and MAC. After a single oral dose of 300mg, clofazimine attains a peak serum concentration of 1.0 mg/L.[44] The drug undergoes extensive tissue distribution and accumulates preferentially in macrophages.[140,141] A substantial portion of the unchanged drug is excreted in faeces but metabolites are also detected in the urine. Common adverse effects include gastrointestinal disorders and skin discolouration.

With the emergence of MDRTB, the potential antituberculosis activity of clofazimine and its analogues have been re-investigated. Gangadharam and colleagues have reported that clofazimine and 2 analogues, B-746 and B-4157, have MIC_{90} values for drug-susceptible and drug-resistant *M. tuberculosis* isolates of ≤1.0 mg/L, 0.5 mg/L, and ≤0.12 mg/L, respectively.[141,142] These concentrations are attainable *in vivo*, particularly within macrophages. These compounds also demonstrated activity, comparable to that of isoniazid and rifampicin, against *M. tuberculosis* H37Rv in J774A.1 macrophages and in a mouse model. The use of clofazimine and its analogues in the treatment of MDRTB deserves further investigation based on these *in vitro* and *in vivo* results. So far, there have only been anecdotal reports of successful treatment of MDRTB with regimens containing clofazimine.[143]

6.5 Amoxicillin-Clavulanic Acid

The potential antituberculosis activity of β-lactam antibiotics has been largely ignored. β-lactam antibiotics can penetrate the cell wall of *M. tuberculosis* and bind with high affinity to 4 penicillin-binding proteins.[144] The principal mechanism of resistance is therefore not impermeability but rather the presence of at least 2 β-lactamases.[144,145] The major β-lactamase of *M. tuberculosis* is a class A enzyme with mainly penicillinase activity that can be inhibited by β-lactamase inhibitors (e.g. clavulanic acid, sulbactam), or circumvented by the use of carbapenems (e.g. imipenem) which are penicillinase-resistant.[144] *In vitro*, amoxicillin-clavulanic acid was bactericidal for 14 of 15 *M. tuberculosis* isolates at an amoxicillin concentration of 4 mg/L and a clavulanic acid concentration of 2 mg/L or less.[146]

Two papers have reported the incorporation of amoxicillin-clavulanic acid in 'secondline' regimens to treat a total of 7 patients with MDRTB.[147,148] Amoxicillin-clavulanic acid was well tolerated, and 4 patients responded with sputum conversions 1 to 4 months after commencing treatment. Naturally, multidrug regimens were used to treat these patients with MDRTB so it is difficult to ascertain the individual contribution of amoxicillin-clavulanic acid in these successful outcomes. Chambers et al.[149] have, therefore, administered amoxicillin-clavulanic acid for 7 days to selected patients with pulmonary TB to gauge the early bactericidal activity of this drug (the patients then received a standard 4 drug regimen). After 2 days of treatment, amoxicillin-clavulanic acid (1000mg/250mg 3 times a day) had reduced the colony forming units (cfu) in sputum by a mean (± SD) rate of 0.34 ± 0.03 $\log_{10}$ cfu/ml. This early bactericidal activity is comparable to that of other antituberculosis drugs except isoniazid. However, little reduction in cfu counts was noted after the third day and this phenomenon requires further investigation.

In summary, β-lactam antibiotics penetrate the mycobacterial cell wall and, in combination with a β-lactamase inhibitor, have proven bactericidal activity against *M. tuberculosis*. Further animal and clinical trials are definitely indicated to confirm the utility of β-lactam-β-lactamase combinations in the treatment of MDRTB.

6.6 Metronidazole

Mycobacteria have been dogmatically categorised as strict aerobes but Wayne and colleagues[150] have demonstrated that *M. tuberculosis* can survive in low oxygen conditions. They have shown that *M. tuberculosis* adapts to low oxygen levels as the bacilli slowly settle through a self-generated O_2 gradient into the sediment of unagitated cultures. These microaerophilically-cultured bacilli may represent an *in vitro* model of the dormant organ-

isms that persist in the infected but asymptomatic host. These stationary phase organisms undergo orderly metabolic changes to survive anaerobiosis and become susceptible to drugs (i.e. metronidazole and 2 other nitroimidazole compounds) that are generally active against anaerobic organisms.[151]

Theoretically, if metronidazole and related anti-anaerobic drugs are bactericidal for dormant organisms, these antibiotics may have a role in eradicating persisting bacilli during the sterilisation phase of treatment, and in chemoprophylaxis. These compounds would presumably be equally effective against MDRTB strains as against drug-susceptible *M. tuberculosis*. Unfortunately, Dhillon et al.[152] have recently reported that metronidazole has no activity against dormant bacilli *in vivo* in the Cornell mouse model. However, the lesions of murine tuberculosis may not be sufficiently anaerobic for metronidazole to act. Other animal models will need to be used that produce caseating microaerobic lesions comparable to human pulmonary TB before excluding the potential role of metronidazole in TB treatment.

