

MANAGEMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS AND EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS: CURRENT STATUS AND FUTURE PROSPECTS

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Abstract Resistance in *Mycobacterium tuberculosis* arises from man-made selection of genetic mutants that result from spontaneous chromosomal alterations. Thus, drug-resistant tuberculosis (TB) is generally due to inappropriate treatment regimen, poor drug quality, erratic drug supply and poor patient adherence to treatment, reflecting failure in the implementation of an effective TB control programme. Multidrug-resistant TB (MDR-TB) usually denotes bacillary resistance to at least isoniazid and rifampicin. Proper implementation of the directly observed treatment, short-course (DOTS) strategy should achieve a high cure rate for disease and curtail the development of drug resistance. Innovations in reinforcement of this strategy should further facilitate its delivery and enhance its effectiveness. However, established MDR-TB is notoriously difficult to treat, and necessitates the use of alternative specific antituberculosis chemotherapy regimens. These regimens comprise combination use of second-line antituberculosis drugs, that are generally more costly and toxic, and have to be given for longer durations. The fluoroquinolones, better tolerated by patients, have a pivotal role in MDR-TB treatment. Optimal delivery of these treatment regimens mandates a programmatic basis which is now included under the Stop-TB Drug-Resistance Programme(s). The key components embrace political commitment, quality-assured drug susceptibility testing, reliable supply of quality drugs, delivery of chemotherapy under directly observed settings, and a sound recording and reporting system to monitor the individual treatment outcome of patient and overall performance of the TB control programme. Adjunctive surgery in selected MDR-TB patients help to improve their treatment success. Further exploration is required regarding the use of immunotherapy. The recent emergence of extensively drug-resistant TB (XDR-TB), representing MDR-TB with additional bacillary resistance to fluoroquinolones and one or more of the second-line injectable drugs—kanamycin, amikacin and capreomycin, threatens the global control of TB. Given the escalating size of the problem of MDR-TB and XDR-TB worldwide, gigantic instillation of resources is required for control of this formidable challenge, largely through more accurate and rapid drug susceptibility testing (especially for rifampicin and fluoroquinolone), regular drug-resistance surveillance, development of new antituberculosis drugs and other therapeutic modalities, intensive infection control, especially in HIV care settings, as well as strengthening of currently functioning DOTS and Drug-Resistance Programmes.

Key words: Multidrug-resistant tuberculosis (MDR-TB), Extensively drug-resistance tuberculosis (XDR-TB), Management

Drug resistance in *Mycobacterium tuberculosis* arises from man-made selection of mutants that result from spontaneous chromosomal alterations. The acquired drug resistance can further lead to primary drug resistance through facilitated transmission due to diagnostic delay, overcrowding and inadequate infection control. Currently, there are about 0.3–0.5 million new cases of multidrug-resistant tuberculosis (MDR-TB), connoting at least dual resistance to rifampicin and isoniazid, emerging worldwide every year¹. Hot spots of the

disease are found in some parts of South America, South Africa, and Eastern Europe, as well as areas in the Asia-Pacific region. China, India and Russia together account for about half of the new cases. South-East Asia and the Western Pacific region harbour the highest disease burden and Eastern Europe has the highest frequency of MDR disease among new patients and previously treated patients with TB¹.

This statement “You cannot cure MDR-TB as fast as you

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can create it" is a rather quotable one²⁾. Thus in addressing the subject of management of MDR-TB, one should start with the preventive measures. Directly observed treatment, short-course (DOTS) is currently the most cost-effective strategy to curtail the development of drug-resistant TB³⁾. Innovations in the delivery of DOTS can enhance the efficacy of this strategy. In a cluster randomized controlled trial conducted in a resource-poor setting, intervention through improved communication between health personnel and patients and choice of DOT supporter, alongside other measures, can reduce the proportion of patients defaulting treatment from 16.8% to 5.5%⁴⁾. The use of fixed-dose combination formulations can also prevent the development of drug resistance as shown by some studies. In one study, 0.47% of overall patients developed acquired drug resistance with treatment with separate drugs or fixed-dose combinations, and only 0.2% patients treated with fixed-dose combination formulations comprising rifampicin and isoniazid did so⁵⁾. Rifapentine is a long-acting cyclopentyl rifamycin that can facilitate the delivery of supervised treatment. However, earlier studies largely employing rifapentine 600 mg once weekly in the continuation phase of treatment of TB were associated with high rates of failure/relapse ($\geq 5\%$), even in HIV-negative patients^{6,7)}. Intensification of the dosaging and frequency of administration of rifapentine could shorten the duration of treatment for cure of TB in the mouse model⁸⁾. Indeed, a number of studies are now ongoing in the different parts of the world to evaluate the efficacy and safety of these enhanced rifapentine regimens. It has been found that serious adverse effects were not observed with higher dosages of rifapentine although more data are apparently required⁹⁾. Rifapentine is also evaluated in a number studies in combination

