ERJ Express. Published on September 16, 2010 as doi: 10.1183/09031936.00033010

TREATMENT OF TUBERCULOSIS

UPDATE 2010

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ABSTRACT

Currently, the standard short-course chemotherapy for tuberculosis comprises a six-month regimen, with a 4-drug intensive phase and a 2-drug continuation phase. Alternative chemotherapy using more costly and toxic drugs, often for prolonged durations generally more than 18 months, is required for multidrug-resistant and extensively drug-resistant tuberculosis. Directly observed treatment, as part of a holistic care programme, is a cost-effective strategy to ensure high treatment success and curtail development of drug resistance in tuberculosis. New antituberculosis drugs are urgently needed to improve the present standard short-course chemotherapy and alternative chemotherapy, by shortening administration durations and increasing cure rates, through the greater potency of these agents. At the same time, the role of adjunctive surgery for drug-resistant tuberculosis has to be better defined. Immunotherapy might improve treatment outcomes of both drug-susceptible and drug-resistant tuberculosis, and warrants further exploration.

INTRODUCTION

In the year 2008, 11.5 million people were estimated to be living with tuberculosis, with 9.4 million having incident disease. Among 1.9 million people who died of tuberculosis, 0.5 million were seropositive for HIV [1]. While the present chemotherapy for tuberculosis is highly efficacious, it has the disadvantages of being lengthy and complex, and does not live up to the expectation of adequately controlling the current global tuberculosis situation. In 2008, an estimated 390,000 – 510,000 cases of multidrug-resistant (MDR) tuberculosis with bacillary resistance to at least isoniazid (H) and rifampicin (R) are estimated to emerge every year worldwide, with China and India together accounting for approximately 50% of this global burden. In 2008, MDR tuberculosis caused an estimated 150,000 deaths [2]. Extensively drug-resistant (XDR) tuberculosis, recently emerging, is defined as MDR tuberculosis with additional bacillary resistance to any fluoroquinolone, and one or more of the three (second-line) injectable drugs – kanamycin, amikacin, and capreomycin. Approximately 5.4% of MDR tuberculosis reported worldwide could be categorized as XDR tuberculosis, with the proportion exceeding 10% in some countries [2]. This review examines the current status and future prospects of treatment of tuberculosis. Where appropriate, evidence levels for the recommended treatment regimens / modalities are given in accordance with the grading system of the Scottish Intercollegiate Guidelines Network (Appendix) [3].

Before discussing recommended drug regimens for treating of pulmonary tuberculosis, an understanding of basic mycobacteriology and antituberculosis drug action would be beneficial.

Scientific Basis of Short-Course Chemotherapy

Mycobacterium tuberculosis, the causative organism of tuberculosis, is a slowly growing bacterium, and it can also enter a phase of dormancy which appears drug-refractory. Four hypothetical populations of organisms [4] may exist in a patient with tuberculosis: 1) actively growing organisms, usually present in abundance (extracellularly) within aerated cavities, 2) slow intermittently growing organisms in an unstable part of the lesion, 3) organisms surviving under microaerobic conditions in a low environmental pH, either in inflammatory lesions or within phagolysosomes of macrophages, and 4) completely dormant organisms surviving under anaerobic conditions. The three major actions of antituberculosis drugs [5] are:

- bactericidal action, defined as their ability to kill actively growing bacilli rapidly, e.g. isoniazid, and to a lesser extent, rifampicin and streptomycin (S);
- sterilising action, defined as their capacity to kill the semi-dormant organisms, e.g. rifampicin and pyrazinamide (Z);

- prevention of emergence of bacillary resistance to drugs, e.g. isoniazid and rifampicin; less so for streptomycin, ethambutol (E) and pyrazinamide; least for thiacetazone and para-aminosalicylic acid.

CHEMOTHERAPY OF PULMONARY TUBERCULOSIS

Short-Course Chemotherapy Regimens

Based on a number of clinical trials performed previously, much knowledge has accumulated regarding chemotherapy regimens for new cases of smear-positive pulmonary tuberculosis [6-15]. The shortest duration of treatment required is at present six months (Grade A). The standard regimen today, as categorically recommended by the World Health Organization (WHO) / International Union Against Tuberculosis and Lung Disease (IUATLD) [16] comprises the combination of HRZE for two months, followed by that of HR for another four months. Streptomycin is not generally recommended as a fourth drug in the intensive phase, largely because of its higher resistance rate than that of ethambutol [17], and its requirement for parenteral route of administration. However, in rare occasions when ethambutol use is contraindicated, the aminoglycoside may be considered. Dosages for the conventional first-line antituberculosis drugs are well established, and can be found in standard references [16,18].

Although the 8-month regimen: 2 months of streptomycin, isoniazid, rifampicin and pyrazinamide, followed by 6 months of isoniazid and thiacetazone, combined with

hospitalisation in the first two months, has previously been shown to be effective in controlled clinical trials and programme settings in Africa [11], a randomized study initiated by IUATLD, has revealed that the 8-month regimen: 2HRZE / 6HE was significantly inferior to the 6-month regimen: 2HRZE / 4HR [19]. A systematic review has also shown that regimens utilizing rifampicin only for the first 1 – 2 months had significantly higher rates of failure, relapse and acquired drug resistance as compared to regimens that used rifampicin for 6 months [20]. The WHO currently recommends phasing out of the 8-month regimen [16]. Thus, short-course antituberculosis chemotherapy regimen with both rifampicin and pyrazinamide should contain six months, rather than two months, of rifampicin for better efficacy (Grade A).

A regimen without pyrazinamide in the initial intensive phase must be given for longer than six months (Grade A). Such regimen based on isoniazid and rifampicin [13-15] is only good for pansusceptible tuberculosis with limited bacillary load, and has to be given for nine months (namely 2HRE / 7HR or 9HR). This 9-month regimen is usually not recommended for patients in countries with high rates of isoniazid-resistant tuberculosis, except those who cannot tolerate pyrazinamide.

The administration of pyrazinamide beyond two months has not been shown to offer any advantage on treatment outcome (Grade A) [21,22]. Besides, in cohort and case-control

analyses, from 12 weeks or more after starting treatment, the estimated risk of hepatotoxicity was 2.6% for regimens incorporating pyrazinamide, isoniazid and/or rifampicin and 0.8% for standard regimens containing isoniaizid and rifampicin. Thus adding pyrazinamide to isoniazid and rifampicin increases the risk of hepatotoxicity appreciably [23].

For individual cases with extensive disease and slow sputum bacteriological conversion, administration of pyrazinamide ± ethambutol beyond two months may seem acceptable. This prolongation of intensive phase is not currently supported by WHO [16]. However, WHO has recently raised the possible advantage of using rifampicin, isoniazid and ethambutol rather than rifampicin and isoniazid in the continuation phase of treatment of tuberculosis in populations with known or suspected high levels of bacillary resistance to isoniazid [16]. Initial cavitation and positive sputum culture after two months of treatment have been found to be associated with increased risk of failure / relapse, and possibly justify prolongation of the continuation phase of antituberculosis therapy to give a total duration of nine months [24] (Grade B).

Intermittent regimens comprising two drugs in the continuation phase, following upon an intensive phase of four drugs given on a daily basis, have been proven to be highly efficacious (2HRZS / $4H_3R_3$ or 2HRZS / $4H_2R_2$) [7,10] (Grade A). The WHO does not

generally recommend twice-weekly regimens because of the higher risk of treatment failure when missing doses occur [16]. Intermittent short-course regimens administered thrice weekly all through have been shown to have largely equivalent efficacy to daily regimens [8]. A recent nested case-control study has raised concerns regarding the efficacy of three-times weekly 6-month regimens in preventing disease relapse in the presence of cavitation [25]. The systematic review just alluded [20] has not shown any significant difference in failure or relapse with daily or intermittent scheduling of treatment administration, apart from insufficient published evidence for the efficacy of twice-weekly rifampicin administration throughout therapy. However, major confounding factors, such as cavitation and 2-month culture status, might be heterogeneous across the included studies and not adequately controlled for in this systematic review. Furthermore, rates of acquired drug resistance among the failures / relapses have been shown to be higher with three-times weekly therapy [20]. Dosing schedules in the first nine weeks did not appear to have impact on the risk of hepatotoxicity in another case-control study [26]. Logistic regression analysis has shown that sex was nonsignificant but ageing increased the odds of hepatitis, the risk of which rose from 2.6% to 4.1% as age exceeded 49 years.

WHO currently recommends the use of daily dosing during both the intensive and continuation phase as the most optimal approach (Table 1).

HIV-infected patients who received 6-month rifampicin- or rifabutin-based regimen were shown to have a higher relapse rate than those on longer therapy in an early clinical trial [27] and a more recent treatment cohort [28]. Possibly because of the poor prognosis associated with the underlying HIV infection before the availability of antiretroviral therapy, the lower relapse rate did not translate into improved survival in the former trial [27]. WHO currently recommends that tuberculosis patients who are living with HIV should receive at least the same duration of treatment as HIV-negative patients. Increased risk of treatment failure and acquired rifamycin resistance has also been shown to be associated with intermittent regimens among HIV-infected patients [29-31]. WHO currently recommends that for HIV-positive patients with tuberculosis, and all tuberculosis patients living in HIV-prevalent settings should receive daily treatment, at least during the intensive phase [16].

In many countries, nearly 50% of patients are diagnosed as having active pulmonary tuberculosis on clinical and radiographic grounds, without immediate bacteriological confirmation. In the two smear-negative studies conducted in Hong Kong, it has been found that with 2 – 3 months of daily HRZS treatment, the relapse rates were 32% and 13% for culture-positive patients [32], but the rates were much lower with 4-month treatment (2% for

drug-susceptible tuberculosis and 8% for isoniazid- and streptomycin-resistant tuberculosis) [33].