6.7 Other Experimental Interventions

With few therapeutic alternatives available, novel antibiotics,[153,154] 'non-antibiotics' (i.e. drugs not generally recognised as having antibacterial activity),[155] immunotherapy,[156,157] and gene therapy[158] have been proposed for the treatment of MDRTB. Condos et al.[156] used aerosolised interferon-γ in conjunction with other 'second-line' agents to treat 5 patients with MDRTB. The aim of this treatment was to activate pulmonary macrophages into effective phagocytic cells. Aerosolised interferon-γ was well tolerated and resulted in temporary sputum smear (but not culture) conversions. Similarly, Prior et al.[157] reported the use of *Mycobacterium vaccae* as immunotherapy, in combination with ciprofloxacin, cycloserine and pyrazinamide, in the treatment of a patient with abdominal MDRTB. These immunotherapies remain of unproven benefit and are likely to become no more than adjunctive treatments.

As an initial step in the development of an effective gene therapy for MDRTB, Rom et al.[158] have produced a mutant *rpoB* gene that effectively mimics the mode of action of rifampicin and inhibits transcription.[158] This mutant gene represents a potential suicide gene for MDRTB if a delivery strategy can be developed.

Novel chemotherapeutics are also in development. Oleksijew et al.[153] recently reported that ABT-255, a 2-pyridone which inhibits the bacterial DNA gyrase, had MICs ranging between 0.016 to 0.031 mg/L for drug-susceptible and drug-resistant isolates of *M. tuberculosis*. Similarly, Grandoni et al.[154] found that inhibitors of branched-chain amino acid biosynthesis (e.g. sulphometuron methyl, which is a commercial herbicide) had activity *in vitro* and in a murine model against *M. tuberculosis*, and suggested that these drugs may be useful lead compounds in searching for novel antituberculosis agents.

In addition, certain 'non-antibiotics' have been proposed for MDRTB treatment. Chlorpromazine and thioridazine, which are anti-psychotic agents from the phenothiazine group, inhibit the growth of *M. tuberculosis* in broth cultures and within macrophages.[155] Hence, these phenothiazines and the related antihistamines may be another worthwhile group of compounds for further research.

In summary, all of the treatments described in section 6.7 remain experimental and of uncertain utility. However, they do provide some direction and hope for the development of novel antituberculosis agents that are required for treating patients with MDRTB.

7. Discussion and Conclusions

This review has summarised the epidemiology, treatment and chemoprophylaxis of MDRTB and has highlighted the importance of preventing the development and dissemination of this 'man-made' disease. Industrialised countries can control and treat MDRTB, but at great expense. In New York City in the early 1990s, DOTS programmes with intensive case management were instituted, MDRTB patients were effectively treated,[65,66,69,70] laboratory diag-

noses were expedited, screening and preventative therapy were more widely applied, and hospitals and other public facilities established effective infection control procedures.[29] The absolute number and the rate of MDRTB fell from 441 (11.6% of all cases) in 1992 to 108 (4.4% of all cases) in 1995.[11,30] The total cost of these multiple interventions easily exceeded $US1 billion.[29]

MDRTB presents the greatest problems in countries that lack the money, expertise and infrastructure to mount a 'New York-like' control programme. This article has presented the views espoused by the WHO regarding their DOTS strategy. If the surveys conducted by Pablos-Méndez et al.[9] are extrapolated, approximately 2.2% of TB cases worldwide are a result of multidrug-resistant strains. The WHO has therefore quite rightly focused on effective management of drug-susceptible disease as being the best way of managing the global TB emergency and of preventing MDRTB.[20,52] However, the assertion that effective control programmes based on the DOTS strategy will automatically decrease the levels of MDRTB[9,20] has been questioned recently by Farmer and Kim.[159]