with moxifloxacin, a newer fluoroquinolone with potent bactericidal and sterilizing activities. The RIFAQUIN study evaluates twice-weekly and once-weekly regimens, and the NCT00728507 trial evaluates daily regimens. The phase III REMOX study attempts to explore whether substitution of moxifloxacin for isoniazid or ethambutol can reduce the duration of treatment of TB from 6 months to 4 months. Looking for shorter regimens in treating TB also aims at reduction of the risk of development of drug resistance.

Fig.1 depicts existing and potential strategies in the management of MDR-TB¹⁰⁾. The preventive measures which appear at the top have already been covered. The definitive management of established MDR-TB begins with an accurate diagnosis of the condition. As rifampicin resistance has a high predictive value for MDR-TB in previously treated patients, especially in the setting of high MDR prevalence, it would make sense to concentrate on developing rapid tests for diagnosing rifampicin resistance to act as a surrogate marker for MDR. The line-probe assay that relies on PCR for DNA amplification and reverse hybridization of the product is of great attraction. Currently, there are commercial kits like GenoType MTBDR assays that have high sensitivity and specificity for rifampicin resistance, even when used directly in clinical specimens¹¹⁾. However, these methodologies might not be totally applicable to the developing countries, not only because of costs involved but also through lack of infrastructure required to operate the equipment and deliver the specimens to the point of testing. Thus innovations to develop less intricate technologies might also be warranted. An example is the microscopic observation drug susceptibility assay or

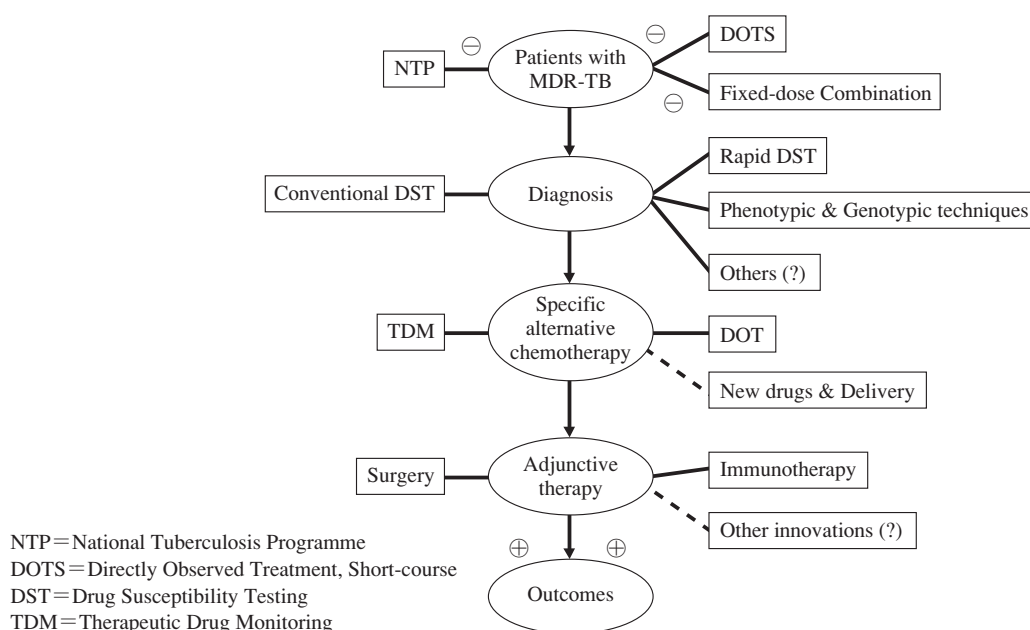


Fig. 1 Strategies in management of MDR-TB

MODS¹²). In a recent systematic review performed to evaluate the performance of rapid drug susceptibility tests for MDR-TB using rifampicin resistance as a surrogate, it has been found that although rapid assays appear fairly reliable to rule out MDR-TB, careful consideration of the clinical risk factors is required before using these tests to rule in MDR-TB under different epidemiological settings. The risk factors for drug-resistant TB are as depicted (Table 1).