Thus, it appears that at least 4 months of treatment is required for smear-negative pulmonary tuberculosis in non-HIV-infected patients (Grade C). The WHO currently recommends the use of a 6-month regimen of daily HRZE for 2 months followed by daily or three times per week HR for another 4 months in the treatment of new smear-negative pulmonary tuberculosis patients [16].

The relapse rates during 6 – 30 months after stopping the standard 6-month short-course chemotherapy regimen are generally less than 5% [6-10]. 78% of relapses occurred within 6 months of stopping treatment, and 91% within 12 months [34].

Retreatment Drug Regimens

For treatment of smear-positive relapse cases of pulmonary tuberculosis as well as retreatment after interruption, an 8-month regimen has been recommended by the WHO/IUATLD, namely 2HRZES / 1HRZE / 5HRE [16] (Grade D). With the increasing availability of rapid tests for bacillary drug susceptibilities, such as line probe assays, it would

be possible to modify this approach according to the results, particularly in areas with high prevalence of MDR / XDR tuberculosis [16]. Using conventional drug susceptibility testing, it might be necessary to start an empiric retreatment regimen active against MDR disease, when the levels of MDR tuberculosis are high in different patient registration groups in the geographical area (Grade D). Patients who have failed two rifampicin-containing regimens: the initial and retreatment ones are very likely to have MDR tuberculosis. These updated recommendations are now incorporated in the current WHO guidelines [16] (Table 2).

Directly Observed Treatment, Short-Course

Directly observed treatment (DOT) was shown to be highly efficacious in ensuring patient adherence by experience gained in Chennai (then Madras) and Hong Kong many decades ago. In 1993, the WHO officially announced the new global strategy for tuberculosis control known as directly observed treatment, short-course (DOTS) that implements the 6-month short-course regimen in a programmatic setting [35,36]. The DOTS strategy has five key components which include (i) a network of trained health-care or community workers to administer DOT, (ii) properly equipped laboratories with trained personnel to perform sputum microscopy for diagnosing tuberculosis, (iii) a reliable supply of high-quality drugs (preferably at no cost to patients), (iv) an accurate record keeping and cohort analysis system for

monitoring case-finding, treatment and outcomes and (v) sustained political commitment and funding. An effectively functioning tuberculosis control programme is clearly essential for good patient outcome [36]. Although some patient characteristics like homelessness, alcohol or substance abuse, behavioural problems, mental retardation, and lack of social or family support are more commonly associated with nonadherence to therapy, it is often difficult to identify poorly adherent patients because the underlying reasons for such behaviour are not only multifaceted and complex, but range from characteristics of the individual patients to qualities of the societal and economic environment [37]. Although a cochrane database systematic review concluded that the results of randomized controlled trials conducted in low-, middle-, and high-income countries did not provide assurance that DOT, compared with self-administered treatment, could impart quantitatively important effect on cure or treatment completion in tuberculosis patient [38], the great merit of reduction of acquired drug resistance with DOT was not addressed [39]. The DOTS strategy is more than DOT alone, it should be viewed as a comprehensive service, or an integral part thereof, which possesses ingredients also inclusive of enablers, incentives, education and holistic care that are conducive to the success of the treatment programme. In a cluster randomized controlled trial examining the effectiveness of a strategy to improve adherence to tuberculosis treatment in a resource-poor setting, the intervention package based on improved patient counseling and communication, decentralization of treatment delivery, patient choice of DOT supporter and reinforcement of

supervision activities led to improved patient outcome compared to the usual tuberculosis control procedures [40]. Apart from good communication skills of healthcare workers, attention regarding management of the treatment associated side-effects and risk of nonadherence, alongside maintaining respect for patient autonomy and integrity is of paramount importance [41]. One study has further demonstrated that both family-member and community DOTS strategies can attain international targets for treatment success under programme conditions [42].

Fixed-Dose Combination Formulations

The use of fixed-dose combination (FDC) formulations comprising 2 - 3 and even 4 drugs may enhance ease of prescription for physicians, reduce inadvertent medication errors, simplify drug procurement and supply, improve treatment adherence by patients, and thereby decrease the risk of development of MDR tuberculosis [43,44]. In a study that compared the levels of acquired drug resistance in patients who had rifampicin and isoniazid FDC, under self-administration settings, the rate was as low as 0.2%, given limitations of the investigation [45]. The WHO has included some FDC tablets in the list of essential drugs [46]. Only formulations of proven good quality should be used [47]. The majority of studies found no significant difference between FDC tablets and single drugs regarding sputum smear

conversion rates, side effects and relapses [48,49]. However, a Singapore study found higher relapse rates at 2 and 5 years of follow-up in patients who received FDC tablets [50]. Furthermore, FDC tablets cannot replace treatment supervision completely as there is still a potential risk of emergence of drug resistance when these combination tablets are taken irregularly [51].

Future Possibilities of Rifamycin Use

Studies have demonstrated the bactericidal and sterilizing activities of rifampicin, as well as their dose and concentration dependence [52-54]. In one study, the maximum dosage of rifampicin tested was 20 mg/kg [53]. Rifampicin at a dosage of >10 mg/kg may also suppress or delay emergence of resistance [54]. Early chemotherapy trials that evaluated the use of high-dose rifampicin have shown better 1-month or 2-month bacteriological conversion but not a more favourable relapse rate, likely due to absence of inclusion of pyrazinamide in the treatment regimens [55]. The safety and tolerability of high-dose rifampicin were not meticulously assessed in the early chemotherapy trials, thus leaving a potential concern for these issues.

Although rifampicin hepatotoxicity was thought to be idiosyncratic in nature [56], it is not possible to exclude interactive toxicity between isoniazid and rifampicin [57]. Thus it may not be entirely appropriate to extrapolate safety data from the use of high-dose rifampicin in treatment of other bacterial infections, such as brucellosis [55]. Mild hepatotoxicity in fact occurred more frequently in a study among patients who received high-dose rifampicin for tuberculosis treatment although no patient developed serious hepatotoxicity [58]. "Flu-like" syndrome has also been associated with high-dose rifampicin, but mainly for intermittent rifampicin administration, and it generally occurs after three months of drug administration [59]. Thrombocytopenia, haemolytic anaemia and acute renal failure may also occur. Since these reactions are immunological in origin, they are not likely to occur more frequently when a higher dosage of rifampicin is used [59]. Further clinical trials would be needed to examine whether such strategy could enhance bacillary sterilization and shorten tuberculosis therapy, without excessive adverse effects [60]. A phase II clinical trial is being conducted to compare the pharmacokinetics and pharmacodynamics of daily doses of 1200mg and 900mg of rifampicin with the standard 600mg dose during the two-month intensive phase of treatment [61].

Early trials of rifapentine, a long-acting cyclopentyl rifamycin, with a plasma half-life of 14 hours, given in a 600mg-dose together with isoniazid on a once-weekly basis during the

continuation phase of treatment in patients with tuberculosis have shown satisfactory efficacy in a subgroup of HIV-negative patients with noncavitary disease and limited bacterial burden, despite an overall failure/relapse rate of 10% [62,63], and emergence of rifamycin monoresistance in relapse cases among HIV-positive subjects [29]. It has been shown that a 900mg-dose of rifapentine had superior pharmacokinetics to the 600mg-dose [64,65], and that a 1200mg-dose of rifapentine produced an optimum pulse and postantibiotic lag on the growth of *M. tuberculosis* [52]. In a murine model, twice-weekly regimens containing rifapentine (15 – 20 mg/kg) have shown marked antituberculosis potency by enhancing the rifamycin exposure [66] and preliminary data using daily dosing of rifapentine have also been encouraging [67]. Rifapentine autoinduction of metabolism has also been noted with interest [68]. Currently there are only enough data on the safety and good tolerance of rifapentine dosed at 900 mg once weekly [69]. However, in an ongoing phase II clinical trial, rifapentine dosed at 10 mg/kg five days per week is being administered [70], and no unusual preponderance of adverse events was reported by the Data and Safety Monitoring Committee so far.

CHEMOTHERAPY OF PULMONARY MDR TUBERCULOSIS AND XDR TUBERCULOSIS

The clinical relevance of antituberculosis drug resistance is first reviewed as a background to the treatment of drug-resistant tuberculosis, especially the MDR and XDR forms.

Clinical Relevance of Antituberculosis Drug Resistance

Resistance to an antituberculosis drug arises spontaneously through chromosomal mutation at a frequency of 10^{-6} to 10^{-8} bacterial replications [36]. The chromosomal loci involved are distinct for the major classes of drugs. Thus, when three or more effective drugs are used in combination, spontaneous emergence of mutants resistant to all drugs is most unlikely with the usual bacterial load in the diseased host. However, sequential genetic mutations may be amplified through human error resulting in clinically drug-resistant tuberculosis. These include "monotherapy" due to irregular drug supply, inappropriate doctor prescription and, poor patient adherence to treatment [36]. Subsequent transmission of resistant *M. tuberculosis* strains from the index patient to others, as facilitated by diagnostic delay and infection-control breach, aggravates the problem [71]. A recent review regarding

epidemiology of MDR tuberculosis has shown that the risk factors for drug resistance pertain to those facilitating the selection of resistance in the community and the specific conditions that appear to increase the vulnerability of some patients, such as in certain HIV or malabsorption settings. The epidemiological situation is principally related to poor treatment practices and poor implementation of control programmes [71].

Isoniazid resistance is the most common form of drug resistance encountered, whether in isolation or in combination with other drugs [2]. Standard short-course chemotherapy for isoniazid-resistant tuberculosis can achieve a good success (>95% cure) when all four drugs are used throughout the six months of treatment (Grade B) [21]. When the four drugs are reduced to rifampicin and isoniazid after 2 months, the relapse rate after 6 months of treatment rises to 10% [22]. As there may be a genuine chance of resistance amplification with additional resistance to rifampicin [20,72], (especially for HIV status and/or intermittent dosing [20,28,31]), some authorities recommend changing to alternative regimens such as REZ, or RE, for more prolonged durations of administration, often up to one year (Grade D) [73,74]. Currently, the most optimal regimen for treatment of isoniazid-resistant tuberculosis appears unknown [16].