There are little published data on the outcome of DOTS programmes in areas with high preexisting levels of MDRTB. Some confusion may have actually been caused by trying to extrapolate from experiences in countries with high prevalences of resistance to isoniazid and/or streptomycin. For example, a recent publication by the WHO-IUATLD authorities referenced studies from New York City,[29,160] Baltimore,[46] Texas,[48] Korea,[161,162] and Algeria[163] to justify the statement that '. . . sound control policies are associated with decreases in drug-resistance levels'.[9]

The paper by Chaulk et al.[46] from Baltimore did not mention any drug susceptibility results. Weis et al.[48] described reductions in drug resistance levels in Tarrant County, Texas, after institution of universal DOT, but these authors defined a multidrug-resistant organism as an isolate resistant to 'at least 2 of the following drugs: isoniazid, rifampin, ethambutol and streptomycin'. This definition does not meet the strict criteria for MDRTB (i.e. resistance to at least rifampicin and isoniazid). Furthermore, the microbiological data were not presented to show whether the incidence of combined resistance to isoniazid and rifampicin actually fell. The studies from Korea and Algeria could be summarised as showing that DOTS programmes incorporating short-course regimens reduce the levels of 'minor' drug resistance to isoniazid and/or streptomycin.[161-163] However, despite the presence of 'model' DOTS programmes that reduced the overall rates of drug resistance, all 3 papers showed that the introduction of rifampicin was associated with the development of rifampicin resistance and the establishment of acquired MDRTB (i.e. combined isoniazid- and rifampicin-resistance) at rates of 14.5%,[161] 17.9%,[162] and 11.0%.[163]

These observations are not made to argue against the use of rifampicin but to emphasise the need for DOTS programmes as recommended by the WHO to limit the development of further rifampicin resistance. The other point to be made from the Korean and Algerian studies is that none of these were established in the setting of high preexisting levels of MDRTB, and none demonstrated that 'model' DOTS programmes reduce the rate of MDRTB.

The WHO-IUATLD authorities[9] also referenced a study by Styblo et al.[164] that described the first 4 years of experience following the introduction of a 'prototype' DOTS programme in Czechoslovakia in the early 1960s. Naturally, this paper from the pre-rifampicin era cannot shed light on whether DOTS programmes using short-course regimens can reduce the rate of MDRTB. Nonetheless, this paper does make some important points that are worth quoting. The study was able to show that 'systematic, adequate treatment of all patients with newly discovered tuberculosis and all of those who had suffered a relapse' reduced the emergence of resistance. However, 'adequate treatment was also given to all existing chronic bacillary excretors' who had high rates of drug-resistant disease and this intervention was said to have 're-

duced to a minimum the number of chronic bacillary excretors'. If the experience of this Czechoslovakian study is extrapolated to the modern day dilemma of MDRTB, the assumption would be that DOTS programmes are required to limit the development of further acquired resistance, but that effective treatment of prevalent MDRTB cases is also necessary.

In the end, the only papers quoted by the WHO-IUATLD authorities[9] that actually show a reduction in MDRTB rates are those from New York City. Multiple interventions (including a 'model' DOTS programme) were instituted in New York City,[29] and the relative contribution of each to the ultimate success is difficult to determine. Further research is obviously needed to determine which interventions are cost effective in controlling MDRTB, to describe the natural history and transmission dynamics of MDRTB, and to measure the efficacy of standard short-course regimens and the rate of additional acquired resistance when DOTS is employed where there is a high background level of MDRTB.[9] However, the assumption that MDRTB treatment is a necessary element of a TB control programme is supported by the fact that one of the interventions in New York City was the adequate care of patients with MDRTB.[65,66,69,70]

The WHO have now recognised the arguments presented by Farmer and Kim,[159] that DOTS alone may not be enough to control the spread of MDRTB. The term 'DOTS plus' has been introduced to describe a system in which an effective TB control programme using short-course chemotherapy is complemented by the facilities to provide individualised retreatment programmes for patients with MDRTB. Industrialised countries have a vested interest, as well as a moral responsibility, to assist in the control of MDRTB. Facilities for treating MDRTB will be difficult to establish in many areas,[20] and will require access to the drugs, the expertise, and the laboratory resources described in this review. Above all, these facilities will require money.

Acknowledgements

We thank Professor Francoise Portaels for her helpful comments during the preparation of this manuscript. Dr Ivan Bastian is supported by a Neil Hamilton Fairley Fellowship (987069) awarded by the National Health and Medical Research Council of Australia. Financial support was also obtained from the Flemish Fund for Scientific Research.

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