Although DOTS is highly efficacious for drug-susceptible TB, it is generally considered insufficient for management of MDR-TB¹³). Among those patients who have apparently achieved chemotherapy success, about 28% would have subsequent relapse¹⁴). In an important analysis, it has been shown that the currently recommended standardized 4-drug and retreatment 5-drug regimens should be re-evaluated in countries where initial MDR prevalence exceeds 3%, in view of the poor treatment outcomes¹⁵). Thus a combined chemotherapy strategy is required for treatment of TB, DOTS for drug-susceptible disease and alternative specific chemotherapy using second-line drugs for MDR-TB. Second-line drugs must be delivered on a programmatic basis with 5 key components built on the DOTS framework¹⁶). These include political commitment, quality drug susceptibility testing, reliable supply of high quality drugs, well designed MDR-TB regimens given under DOT, and a sound recording and reporting system to monitor the outcome of patients and that of the programme. In addition, there should be long-term investment of staff and resources, co-ordinating efforts among various authorities, setting up of specialized units for managing MDR-TB patients and ensuring good adherence of patients to therapy. Furthermore, co-ordinating efforts between the hospital units and the health authority with its chest clinics is of paramount importance. It is mandatory to address the gap in control of TB due to presence of various service providers, in a pragmatic way (Fig. 2). The adherence drivers in the therapy of TB are depicted in Table 2. A holistic approach is required to promote adherence by targeting these drivers. A patient-centred care strategy by respecting the patient's rights and autonomy, as

well as entrusting the patient with responsibility to assist treatment success, would be highly beneficial. Although adverse reactions are commonly encountered during treatment of MDR-TB, most of them are mild and only require supportive treatment¹⁰). However, some serious reactions like neurotoxicity would entail a complicated strategy that embraces intensive supportive treatment and drug modification (Table 3). In brief, the general principles in designing a regimen for drug-resistant TB include the use of at least 4 non-cross-resistant drugs that are certain or likely to be effective¹⁶). These drugs should be taken from a hierarchy of 5 groups (Table 4) with a roughly descending order of potency. It is also necessary to prevent and monitor, as well as, manage adverse drug reactions. Among the second-line drugs, the fluoroquinolones and injectable agents, being the most potent, constitute the pivotal drugs in the MDR-TB treatment regimens. Indeed, in the regimens recommended by WHO for the treatment of MDR-TB with different bacillary resistance patterns, these 2 groups of drugs are generally

Table 1 Risk factors for drug resistance in *M. tuberculosis*

- Failures with initial treatment regimen
- Patients needing retreatment regimen
- Persistent smear positivity at months 2 and 3
- Relapses and returns from default
- Exposure to MDR-TB populations (outbreak etc)
- Living in settings with high MDR-TB prevalence
- Contact with MDR-TB patients
- Previous use of anti-TB drugs with poor or unknown quality
- Treatment under poorly functioning TB programme
- Malabsorption states
- Some HIV settings

Table 2 Adherence drivers in therapy of TB

- Disease education
- Directly observed treatment (DOT)
- Socio-economic interventions
- Psycho-social and emotional support
- Early and effective management of adverse drug reactions
- Monitoring and follow-up for non-adherence

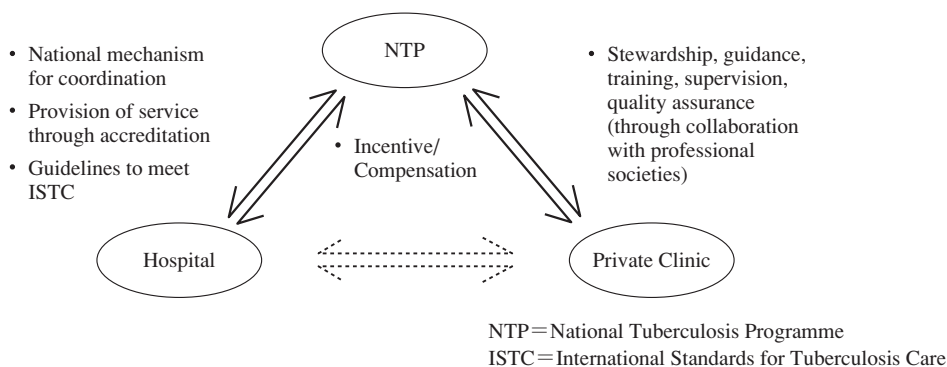


Fig. 2 Addressing the gap in TB control

Table 3 Management strategies for adverse neurological reactions due to second-line antituberculosis drugs