Rifampicin-resistant tuberculosis carries a much more ominous prognosis, as the outcome of standard short-course regimens for such disease is poor in terms of both disease status on cessation of treatment and subsequent relapse [75]. Recommendation has been made to treat such disease with EHZ for 18 – 24 months (**Grade D**) [76]. Some authorities feel that the duration of treatment can be shortened to 12 months by the addition of a fluoroquinolone to this 3-drug regimen (**Grade D**) [24]. Furthermore, rifampicin monoresistance in *M. tuberculosis* is usually rare, except perhaps in HIV-infected patients [28,31,76,77]. Thus, rifampicin resistance generally serves as a surrogate marker for dual resistance to rifampicin and isoniazid, i.e., MDR tuberculosis [78,79], especially for previously treated patients. Short-course chemotherapy can cure less than 60% of MDR tuberculosis cases [80], with a high recurrence rate of about 28% among those with apparent success [81]. A recent analysis has shown that the currently recommended short-course treatment regimens for both initial and retreatment purposes could not achieve good outcomes (with failures, relapses and deaths) in countries having initial MDR rates of greater than 3% [82]. It is quite clear today that alternative specific chemotherapy using second-line drugs is required for the management of this formidable condition [83].

Increased risk for development of bacillary resistance to ethambutol and pyrazinamide likely occurs when a conventional 4-drug regimen for initial treatment and a

conventional 5-drug retreatment regimen are repeatedly administered despite observed treatment failure with the conventional short-course regimens for tuberculosis [84-86]. Pyrazinamide and/or ethambutol resistance, in addition to dual resistance to isoniazid and rifampicin, generally portends a more adverse prognosis in MDR tuberculosis [87], particularly when patients receive only standardised second-line antituberculosis drug regimens with pyrazinamide and ethambutol plus a fluoroquinolone and aminoglycoside / capreomycin.

Fluoroquinolones are generally regarded as having a pivotal role in the treatment of MDR tuberculosis [88-90]. *In-vitro* resistance to fluoroquinolones has been shown to predict a poor outcome in the treatment of MDR tuberculosis [88,91,92]. Most fluoroquinolone resistance in *M. tuberculosis* is associated with the injudicious use of this class of drugs in the management of tuberculosis, particularly MDR tuberculosis [93,94], including the use of suboptimal second-line drug regimens comprising inadequate number and / or dosage / quality of accompanying agents [84]. Overzealous usage of this class of antimicrobials in the treatment of lower respiratory tract and other community-acquired infections might also contribute to development of fluoroquinolone-resistant tuberculosis [95].

As the aminoglycosides or capreomycin have potent antituberculosis activity, the loss of these second-line injectables together with fluoroquinolones through their suboptimal use in the

management of MDR tuberculosis would result in XDR tuberculosis, which in general carries a worse prognosis [96].

Programme Strategies and Implementation

The emergence of drug resistance in *M. tuberculosis* has prompted the WHO to modify the DOTS strategy to a more comprehensive approach – the Stop TB strategy [97]. This Strategy comprises the following components: (1) pursue high-quality DOTS expansion and enhancement, (2) address TB/HIV, MDR tubercuosis, and the needs of poor and vulnerable populations, (3) contribute to health system strengthening based on primary healthcare, (4) engage all care providers, (5) empower people with tuberculosis care, and communities through partnership and (6) enable and promote research. The management of MDR tuberculosis through use of alternative second-line antituberculosis chemotherapy mandates its delivery on a programmatic basis with five key components built on the DOTS framework (Figure 1). Capacity for performing drug susceptibility testing and availability of second-line drugs are not adequate to achieve cure. Other factors, such as a set of standard procedures, clear guidelines on treatment and follow up of patients and administration of DOT, must be included in the programme for MDR tuberculosis management to attain good results [83]. There are basically three possible programmatic approaches for the management of MDR tuberculosis [83]:

- Standardized treatment, in which regimens are designed on the basis of representative drug-resistance surveillance data of specific treatment categories, with all patients in the same group or category being treated by the same regimen.
- Empirical treatment, in which each patient's regimen is individually designed on the basis of the previous history of antituberculosis therapy with the help of representative drug-resistance surveillance data, followed by regimen adjustment when the individual drug susceptibility testing results are known.
- Individualized treatment, in which each patient regimen is designed on the basis of previous history of antituberculosis treatment and individual drug susceptibility testing results.

While a standardized regimen enables simple operation and broadens access to care, there may be a concern for amplification of multidrug resistance if the number of available second-line drugs in the regimen is low [98,99]. Individualized treatment strategies rely heavily on capable laboratory services, but have the advantage of avoiding placing patients on toxic and expensive drugs to which the *M. tuberculosis strain* is resistant. One caveat, however, is the unsatisfactory reliability of second-line drug susceptibility testing results, for many agents aside from the fluoroquinolones and the injectables, arising partly from the difficulty in standardizing testing methodology [100-102]. Some progress has, however, been made accordingly [103]. Patients who had previous treatment with second-line drugs would

likely benefit more from administration of individualized regimens. When retreated patients are presumed to have a high likelihood of MDR tuberculosis, an empiric regimen can be administered while awaiting results of conventional drug susceptibility testing [16].

Regardless of the strategy advocated, there are significant cost issues in the management of MDR tuberculosis patients [104]. From a previous decision analysis, more patients would die from tuberculosis, if the implementation of drug-resistance programme is associated with even minimal decreases in the effectiveness of DOTS [105]. Nevertheless, the feasibility and cost-effectiveness of treatment of MDR tuberculosis is now quite well established even in resource-limited settings [106,107]. In countries with significant financial difficulties, additional support, besides technical assistance, from international organizations and governments of industrialized countries would be needed, further to that obtained from local governments [108]. In this regard, the Green Light Committee of the Stop TB Partnership involving the WHO and collaborators has played a significant role in helping the implementation of these programmes in countries with an affordability problem in the management of MDR tuberculosis [109].

Design of Drug Regimens

Guidelines on the treatment of MDR tuberculosis are often formulated on experience and observational studies, as data from randomized trials are lacking. A detailed review has addressed the evidence and controversy of treatment of MDR tuberculosis, focusing on the number of antituberculosis drugs required to treat MDR tuberculosis, the most rational use of effective drugs against the disease, the advisable length of parenteral drug administration or of the initial phase of therapy, the contribution of surgery to the management of MDR tuberculosis and the optimal approach for treating MDR disease – standardized versus individualized regimens. However, little evidence but much controversy were found regarding the the treatment of MDR tuberculosis [110]. Randomized controlled trials regarding chemotherapy of MDR tuberculosis should be undertaken to provide more evidence-based recommendations [111]. The updated WHO guidelines in 2008 and 2009 recommend designing treatment regimens with a consistent approach based on the hierarchy of five categories of antituberculosis drugs (Table 3) [16,112]. The potency of these drugs is in a descending order. Thus the drugs are so selected from these five groups accordingly. A brief review of the utility of these drugs is detailed below.

While isoniazid in conventional dose has limited usefulness, high-dose isoniazid (>10 mg/kg) has demonstrated some efficacy (clinical, bacteriological and radiographic) as well as reasonable patient tolerance in a recent study [113]. After adjustment for potential

confounders, subjects who received high-dose isoniazid had a 2.37 times higher likelihood of becoming culture negative at six months. Isoniazid-resistant *M. tuberculosis* organisms belonging to the low-resistance phenotype often have cross-resistance to ethionamide, while those of high-resistance phenotype are more susceptible. Adding high-dose isoniazid kills the former, leaving the latter that are more susceptible to ethionamide included in the MDR tuberculosis regimen. Ethambutol and pyrazinamide should be included in the treatment regimen if they are likely to be effective from laboratory evidence or clinical history.

Fluoroquinolone (in **Category 2**) therapy is independently associated with better treatment outcomes. Losing this drug category increases risk of death and failure [89,114]. Thus, a fluoroquinolone should be included whenever possible, although potential cross-resistance among the class members may hamper their utility in XDR tuberculosis [115]. Older fluoroquinolones, especially ciprofloxacin, are not recommended, as there could be slower sputum culture conversion and higher relapse rate [116]. Newer fluoroquinolones, moxifloxacin and levofloxacin, can be active against some ofloxacin-resistant strains of *M. tuberculosis* [117,118].

With the high rate of streptomycin resistance among MDR bacillary strains, an injectable agent from **Category 3**, capreomycin, kanamycin or amikacin, should form part of the regimen

as far as possible. Capreomycin may have a further advantage owing to its incomplete cross-resistance with kanamycin and amikacin in some *M. tuberculosis* strains [119,120]. However, variable cross-resistance exists among these three second-line injectables. Injectable agents are generally recommended for at least 6 months, or 4 months after culture conversion, with modification according to bacillary resistance or patient intolerance [83].

Category 4 agents are generally less efficacious and difficult to tolerate. Cycloserine / terizidone have potentially serious neurotoxicity. The use of thioamides and para-aminosalicylic acid are notoriously associated with gastrointestinal reactions and other adverse events [83,117]. They are added according to estimated bacillary susceptibility, drug history, efficacy, side-effect profile and cost.

Category 5 drugs, including linezolid, amoxicillin-clavulanate, imipenem / cilastatin and clofazimine, are not generally recommended in drug-resistant tuberculosis because their roles are uncertain [112]. However, they have potential role in situations without other options, especially in patients with XDR tuberculosis [16,121].

Clinical experience on linezolid has been slowly accumulating after the first report of its good *in vitro* activities against *M. tuberculosis* a decade ago [122]. In one study, 9 out 10

MDR tuberculosis patients given linezolid and other drugs under DOT setting were cured, despite substantial haematological and neurological toxicities [123]. Use of linezolid at half-dose (600 mg) daily helped to reduce bone marrow suppression, but not peripheral and optic neuropathy [124]. Fatal lactic acidosis can also occur after prolonged therapy [125]. A sizeable retrospective study has confirmed these adverse effects [126]. Most of them occurred after 60 days of therapy [126]. More major side-effects occurred with twice-daily than once-daily dosing, with no difference in efficacy. Outcomes were similar in patients treated with or without linezolid, although linezolid use was assocated with more extensive resistance to first-line and second-line drugs. Thus it appears that linezolid 600 mg once daily, when added to an individualized multidrug regimen, may improve bacteriological conversion and treatment success in the most complicated MDR or XDR tuberculosis cases [126]. Its use might not be warranted where better tolerated alternatives are available. Further evaluation of linezolid at 600 mg daily dose is being conducted in a phase I/II clinical trial in South Africa [127]. Linezolid 300 mg daily, apart from safety, appears to have reasonable efficacy in a recent study [128]. However, concerns have been raised regarding the method of analysis and possible emergence of drug resistance [129]. For other oxazolidinones, PNU-100480, has demonstrated more potent activity *in vitro* and in the murine model [130], while AZD5847 is undergoing phase I trial in healthy volunteers [131].

Amoxicillin-clavulanate has some early bactericidal effect against *M. tuberculosis* [132] and distinct inhibitory activity on MDR strains [133]. Other β-lactam-β-lactamase inhibitor combinations have also shown similar *in vitro* activity [134], but clinical efficacy data are limited [135,136]. Imipenem / cilastatin is active against MDR and XDR strains *M. tuberculosis in vitro* [137]. There are also some limited efficacy data of imipenem in mice and humans [138]. When meropenem, a carbapenem – a newer congener of imipenem, was combined with the β-lactamase inhibitor clavulanate, potent activity against laboratory strains of *M. tuberculosis* was observed, with sterilisation of aerobically grown cultures achieved within 14 days [139]. In addition, this combination exhibited activity against anaerobically grown cultures that mimic the mycobacterial persisters, and inhibited the growth of 13 XDR strains of *M. tuberculosis* at the same levels as observed for drug-susceptible strains [139]. Thus, meropenem-clavulanate might have a potential role in the treatment of tuberculosis [140].

Clofazimine, a riminophenazine, and some of its analogues, have been shown to possess *in vitro* and *in vivo* activities against *M. tuberculosis*, including drug-resistant ones [141,142]. Clofazimine is primarily used in the treatment of leprosy but is sometimes incorporated in the treatment regimens for MDR tuberculosis, although data on its clinical efficacy [143] and

tolerance [144] are limited and conflicting. Rifabutin, has very limited potential utility in treatment of MDR tuberculosis due to its high cross-resistance rate with rifampicin [16].

MDR and XDR tuberculosis should be treated aggressively. The fluoroquinolones and injectables are the most potent second-line agents for MDR tuberculosis (Grade C). In the initial six months, the treatment regimen should consist of at least 4, non-cross-reacting drugs to which the organism is, or is likely to be, susceptible (Grade C). Generally speaking, those patients who have previously received second-line drugs are more likely to need a higher number of drugs. So do patients with more extensive radiographic disease and more formidable drug resistance patterns. The use of capreomycin/kanamycin/amikacin, fluoroquinolone, ethambutol, pyrazinamide, ethionamide/prothionamide for disease with bacillary resistance to RH (with/without S), and the use of capreomycin/kanamycin/amikacin, fluoroquinolone, ethionamide/ prothionamide, cycloserine, para-aminosalicylic acid for disease with bacillary resistance to RHEZ (with / without S) constitute important examples of these regimens. The possibility of further acquired resistance should be considered. A single drug should never be added to a failing regimen, for fear of selecting mutants that are resistant to the newly added drug (addition phenomenon) [84]. Care is also warranted in chemotherapy trials involving newly developed antituberculosis drugs. Linezolid resistance among *M. tuberculosis* is fairly well known today, and may serve as a warning [145,146].

The dosages of second-line drugs used in the treatment of MDR and XDR tuberculosis are listed in Table 4 [83,112,147]. The maximum dosage of cycloserine and ethionamide / prothionamide should generally be 750 mg when once-daily dosing is used, as there is concern with toxicity for higher doses. The same likely applies also for aminoglycosides / capreomycin given 3 – 5 times per week [147]. Some of the patients weighing >70 kg might tolerate 1000 mg for these three classes of drugs [112]. The maximum once-daily dosage of moxifloxacin and levofloxacin is 400 mg and 750 – 800 mg, respectively. While the efficacy of 1000 mg levofloxacin per day is high [148], the tolerance data are still limited.

The WHO recommends treatment duration of at least 18 months after culture conversion even for HIV-negative patients (Grade D) [83]. However, a proportion of immunocompetent patients who managed to achieve sustained sputum culture conversion early might be adequately treated with 12 months of fluoroquinolone-containing regimens [88,149]. It appears, however, that patients who are immunocompromised (including those with diabetes mellitus and silicosis), or have extensive radiographic evidence of disease (particularly with cavities), extensive drug resistance, delayed sputum culture conversion (i.e. after more than three months of chemotherapy) or extrapulmonary involvement should receive more than 12 months of therapy [88].

Another important principle in the chemotherapy of MDR tuberculosis / XDR tuberculosis is to exercise vigilance to prevent and manage adverse reactions.

Second-line drugs for treating MDR tuberculosis are generally more toxic and difficult to tolerate. In a study on MDR tuberculosis in Hong Kong, about 40% experienced adverse drug reactions of varying severity [88]. However, only half of them patients required modification of their drug regimens. These results corroborated the findings of a study of MDR tuberculosis patients in Peru where the adverse drug reactions never resulted in discontinuation of antituberculosis therapy, and only occasionally (11.7%) resulted in suspension of an agent [150]. In a reported series of MDR tuberculosis patients in Turkey, about 70% of them experienced adverse effects to the second-line agents, and 55.5% required treatment modification [151]. With timely and appropriate management, the treatment success rate (77.6%) did not appear to be compromised markedly. Indeed, the results from Turkey largely paralleled those pooled from five sites (Estonia, Latvia, Peru, the Philippines and the Russian Federation) in resource-limited settings [107].

The second-line antituberculosis drugs are handled in patients by different pathways, including diverse metabolic ones. There is a potential for them interacting with different classes of antiretroviral drugs [152].

Close clinical monitoring is necessary to ensure that adverse drug effects are recognized quickly. Apart from clinical monitoring, ancillary investigations, such as audiometry screen, vestibular assessment and biochemical tests including those of liver and renal functions, electrolytes and thyroid functions, are helpful. On top of assessment of visual acuity, tests to detect peripheral neuropathy are needed occasionally. The optimal intervals at which these investigations should be performed are unknown. Physicians should be aware, that some of the adverse effects that can occur during the continuation phase of an extended course of antituberculosis therapy can emerge within a few days. When an adverse reaction is mild and not dangerous, such as a gastrointestinal one, continuation of therapy alongside supportive treatment is sufficient. If an adverse event is severe or potentially dangerous, such as a neurological effect, a more intensive management strategy embracing supportive treatment and drug discontinuation or dosage adjustment is required [83]. Psychosocial support is also an important element in the management of adverse reactions. Education, counseling and encouragement can all contribute [83].

Patients developing nephrotoxicity were found to have a significantly longer duration of treatment with aminoglycosides and received a higher total dose. For ototoxicity of aminoglycosides, predisposing factors are less well characterized, except perhaps for old age, renal impairment and prolonged therapy [153]. Ototoxicity due to aminoglycosides can be irreversible and patients need to be counselled to report symptoms at the earliest signs of occurrence.

Treatment Outcomes

Treatment outcomes of MDR and XDR tuberculosis vary greatly between studies [88-90, 92,154-167], possibly related to variations in method of analysis, definition of treatment success and failure, drug susceptibility testing, clinical follow-up, and missing data. The outcomes also likely depend on adverse events due to drugs and their management, as well as supply / availability of the agents for treatment.

For MDR tuberculosis, success rates (cures + treatment completions) are around 50 – 70% [88-90,92,154-167]. In a recent systematic review [168], MDR tuberculosis treatment success rate improved with treatment duration of at least 18 months and DOT throughout treatment. Studies that combined both factors had significantly higher pooled success rate than other studies (69% vs 58%). Individualised treatment regimens conferred higher success (64%) than standardized regimens (54%) although the difference was not statistically significant. Patients with XDR tuberculosis in general had worse treatment success rates: ≤50% [164-166], although a study has shown a remarkable treatment success rate of 60.4%, quite comparable with that (66.3%) of MDR tuberculosis in the same locality [169].

Prior antituberculosis therapy [89,90,92,154,157,167], extensive *in-vitro* drug resistance [87,89,92,157,165], fluoroquinolone resistance [88,90,92,158,167] or its prior use [158], capreomycin resistance [96], positive sputum smear [167], radiological cavitation [88,89,158], HIV seropositivity [156,161,163,166,167], other immunocompromised states [159], history of incarceration [92], low BMI (<18.5/<20 $kg.m^{-2}$) [92,160], hypoalbuminaemia [164], older age [89,158], male sex [154], low haematocrit [160], and early (<1 year of treatment) default [163] constitute important risk factors for poor outcomes.

In a recent systematic review on XDR tuberculosis, it has been shown that strategies to support adherence, as well as psychological, nutritional and even financial interventions, might further contribute to improved outcomes in patients with XDR tuberculosis [170]. The encouraging results from some countries in Asia and Europe have also suggested that management in specialised reference centre would improve outcome, although high success rates could be achieved with treatment in some community settings [170].