Adverse event	Possible causative agents	Suggested management
Peripheral neuropathy	Cycloserine Thioamides Ethambutol Fluoroquinolones Linezolid Aminoglycosides	<ul style="list-style-type: none"> • Increase pyridoxine to maximum daily dose • Try tricyclic antidepressant therapy if no contraindications • Nonsteroidal anti-inflammatory drugs or paracetamol may be tried for symptoms • Modify dosage or discontinue suspected causative agent • Substitute incriminated agent if possible (e.g. aminoglycoside by capreomycin)
Psychosis	Cycloserine Fluoroquinolones Thioamides	<ul style="list-style-type: none"> • Stop suspected agent for 1 to 4 weeks while controlling psychosis • Initiate appropriate antipsychotic therapy • Modify dosage or discontinue suspected agent • Substitute incriminated agent if possible (e.g. cycloserine by para-aminosalicylic acid)
Seizure	Cycloserine Fluoroquinolones	<ul style="list-style-type: none"> • Suspend suspected agent pending resolution of convulsion • Initiate appropriate anticonvulsant therapy • Increase pyridoxine to maximum daily dose • Recommence suspected agent at a lower dose if considered crucial to regimen. Otherwise discontinue it

Table 4 Categories of antituberculosis drugs*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 for routine use in treating patients with drug-resistant TB generally)

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

incorporated. Aside from these standardized regimens, the design of which is based on representative drug susceptibility data in well-defined patient populations, another approach is to use individualized regimens based on drug susceptibility testing results of each single patient¹⁶. In a recent systematic review and meta-analysis, it has been shown that the proportion of patients treated successfully improved when treatment duration was at least 18 months and if patients received DOT. Individualized regimens conferred a higher treatment success than standardized regimen, although the difference did not reach statistical significance¹⁷.

Resistance to ofloxacin constitutes an important independent variable for adverse treatment outcome in MDR-TB patients¹⁸. Fluoroquinolone-resistant TB generally results from suboptimal treatment of TB, especially MDR-TB, using inadequate number of active drugs and/or poor quality drugs¹⁹. The overzealous use of unsatisfactory standardized regimens that often only contain the fluoroquinolone and injectable agent as the solely effective components might be the culprit²⁰. Another mechanism for the development of fluoroquinolone-resistant TB might be related to the exuberant use of these antimicrobials in a recurrent and/or prolonged way for treatment of bacterial infections, especially in the community²¹. With the loss of the other potent class of second-line drugs, the injectables, extensively drug-resistant TB emerges²². The hot spots of XDR-TB worldwide do largely overlap with those of MDR-TB, reiterating that XDR-TB emerges largely as a result of poor treatment of MDR-TB. XDR-TB have very poor prognosis in terms of low treatment cure rate (<50%) and high all-cause and TB-specific mortality²³. In a recent analysis it has been suggested

that if case detection rate of MDR-TB rises with no concomitant improvement in the cure rate, then the XDR-TB scenario would worsen exponentially²⁴). Thus, new drugs are needed to combat MDR-TB and XDR-TB²⁵). Novel drugs with potent bactericidal and sterilizing activities such as the ATP synthase inhibitors (or DNA gyrase inhibitors) might be promising agents, so are drugs with multiple targets of action, especially the nitroimidazoles. The current global portfolio of new anti-tuberculosis drugs under various phases of clinical development is as shown (Fig. 3). In a recent Phase II b study, the efficacy of TMC-207, a diarylquinoline with unique activity against mycobacterial ATP synthase, has been well demonstrated by the higher proportion and more rapid sputum culture conversion in the treated MDR-TB patients²⁶). The drug also appeared well tolerated up to 2 months. More evaluation is now undertaken in further studies. Another Phase II trial is evaluating OPC-67683, a nitroimidazo-oxazole for its efficacy and tolerance in MDR-TB treatment²⁷). PA-824 is a nitroimidazo-oxazine with good bactericidal activity comparable to that of isoniazid. In the mouse model it has good bactericidal and sterilizing activities against *M. tuberculosis*, when used alongside moxifloxacin and pyrazinamide²⁸). Currently, most of the recommendations on MDR-TB treatment is based on observational studies and expert opinion, it appears that time is now ripe to conduct randomized controlled trials in the treatment of MDR-TB, as the expansion of drug-resistant programmes in different parts of the world can provide fertile grounds for such implementation²⁹).