The impact of HIV on the outcomes of MDR and XDR tuberculosis has been most serious in South Africa. Among 272 MDR and 382 XDR tuberculosis patients, with HIV-coinfection rates of 90% and 98%, one-year mortality was 71% and 83%, respectively. This mortality has improved, however, from 2005 to 2007, though the majority of death still occurred within the

first 30 days [166]. In the systematic review just alluded [170], it was remarked that additional data for HIV-infected individuals would be required to determine the role of HIV coinfection in XDR tuberculosis treatment outcome, and to evaluate interventions that might contribute to improve outcomes in HIV-infected XDR tuberculosis. The high case-fatality rate in the Tugela Ferry outbreak could represent a combination of factors at play – not only host immunocompromisation, but also lack of access to adequate diagnosis and treatment [170].

Palliative Management and End-of-Life Care

At a certain time-point, recourse to palliative care is indicated for selected patients with "difficult" MDR or XDR tuberculosis, in the interest of both the individual patient and the community as a whole. Such management aims to provide uninterrupted medical and psychological care, as well as to ensure a dignified termination of the patient [83,147].

NEW DRUGS FOR TREATMENT OF TUBERCULOSIS

New antituberculosis drugs are needed to simplify treatment of drug-susceptible tuberculosis and to improve outcome of drug-resistant tuberculosis [171]. Only four compounds would be discussed in some depth for the purpose of this review, as these drugs appear to have sufficient potential for utilization to improve tuberculosis therapy in the coming decade.

Moxifloxacin

Moxifloxacin is a 8-methoxy fluoroquinolone with a long plasma half-life of approximately 11 hours. It has potent bactericidal and sterilizing activity against *M. tuberculosis*, as shown in murine studies [172,173]. In the TB Trials Consortium (TBTC) Study 27, a Phase II trial, substituting moxifloxacin for ethambutol in the first 8 weeks of therapy did not change the 2-month culture negativity rates (71%), but there appeared to be higher activity at earlier time point [174]. On the other hand, a study with nearly the same design conducted in Brazil has shown better culture conversion (80%) in patients receiving moxifloxacin during the initial phase of treatment, compared with the ethambutol arm (63%) [175]. Another similar Phase II clinical study has also shown that patients in moxifloxacin -containing arm

cleared their sputum bacilli more quickly [176]. Based on the rapid sterilization results of isoniazid-sparing regimen in murine models, the TBTC Study 28 was designed as a double-blind, placebo-controlled study to evaluate the 2-month culture conversion rates with the substitution of moxifloxacin for isoniazid in the 2-month intensive phase of treatment of pulmonary tuberculosis. Only a small nonsignificant increase in the 2-month culture negativity was achieved [177]. More rapid sputum culture conversion was also observed with the addition of moxifloxacin to the standard short-course regimen in a non-randomized study [178]. In these studies, moxifloxacin appeared to be well tolerated by most patients, apart from an increased incidence of nausea. QTc prolongation was observed in some patients but might not have clinical significance [175,177]. Further evaluation of the fluoroquinolone is ongoing in a phase III REMox study [179]. This study will explore whether moxifloxacin substitution for isoniazid or ethambutol can shorten the conventional therapy from 6 months to 4 months.

Moxifloxacin and rifapentine based regimens are also under investigation. It should be noted that when given together, rifapentine may induce enzymes that metabolize moxifloxacin, resulting in modestly reduced moxifloxacin concentrations [68]. Using a murine model of tuberculosis, regimens consisting of isoniazid or moxifloxacin plus rifapentine and pyrazinamide administered either daily or three-times weekly were evaluated for bactericidal

activity and treatment-shortening potential. The duration of treatment necessary to achieve stable cure was 10 weeks for daily regimens and 12 weeks for thrice-weekly regimens, regardless of whether isoniazid or moxifloxacin was used with rifapentine and pyrazinamide [180]. By contrast, for the 12-week regimen of RHZ, all mice relapsed. The treatment-shortening potential of more frequent and /or higher doses of rifapentine than 600 mg once weekly are being explored in both animal experiments and clinical trials, as discussed in the section on treatment of smear-positive pulmonary tuberculosis. Furthermore, in a Phase II clinical trial that commenced in 2009, smear-positive pulmonary tuberculosis patients are being randomized in the initial 2 months to receive either H-rifapentine-Z-moxifloxacin or RHEZ, followed by the standard nonexperimental regimen in the continuation phase. The efficacy in terms of sputum conversion rates and treatment outcomes, as well as safety and tolerability of the rifapentine-moxifloxacin-containing regimens, will thus be evaluated [181]. Notwithstanding these somewhat encouraging results, the high rates of fluoroquinolone-resistant tuberculosis in many parts of the world, especially coinciding with high disease burden, poses concern regarding the potential utility of the new fluoroquinolones in shortening tuberculosis treatment [182]. Regarding the role of moxifloxacin in the treatment of MDR tuberculosis / XDR tuberculosis, there has been some promising results lately [183], although the issue of partial cross-resistance among *M. tuberculosis* strains still casts concern [184].

TMC207

TMC207 is a novel diarylquinoline with unique activity on the mycobacterial ATP synthase [185]. It is active against both drug-resistant and drug-susceptible *M. tuberculosis*, as well as other mycobacterial species. It has a long half-life in plasma and tissues of nearly 24 hours. Data have also suggested that TMC207 might kill dormant bacilli as effectively as aerobically grown bacilli. TMC207 is metabolized by CYP3A4, thus, its plasma level may be reduced by half through interaction with rifampicin. However, data from the mouse model have demonstrated that TMC207 had significant activity, even when its exposure was reduced by 50% and when it was added to a strong background regimen of RHZ. The bactericidal effect of TMC207 in mice was modest during the first week of treatment but increased in the following three weeks [186]. TMC207 probably acts synergistically with pyrazinamide to exert sterilization activity. In the mouse model, 2-month treatment regimens containing TMC207 and pyrazinamide led to sterilization, suggesting treatment-shortening potential [187]. In another mouse model study, the triple combination of TMC207-rifapentine-pyrazinamide given once weekly was more active than the current regimen of RHZ given five-times per week and led to satisfactory lung culture negativity at two

months [188]. Such unprecedented activity has suggested that it might be feasible to develop a fully intermittent, once-weekly regimen.

In a mouse model to evaluate the use of TMC207 in MDR tuberculosis, treatment was given five times per week with TMC207 alone or various combinations of TMC207 plus pyrazinamide or other second-line drugs [189]. All TMC207-containing regimens were significantly more active than the non-TMC207-containing regimens after one month of therapy.

An early bactericidal activity study with ascending doses of TMC207 has demonstrated a delayed onset of bacteriolysis, with significant activity from day 4 – 7 when given at a daily dose of 400 mg, which was similar in magnitude to those of isoniazid and rifampicin over the same period [190].

A double-blind, randomized Phase II clinical trial with TMC207 began in 2007 in MDR tuberculosis patients [191]. The study is being conducted in two consecutive stages. In the first exploratory stage for safety and dose determination, newly diagnosed sputum smear-positive patients with MDR tuberculosis were randomized to receive either TMC207 or placebo for eight weeks on top of a background regimen. The dosing scheme for TMC207

was validated for further testing in the second stage, being 400 mg daily for two weeks followed by 200 mg three-times weekly. In the second stage planned for proof of effectiveness, patients are randomized to receive either TMC207 or placebo for 24 weeks on top of a background regimen. After finishing 24 weeks of treatment, patients will continue to receive MDR tuberculosis treatment as per national treatment guidelines. Study subjects will be followed for safety, tolerability, pharmacokinetics, and microbiological efficacy for 96 weeks after receiving their last dose of TMC207 [191]. Preliminary results in the first stage indicated high efficacy (faster rate and higher proportion of culture conversion) and good tolerance of TMC207 [192]. Further results are awaited with great interest. Like moxifloxacin, QTc prolongation with uncertain clinical significance was observed in some patients, aside from gastrointestinal upset [192]. TMC207 can have a role in treatment of MDR tuberculosis and XDR tuberculosis, subjected to confirmation of its tolerance and safety on long-term use. Its interaction with rifampicin might hamper its utility in treatment of drug-susceptible tuberculosis.

OPC-67683

OPC-67683 is a nitroimidazole with high potency *in vitro* and *in vivo* against *M. tuberculosis*, inclusive of MDR strains. It probably acts through inhibition of cell wall

biosynthesis, a mechanism similar to that of PA-824 [193], but is approximately 20-times more potent. OPC-67683 and PA-824 are closely related compounds and appear to show cross-resistance. OPC-67683 has a long half-life at approximately 7 – 8 hours, with no cross-resistance or antagonistic activity with first-line antituberculosis drugs. In addition, it has promising post-antibiotic effects against *M. tuberculosis* intracellularly, comparable to that of rifampicin [193]. In mice, 2 months of OPC-rifampicin-pyrazinamide followed by another 2 months of OPC-rifampicin led to complete culture negativity, suggesting that OPC-67683 in combination with other existing drugs could potentially shorten tuberculosis therapy [193]. A randomized, double-blind, multicentre Phase II clinical trial has been underway since 2008 to evaluate its safety, efficacy and pharmacokinetics in the treatment of MDR tuberculosis. In the first 56 days, patients receiving an optimized background regimen were randomized to receive either placebo or OPC-67683 at a dose of 100 or 200 mg twice daily. Thereafter, the study subjects will complete their optimized background regimen [194].