Adjunctive surgery is beneficial in selected patients with MDR-TB or XDR-TB, largely for those with extensive bacillary resistance, localized disease and adequate cardiopulmonary reserve. The Denver experience in USA has demonstrated quite convincingly the escalation in cure rate and lowering of mortality by the addition of surgery and fluoroquinolones to the treatment armamentarium of MDR-TB. When analysed statistically, these 2 modalities were associated with high odds ratios for success (OR 4.63, 95% CI 1.89–11.37 and OR 3.11, 95% CI 1.21–7.95)³⁰). The use of fluoroquinolones also conferred a survival benefit ($P < 0.05$), and the use of surgery produced a trend in survival benefit in patients with

non-extensive disease, although this did not reach statistical significance³⁰). In another series of patients with MDR-TB in Turkey, the highest long-term treatment success and survival rates were achieved in patients who both received fluoroquinolones and underwent surgery³¹). However, an additional significant benefit from surgery could not be demonstrated. There has not been any randomized study to compare the efficacy of chemotherapy plus surgery versus that of chemotherapy alone. However, a study on a limited number of MDR/XDR-TB patients treated by surgery followed by first-line chemotherapy could achieve rather durable cures in 15 subjects (78.9%), perhaps suggesting an independent role of surgery for these conditions³²). In experienced hands, the outcomes of adjunctive surgery in patients with MDR-TB have been rather rewarding with success rates generally reaching 90%, operative mortality not exceeding 4%, and postoperative complication rates amounting to about 20%¹⁰). In patients who are frail and cannot tolerate lung resections, collapse procedures such as pneumothorax might be contemplated. One randomized study has recently shown encouraging bacteriological and radiological outcomes with artificial pneumothorax in MDR-TB patients, especially for new cases³³). The immunopathogenesis of TB centres on the interaction between the macrophage and various lymphocyte types, alongside their elaborated cytokines. In the mouse model, several mechanisms such as apoptosis, autophagy and CD8 cytotoxic T lymphocytes might constitute protective immunity³⁴). CD8 cells can activate macrophages or be engaged in direct bacteriolysis and apoptosis. Lately much attention has been focused on the phenomenon of autophagy, which in simplistic terms can be viewed as limited apoptosis. *Mycobacterium tuberculosis*, an intracellular pathogen, persists within the phagosomes, through interference with phagolysosome biogenesis. Stimulation of autophagic pathways in macrophages causes mycobacterial phagosome to mature into phagolysosomes³⁵). It has now been shown that drugs like rapamycin or the small molecule enhancers of rapamycin-induced target of rapamycin inhibition can promote autophagy. These findings might have potential immunotherapeutic implications. Preliminary studies in MDR-TB treatment using supplementary effector cytokines, largely interferon-gamma, has yielded rather encouraging results in

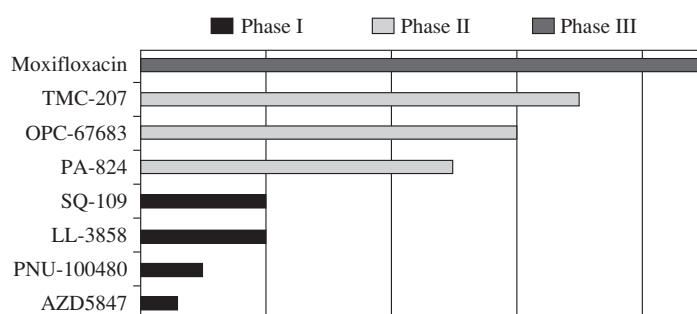


Fig. 3 New anti-tuberculosis drugs: Global Clinical Portfolio

terms of radiographic improvement and lowering of bacillary load, except for a study using subcutaneous instead of aerosolized cytokine¹⁰. In a recently published report regarding TB patients in South Africa, aerosolized interferon-gamma could bring about favourable effects on the inflammatory cytokines and CD4 lymphocytes, alongside more rapid bacteriological clearance and clinical improvement³⁶. Such effects were however not seen with the subcutaneously administered cytokine. Another cytokine that might be involved in protective immunity in TB is interleukin-12, but more needs to be known regarding its safety profile.