PA-824

PA-824 is a nitroimidazopyran, a class of novel antibacterial agents. It is active against drug-susceptible and drug-resistant, and both dividing and nonreplicating *M. tuberculosis* [195]. From studying colony-forming-unit counts in the lungs of mice, PA-824 showed

bactericidal activity comparable to that of isoniazid in the first eight weeks and sterilizing activity comparable to that of HR in the continuation phase [196]. A follow-up experiment in mice showed advantages in relapse rate with the same combination of drugs when PA-824 was given at a higher dose of 100 mg/kg [197]. With the novel combination of PA-824-moxifloxacin-pyrazinamide, mice were cured more rapidly than with the first-line regimen of RHZ, suggesting that this combination might radically shorten the treatment of MDR tuberculosis in humans [198].

No serious adverse events were reported in Phase I single-dose and multiple-dose trials in healthy volunteers [199]. An extended early bactericidal activity study was conducted recently in South Africa, evaluating the efficacy, safety and pharmacokinetics in newly diagnosed sputum smear-positive patients with drug-susceptible tuberculosis [200]. Based on findings from the preclinical and Phase I studies, escalating doses of PA-824 were administered for 14 consecutive days for four groups of patients and compared with a fifth cohort receiving standard first-line antituberculosis treatment. The study showed substantial and continued early bactericidal activity over 14 days with equivalent efficacy at all doses from a daily dose of 200 – 1200 mg. One important feature of PA-824 is its high protein binding (94%). Thus, it is necessary to ensure that sufficiently high concentrations of the free drug can be reached in cavities of pulmonary tuberculosis to exert bactericidal activity [201]. Both OPC-67683 and

PA-824 appear to have potential roles in treatment of drug-susceptible and drug-resistant tuberculosis. Again, the most critical determinant would be their safety profiles.

Other Potential Candidates

Important examples of two such compounds include a pyrrole derivative LL3858 and a diamine compound SQ109. Both have been subjected to Phase I testing and further progress is ongoing [55,202,203]. Other potential candidates would be those have both potent bactericidal and sterilizing activities. Examples might include ATP synthase inhibitors, gyrase inhibitors and peptide deformylase inhibitors [203]. Aside from these new drugs under development, a neuroleptic thioridazine with impressive antituberculosis activity might also warrant repurposing to constitute a new agent for treating MDR tuberculosis and XDR tuberculosis [204].

ADJUNCTIVE SURGERY FOR PULMONARY TUBERCULOSIS

While chemotherapy using antituberculosis drugs constitutes the primary treatment modality for pulmonary tuberculosis, emergence of MDR and XDR tuberculosis has rekindled the enthusiasm in recourse to adjunctive surgery to improve the chance of cure in some patients in these drug-resistant scenarios [205]. Other indications of surgical treatment of tuberculosis centre on management of empyema, post-tuberculous bronchiectasis and mycetoma [206].

There are three basic selection criteria for adjunctive surgery in MDR tuberculosis patients [205]. These include:

- drug resistance, as revealed by *in vitro* susceptibility testing, is so severe or extensive that there is a high probability of failure or relapse with medical therapy alone
- disease is sufficiently localized that the great preponderance of radiographically discernible disease can be resected with expectation of adequate cardiopulmonary capacity post-surgery
- drug activity is sufficient to diminish the mycobacterial burden to facilitate healing of bronchial stump after lung resection

Patients should receive chemotherapy prior to surgery for at least 3 months [205,207]. If possible, they should be rendered culture negative before lung resection. However, this may not always occur. In some cases, sputum culture conversion only appears with prolonged medical therapy after surgery. Ventilation / perfusion scan, pulmonary function tests and computed tomography of the chest are important investigations for pre-operative assessment [205,206]. For some patients, assessment of pulmonary artery pressure and bronchial tree anatomy / pathology needs to be performed. Bilateral disease does not necessarily preclude surgical intervention, unless extensive [208]. Such disease would, however, require staged bilateral resection. In experienced hands, the outcome of lung resection has been found to be rather rewarding. The cure rates could reach ≥90% with post-surgery chemotherapy [209-222]. (**Table 5**) In resource-limited areas, the cure rates might be lower (63 – 75%), but lung resection still appears useful as adjunctive management for this formidable disease [218]. However, adjunctive surgery necessitates expertise and financial instillation which are often not readily available in many areas where MDR tuberculosis prevail [223].

Two rather sizable cohort studies have shown that the best outcomes of MDR tuberculosis patients were achieved by the use of fluoroquinolones and adjunctive surgery [89, 224]. Although there has been no randomized study to compare chemotherapy alone versus combined chemotherapy and surgery in the management of MDR tuberculosis, one recent

small series reported significant and durable improvement with lung resection and post-operative first-line antituberculosis chemotherapy in patients with MDR and XDR tuberculosis [225]. This finding suggests the possibility of an independent role of lung resection in the management of these difficult drug-resistant scenarios.

With the emergence of XDR tuberculosis, adjunctive surgery becomes more relevant [121,225]. Notwithstanding its use in some patients, the outcome of XDR tuberculosis is generally worse than that of MDR tuberculosis, with an overall success rate of about 50% [121,227]. However, in selected patients, sustained sputum bacteriological conversion can be satisfactorily maintained [228]. From two large series, patients who had adjuvant surgery experienced better outcomes [89,229].

Regarding the factors governing outcome of surgery for drug-resistant tuberculosis, a low body mass index (<18.5 kg/m^2), bacillary resistance to fluoroquinolones and presence of cavity beyond the range of surgical resection portended poor prognosis in a carefully performed study [219]. The major complications of surgical treatment of pleuro-pulmonary tuberculosis include broncho-pleural fistula, residual space problem and empyema. Other complications include wound and other infections, bleeding, cardiovacular embarrassment, atelectasis, and recurrent laryngeal nerve injury. The risk factors for broncho-pleural fistula mainly include

sputum-smear positivity, low FEV_1, old age, and perhaps the technique of stump closure and reinforcement [230]. There have been no randomized controlled studies that compared bronchial stump reinforcement versus nothing or stapling versus suturing as a means of closure of the stump. Many authorities, however, have recommended reinforcement of the bronchial stump, especially in selected patients at risk of such complications [222,230].

In some frail patients with MDR tuberculosis, who usually have limited cardiopulmonary reserve and thus would not withstand lung resection, collapse therapy using thoracoplasty [231], plombage [232] and artificial pneumothorax [233] can be considered. Thoracoplasty, aside from causing cosmetically unappealing deformity of the thoracic cage, can be associated with obstructive and restrictive lung function defects after the procedure. Extra-pleural lucite sphere plombage can give rise to pressure effects, migration, and foreign-body irritation problems. The use of artificial pneumothorax has been reappraised in a recent study with rather encouraging radiographic and bacteriological results [233]. In the intervention group, culture negativity was achieved in all new cases and 81.1% retreatment cases (About 80% patients had MDR tuberculosis). Cavity closure occurred in 94.6% and 67.9%, respectively. In the control group, culture negativity was achieved in 70.9% and 40.0%, respectively, and cavity closure occurred in 56.3% and 24.0% respectively.

ADJUNCTIVE IMMUNOTHERAPY IN TUBERCULOSIS

Macrophages, dendritic cells, natural killer cells, γδT cells and CD1-restricted T cells are involved in the initial cell-mediated immune response to *M. tuberculosis*, and determine the local / distant progression of infection to disease, versus containment of the infection. Antigens of *M. tuberculosis* are processed by the antigen-presenting cells. Subsequently CD4+ cells are involved. T helper (Th) cells, largely CD4+ cells, generally mature into two functionally different phenotypes, often termed Th1 and Th2 cells. The former secrete principally interleukin-2 and interferon-γ, while the latter largely secrete or induce interleukin-4, interleukin-5, interleukin-6 and interleukin-10. Interleukin-12 produced by macrophages, expands Th1 cell population and upregulates its functions. Cell-mediated protective immunity appears to be associated with a Th1 response [234]. Interleukin-18, another cytokine linked to Th1 pathway, may also have a putative role in cell-mediated protection against mycobacterial infection [235]. Tumour necrosis factor alpha (TNF-α), released largely from macrophages, contributes to protect the host by promoting granuloma formation [236]. However, TNF-α can also cause tissue necrosis under subversive T-cell influence. There is some evidence this sabotage effect comes from interleukin-4 overactivity [237]. **Figure 2** summarizes the immunopathogenesis of tuberculosis. Thus, the complex

immunopathogenesis of tuberculosis embraces host tissue inflammation and damage, on top of protective immunity against the tubercle bacilli.

Athough a recent in-depth review on the immunotherapy for tuberculosis has revealed a number of potentially useful agents for immuno-regulation, immuno-augmentation or immuno-suppression, no evidence-based recommendation can yet be formulated regarding their clinical utility [238].

Adjunctive corticosteroids have been used as an attempt to ameliorate the inflammation. Cochrane reviews have shown improved mortality of patients with tuberculous pericarditis [239] and tuberculous meningitis [240] with steroid therapy, but inconclusive effects for pericardial constriction. Neurological deficit / disability was improved among survivors with tuberculous meningitis. There is currently inadequate evidence on whether steroids are effective in tuberculous pleural effusion [241]. In HIV-infected patients, steroids have been shown to be beneficial in tuberculous meningitis, although the overall prognosis is still poor [242]. Steroid use in tuberculous pleural effusion in HIV-infected patients was associated with a higher incidence of Kaposi's sarcoma [243]. An additional concern is that adjuvant steroid therapy of HIV-related tuberculosis has been associated with a transient increase in HIV

viral load [244]. In these two latter studies, the dosages of prednisolone used were 50 mg/day and 2.75 mg/kg/day, respectively, with gradual tapering off in eight weeks [243,244].