As a response to the emergence of XDR-TB, the WHO has recommended the following strategies for the control of the disease²⁵. These include accelerating access to rapid drug susceptibility testing, especially for rifampicin, strengthening laboratory capacity to diagnose and survey drug resistance, enhancing programmatic management of MDR-TB, especially with quality drugs and DOT, and ensuring access to anti-retroviral drugs and good clinical management of HIV coinfection, accelerating implementation of infection control to reduce disease transmission especially in HIV settings, and initiating information-sharing strategies to enable global control of XDR-TB. In addition, the WHO recommends expanding MDR-TB and XDR-TB surveillance to better understand the magnitude and trends of drug resistance and links with HIV, strengthening advocacy, communication and social mobilization, pursuing resource mobilization and promoting research and development into new diagnostics, drugs and vaccines. The fund gap in MDR-TB/XDR-TB control globally needs to be met. To achieve the target set out in the Global Plan to Stop TB, 1.4 million MDR-TB/XDR-TB cases have to be treated from 2009–2015. Asia alone needs \$7.1 billion US. A prioritized research agenda in drug-resistant TB should also be set up, inclusive of those pertinent to laboratory support, treatment strategies of drug-resistant TB, programmatic relevance, disease epidemiology and management of contacts of patients with drug-resistant TB²⁵.

Finally, some current management guidelines for patients with documented or almost certain XDR-TB will be discussed²⁵. Regarding the use of newer generation fluoroquinolone in the treatment of this difficult scenario, it would be important to appreciate the phenomenon of cross-resistance among members of this drug class. However, clinically it has been noted that levofloxacin (a newer generation fluoroquinolone as well) has very powerful early bactericidal activity, when given in a high dose (such as 1000 mg)³⁷. In a study in Hong Kong, levofloxacin use was associated with more favourable outcome in MDR-TB patients, as compared with ofloxacin³⁸. Indeed some patients with ofloxacin-resistant MDR-TB could still be cured by levofloxacin. In another recent study on XDR-TB patients in South Africa, the use of moxifloxacin was associated with better survival independently³⁹. Regarding the use of the

Group 5 drugs i.e. those with not totally certain activity, linezolid, an oxazolidinone, has shown some definite bactericidal activity although this is still lower than that of isoniazid. In this rather sizable retrospective assessment of linezolid in MDR-TB patients in Europe, the drug has shown some anti-tuberculosis efficacy⁴⁰. However about 40% of patients experienced major adverse reactions (haematological and neurological toxicities), occurring generally after 60 days of treatment, and were more commonly associated with twice-daily compared to once-daily dosing. Thus, linezolid once daily when added to an individualized regimen could improve chances of bacteriological conversion and eventual cure. However its use should only be restricted to the most complicated/difficult cases of MDR-TB or XDR-TB³⁹. Recently, data from South Korea have also shown that linezolid 300 mg was very well tolerated by MDR-TB and XDR-TB patients, alongside suggestive efficacy⁴¹. However, there is still a concern for emergence of linezolid resistance in *M. tuberculosis* which has been reported in Asia⁴². Another oxazolidinone that has rather potent antituberculosis activity is PNU-100480. In the mouse model it has shown good activity when used together with moxifloxacin and pyrazinamide⁴³. In a randomized study using high-dose isoniazid (>10 mg/kg) on top of second-line drugs in the treatment of MDR-TB, efficacy was observed in terms of more rapid and more frequent bacteriological response, alongside radiographic improvement⁴⁴. The underlying rationale might be the combined efficacy of high-dose isoniazid and prothionamide against the low- and high-resistance phenotype organisms. In a South Korean study, the treatment success rate did not differ significantly between non-XDR, MDR-TB patients and those with XDR-TB (66% vs 67%)⁴⁵. However surgical resection was performed more frequently for patients with XDR-TB (48% vs 17%), perhaps alluding to an independent efficacy of surgery in XDR-TB. In another analysis from South Korea regarding non-HIV infected patients with XDR-TB, the use of linezolid and surgical resection were found as independent factors associated with favourable outcome⁴⁶. In some patients with MDR-TB and XDR-TB, recourse to palliative management has to be undertaken at certain time-points for the benefit of the patients and the community¹⁰. The supportive measures and end-of-life care for these patients include pain and cough relief, dyspnoea relief, nutritional support, medical and psychological care and finally hospice or home nursing care to enable a dignified termination of these poor patients.

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