Cytokine supplementation was initially thought to be promising adjunctive therapy in tuberculosis [245], including drug-resistant forms. Table 6 depicts the results of a number of preliminary studies regarding the use of cytokines especially interferon-γ) [246-251] and *Mycobacterium vaccae* (NCTC 11659) [252], an avirulent vaccine from a nontuberculous mycobacterial species, in the management of MDR tuberculosis. In a more recent study, nebulised interferon-γ1b adjuvant therapy has also been found to improve constitutional symptoms, reduce inflammatory cytokines in bronchoalveolar lavage, and improve clearance of acid-fast bacilli from sputum in cavitary pulmonary tuberculosis [253]. While the results from some of these studies are encouraging, the limited number of enrolled patients, alongside often uncontrolled experimental designs, leaves great uncertainty regarding the definitive role of these cytokines and allied forms of immunotherapy in tuberculosis treatment.

By enhancing mycobacterial killing in macrophages, vitamin D might have the potential to enable shortening of treatment duration for tuberculosis, reducing infectiousness, and improving response in drug-resistant forms of the disease [254]. However, a double-blind, randomized, placebo-controlled trial [255] has recently shown that vitamin D, as

supplementary therapy, did not improve clinical outcome (as assessed by clinical score severity and sputum smear conversion) among patients with tuberculosis. There was also no overall effect on tuberculosis mortality at 12 months. One caveat might be the possibly insufficient dose of vitamin D used. The clinical role of vitamin D in immunotherapy of tuberculosis is currently uncertain.

In addition, there appears to be some agents that can promote intracellular killing of *M. tuberculosis* by macrophages, through affecting the transport of K^+ and Ca^{2+} from the phagolysosome, thereby resulting in better acidification and activation of hydrolases [256]. This might be a promising direction of developing therapy for drug-resistant tuberculosis.

CONCLUSION

In 2010, the prevailing challenges of HIV infection and drug resistance still undermine the global control of tuberculosis. With clear indications that XDR tuberculosis results from mismanaged cases of drug-susceptible and MDR tuberculosis, it would be imperative to treat drug-susceptible tuberculosis appropriately to completion, and to provide rapid diagnosis, and aggressive as well as appropriate treatment of MDR tuberculosis to avoid the unnecessary development of additional cases of XDR tuberculosis. The main priority interventions would be (1) strengthening control of tuberculosis (through sound implementation of the Stop TB Strategy, with special focus on laboratory capacities and infection control (including HIV control) (2) improvement of programmatic management of drug-resistant tuberculosis, based on updated guidelines, largely from WHO, and (3) promotion of research and development of new diagnostics, vaccines and drugs, as well as other modalities of therapy.

While scientific advancement is crucial to better the care of tuberculosis patients and is earnestly awaited, existing tools must be harnessed in sound public health settings to curb the epidemic of tuberculosis today [257].

Table 1 Recommended Dosing Frequency for Standard Six-Month Regimen (Adapted with permission from WHO/HTM/TB/2009.420)

Dosing frequency		Comments
Intensive phase	**Continuation phase**	
Daily	Daily	Optimal
Daily	3 times per week	Acceptable alternative for any new tuberculosis patient receiving directly observed therapy
3 times per week	3 times per week	Acceptable alternative provided that the patient is receiving directly observed therapy and is NOT living with HIV or living in an HIV-prevalent setting

Table 2 Suggested Antituberculosis Retreatment Regimens for Previously Treated Patients (Adapted with permission from WHO/HTM/TB/2009.420)

DST	Likelihood of MDR-TB	
Routinely available	High (Failure patients)	Medium/Low (Relapse/Default patients)
Rapid molecular tests	DST results available in 1 – 2 days to confirm or exclude MDR-TB to guide treatment regimen used	
Conventional phenotypic tests	While awaiting DST results Empiric MDR-TB regimen (to be modified once DST results are available)*	While awaiting DST results 2HRZES/HRZE/5HRE (to be modified once DST results are available)*

DST = Drug susceptibility testing

MDR-TB = Multidrug-resistant tuberculosis

*Standardized / Individualized regimen if MDR-TB is confirmed

Table 3 Categories of Antituberculosis Drugs (Adapted with permission from WHO/HTM/TB/2009.420)

Category 1: First-line oral drugs

Isoniazid
Rifampicin
Ethambutol
Pyrazinamide

Category 2: Fluoroquinolones

Levofloxacin
Moxifloxacin
Ofloxacin

Category 3: Injectable agents

Capreomycin
Amikacin
Kanamycin
Streptomycin

Category 4: Oral bacteriostatic second-line agents

Ethionamide
Prothionamide
Para-aminosalicylic acid
Cycloserine
Terizidone

Category 5: Agents with efficacy that is not totally clear / certain (not recommended by the WHO for routine use in treating patients with drug-resistant tuberculosis generally)

Isoniazid (high-dose: >10 mg/kg)
Linezolid
Amoxicillin-clavulanate
Clarithromycin
Clofazimine
Imipenem / cilastatin (+ clavulanate)
Thiacetazone
Rifabutin

Table 4 Dosages of Antituberculosis Drugs Used in Treatment of MDR tuberculosis in Adults

Group	Drug	Daily dosage/kg†	Usual daily dosage†
Aminoglycosides + allied injectable peptide antibiotics	Streptomycin	15 mg/kg	750 mg‡
	Kanamycin	15 mg/kg	750 mg‡
	Amikacin	15 mg/kg	750 mg‡
	Capreomycin	15 mg/kg	750 mg‡
Fluoroquinolones	Ofloxacin	-	600 – 800 mg‡
	Levofloxacin	-	500 – 750 mg‡¶
	Moxifloxacin‡‡		‡‡400 mg‡
Thioamides	Ethionamide§	15 mg/kg	500 – 750 mg‡
	Prothionamide§	15 mg/kg	500 – 750 mg‡
Oral bacteriostatic first-line drugs	Ethambutol	15 mg/kg	-
	Pyrazinamide	20 – 30 mg/kg	1 – 2 g‡
Oral bacteriostatic second-line drugs	Cycloserine§	15 mg/kg	500 – 750 mg‡
	Terizidone§	15 mg/kg	600 mg‡
	Para-aminosalicylic acid§§	0.2 g/kg	8 – 12 g‡
	Thiacetazone¶¶	2.5 mg/kg	150 mg‡
Oral reserve drugs with uncertain / not totally clear antituberculosis activities	Clofazimine	-	‡‡100 mg‡
	Amoxicillin-clavulanate§§††	-	‡‡875 – 125 mg 2X/day‡ or
		-	‡‡500 – 250 mg 3X/day‡
	Linezolid§§††		‡‡600 mg 2X/day‡ or ‡‡600 mg

† *Drugs are generally given on a daily basis except for aminoglycosides and the allied injectable antibiotics, which are given 3X to 5X/week, as well as those otherwise specified*

‡ *Usually the maximum daily dosage (Some of the patients weighing >70 kg can tolerate higher dosages – See text)*

§ *May require administration in 2 split doses per day*

¶ *Higher dosage usually given for fluoroquinolone-resistant disease*

†† *Long-term safety not fully confirmed*

‡‡ *Optimal dosage not fully delineated*

§§ *Requires administration in split doses per day*

¶¶ *Should only be used in patients documented to be HIV-negative, and usually not be chosen over other oral bacteriostatic second-line drugs*

Table 5 Surgical Treatment of MDR Tuberculosis*

Investigator	Patient number	Treatment success rate (%)	Operative mortality rate (%)	Postoperative complication rate (%)
Treasure *et al* [209]	19	89	0	9
van Leuven *et al* [210]	62	75	2	23
Sung *et al* [211]	27	96	0	26
Pomerantz *et al* [212]	172	98	3	12
Chiang *et al* [213]	27	92	4	11
Park *et al* [214]	49	94	0	16
Naidoo *et al* [215]	23	96	0	17
Takeda *et al* [216]	26	89	3	14
Kir *et al* [217]	79	95	3	5
Somocurcio *et al* [218]	121	63	5	23
Kim *et al* [219]	79	72	1	23
Mohsen *et al* [220]	23	96	4	35
Wang *et al* [221]	56	87	0	25
Shiraishi *et al* [222]	56	98	0	16

** Most patients had lung resections in form of pneumonectomy or lobectomy (A minority also had segmentectomy).*

Table 6 Preliminary Studies on Adjunctive Immunotherapy of MDR Tuberculosis

Investigator	Immunomodulator/ Cytokine	Outcome
Condos *et al* [246]	IFN-γ (aerosolised)	Bacillary load lowering, radiographic improvement (CT)
Johnson *et al* [247]	rhuIL-2 (subcutaneous)	Reduced bacillary load, radiographic improvement
Palmero *et al* [248]	r-IFN-α2b (subcutaneous)	Bacillary load reduction
Giosue *et al* [249]	IFN-α (aerosolised)	Bacillary load reduction, radiographic improvement (CT)
Grahmann *et al* [250]	IFN-γ (aerosolised)	Bacillary load lowering, radiographic improvement
Park *et al* [251]	IFN-γ (subcutaneous)	No bacteriological conversion on smear and culture, no radiographic improvement (CT)
Stanford *et al* [252]	*Mycobacterium vaccae* (intradermal)	Disease ≤ 2 yr: Cure rate: 82% (1 to 2 doses) Chronic cases: Cure rates: 7.6% (1 dose) 37.9% (7 doses) 41.6% (12 doses)

CT	computed tomograph
IFN-α	interferon-alpha
IFN-γ	interferon-gamma
rhuIL-2	recombinant human interleukin-2
rIFN-α2b	recombinant interferon-alpha2b

Figure 1 DOTS Framework Applied to the Management of Drug-Resistant Tuberculosis (Adapted with permission from WHO/HTM/TB/2006.361)

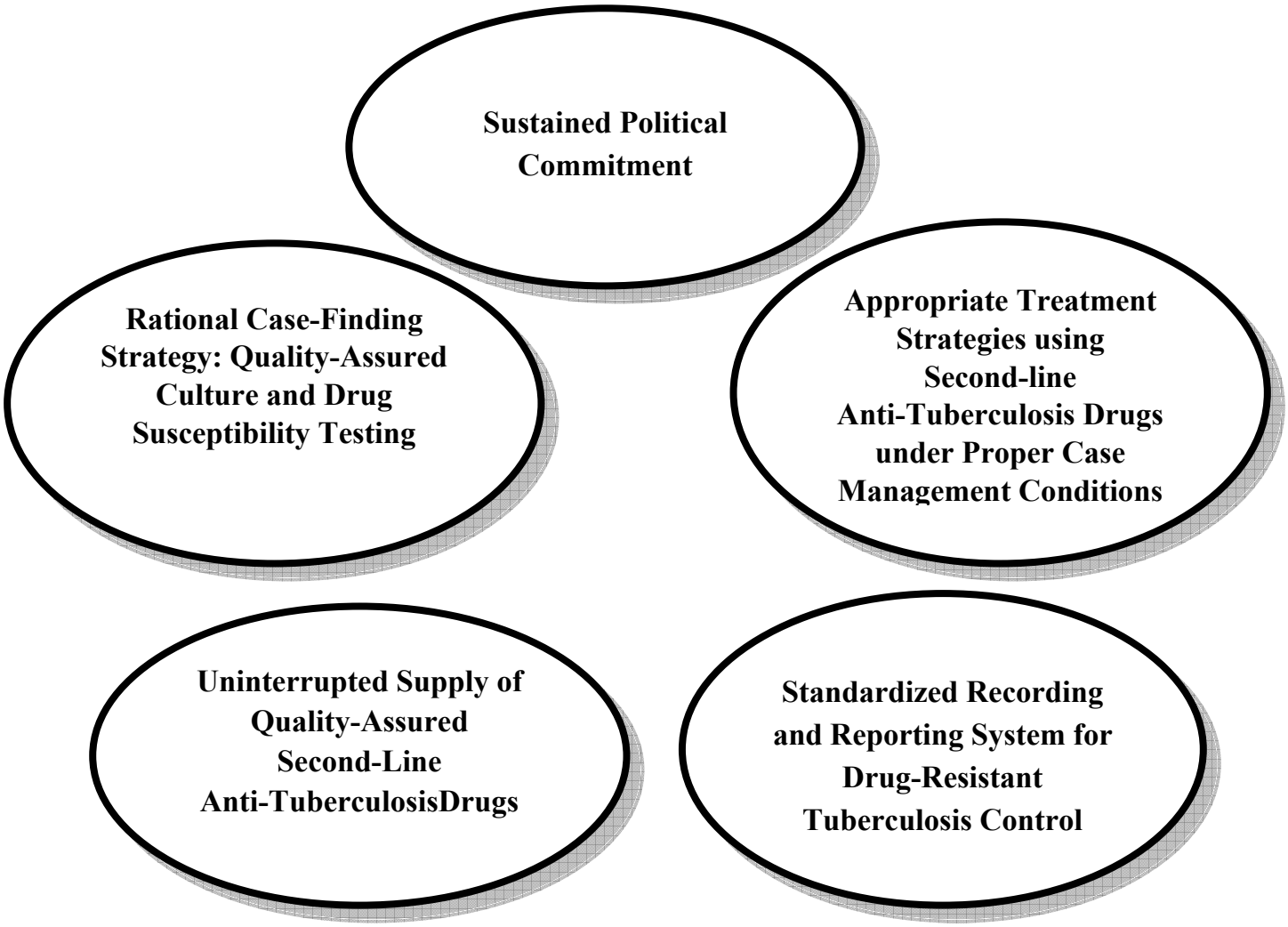
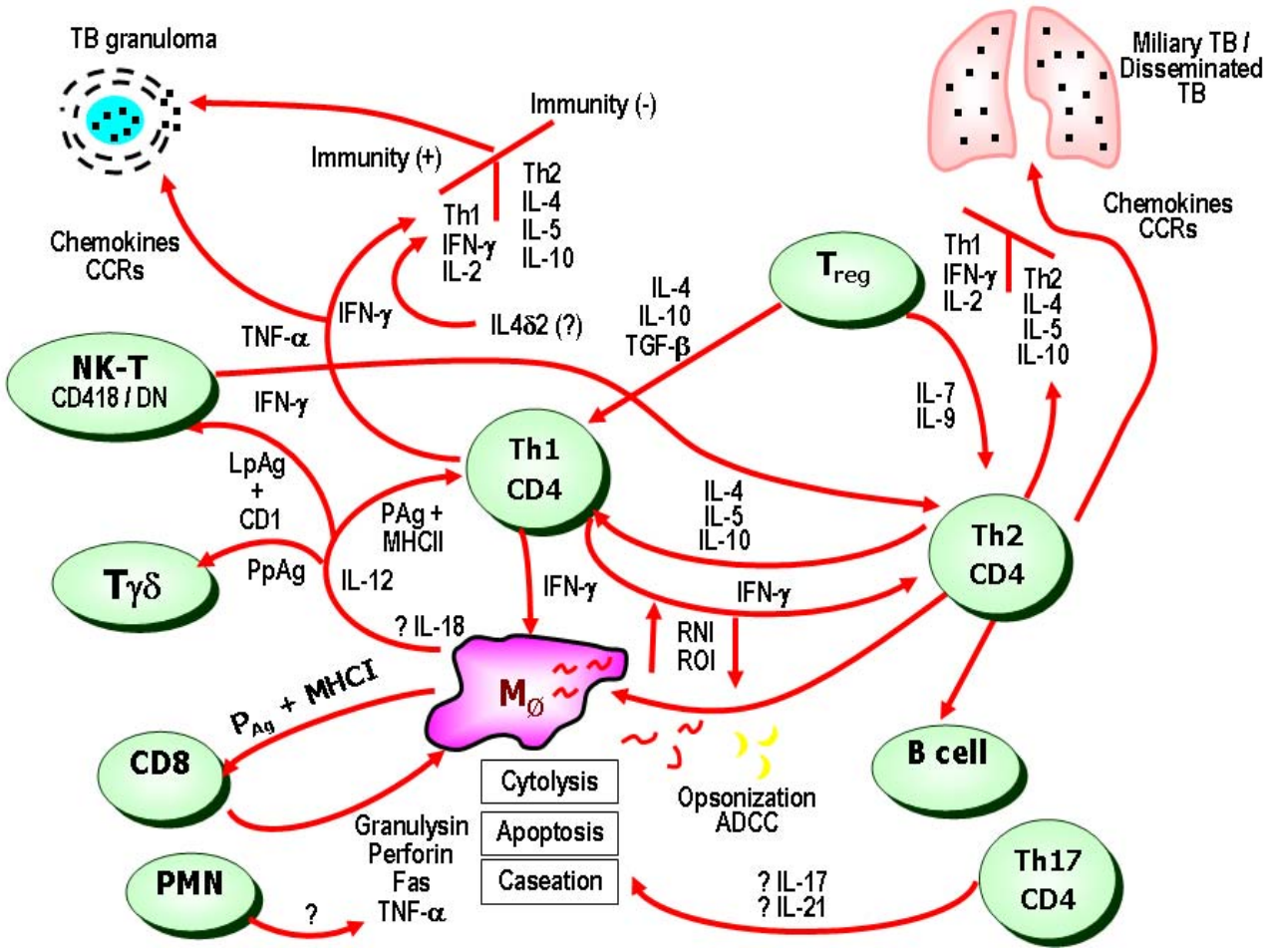


Figure 2 Immunopathogenesis of Tuberculosis



ADCC, antibody-dependent cell-mediated cytotoxicity; CCR, cc chemokine receptor; DN, double negative; Fas, cell receptor inducing apoptosis; IFN-γ, interferon-gamma; IL, interleukin; LpAg, lipopolysaccharide antigen; MHCI, major histocompatibility antigen 1; MHC2, major histocompatibility antigen 2; NK-T, natural killer cell; PAg, peptide antigen; PpAg, phospho-antigen; PMN, polymorphonuclear neutrophil; RNI, reactive nitrogen intermediates; ROI, reactive oxygen intermediates; TGF-β, transforming growth factor-beta; Th, T helper; TNF-α, tumour necrosis factor-alpha; Treg, T regulatory lymphocytes.

Appendix: Grading of Evidences for Recommendations (Scottish Intercollegiate Guidelines Network)

<table>
<tr><th>Study Rating</th><th>Study Design</th><th>Number of Studies</th><th>Target Population</th><th>Grades of Recommendation</th></tr>
<tr><td>1++</td><td>High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias</td><td>At least 1 study</td><td>Directly Applicable</td><td rowspan="2">A</td></tr>
<tr><td>1+</td><td>Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias</td><td rowspan="2">Studies with overall consistency</td><td>Directly Applicable</td></tr>
<tr><td>1++ / 1+</td><td>As above</td><td>Extrapolated</td><td rowspan="2">B</td></tr>
<tr><td rowspan="2">2++</td><td rowspan="2">High quality case control/cohort studies or their systemic reviews, with very low risk of confounding/bias and high probability of causal relationship</td><td rowspan="2">Studies with overall consistency</td><td>Directly Applicable</td></tr>
<tr><td>Extrapolated</td><td rowspan="2">C</td></tr>
<tr><td rowspan="2">2+</td><td rowspan="2">Well-conducted case control/cohort studies with low risk of confounding/bias and a moderate probability of causal relationship</td><td rowspan="2">Studies with overall consistency</td><td>Directly Applicable</td></tr>
<tr><td>Extrapolated</td><td rowspan="3">D</td></tr>
<tr><td>3</td><td>Non-analytic studies, e.g. case reports, case series</td><td></td><td></td></tr>
<tr><td>4</td><td>Expert opinion</td><td></td><td></td></tr>
</table>

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