Review Article

The Probable Factors That Lead to Multi-Drug Resistant Tuberculosis and its Control: A Critical Review

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ABSTRACT

The clinical relevance of anti tuberculosis drug resistance will be reviewed first as a background to the identification of drug resistant tuberculosis (TB), especially the multi drug-resistant (MDR) and extensively drug-resistant (XDR) forms, their treatment and management principles. While many of the general concepts regarding drug-resistant TB will be covered here, a significant amount of the material will focus on multidrug-resistant TB (MDR-TB). Unfortunately, the origin and cause of the problem is largely man-made. In this write-up, various probable clinical errors and programmatic factors that can lead to the development of drug resistance and the various signs of treatment failure that trigger an evaluation for drug resistance and treatment adjustment are critically reviewed. The solution offered by the knowledge of cause is to prevent MDR-TB than to treat because the treatment of MDR-TB is not only costlier but also deadly difficult. Expert consultation is often recommended when MDR-TB is suspected and the patient can be treated with either a standardized or an empiric regimen at the outset until drug-susceptibility test results are known. Patient-centered approach is essential to monitor the drug resistance treatment supervision and support.

Keywords: Anti tuberculosis, Drug-susceptibility testing, Extensive drug-resistance, Multi drug-resistance, Second-line drugs.

INTRODUCTION

Anti-tuberculosis drug resistance is classified into four types: mono-resistance (isolates of *M. tuberculosis* confirmed to be resistant in vitro to one first-line anti-tuberculosis drug), poly-resistance (isolates are resistant in vitro to more than one first-line anti-tuberculosis drug other than both isoniazid and rifampicin), multidrug-resistant TB (MDR-TB) (isolate with in vitro resistance to at least isoniazid and rifampicin) and extensively Drug-resistant TB (XDR-TB) (In vitro resistance to at least isoniazid and rifampicin (i.e., MDR-TB) plus resistance to any fluoroquinolone and any one of the second-line anti-tuberculosis injectable drugs (kanamycin, amikacin or capreomycin). In 2008, the number of people living with tuberculosis was estimated to be 11.5 million, with 9.4 million of them having incident disease. Among those 1.9 million people who died of tuberculosis, 0.5 million people were found to be seropositive for HIV.[1] The present chemotherapy available for tuberculosis apart from being highly efficacious, it is worth worthy to note that it does not live up to the expectation of adequately controlling the current global tuberculosis situation because of its lengthy and complex treatment regimen.[2] In 2008, an average of 390,000–510,000 cases of multidrug-resistant tuberculosis (MDR-TB) 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, 50% of this global burden. In 2008, MDR tuberculosis caused an estimated 150,000 deaths.[3]

Understanding how MDR-TB develops and how to prevent MDR-TB is of the utmost importance because MDR-TB is a manmade problem. It is costly, deadly, debilitating and is a major threat to our current control strategies. The development of MDR-TB is largely man-made and therefore preventable. Often it is a consequence of suboptimal regimens and treatment interruptions. Clinical misjudgments, co-morbid conditions, and programmatic shortcomings may all contribute to the emergence of drug resistance. The impact of MDR-TB is significant; both to the individual and to the healthcare system.[4] MDR has a major adverse effect on the outcome of treatment. Patients with TB caused by MDR organisms generally require treatment with second line drug regimens. XDR-TB cases are often resistant to all four 1st-line agents. Consequently, patients with XDR-TB are significantly more difficult to treat and require specialized care. Approximately 5.4% of MDR tuberculosis reported worldwide could be categorized as XDR tuberculosis, with the proportion exceeding 10% in some countries.[3]

Investigators from WHO have calculated estimates of MDR cases globally, based on a number of assumptions, using data reported from 184 countries. It is notable that the estimated percentage of MDR-TB among previously treated TB cases is about 6 times greater than the estimated percentage of MDR-TB among new (previously untreated) cases. This finding highlights the increase risk for MDR-TB among individuals previously treated. The total case estimates indicate that 4.3% of all cases of TB beginning treatment in 2004 had MDR organisms (Table 1).[5]

The cost of MDR is astounding. In the US the average direct medical costs per MDR case (US$27,752) are far higher than for treatment of drug-susceptible TB. This is due to the costs of hospitalization, which is much more

likely to be necessary for patients with MDR, and the much longer duration of treatment with costlier drugs. Treatment is more toxic than with standard 1st-line agents and duration is always at least 18 months. There may be longer periods of isolation for these patients because of lower effectiveness of second-line agents, which may result in a longer time before sputum smears convert to negative. Because of the ongoing effects of having a chronic illness, depression is common and may interfere with adherence to treatment. The patient may face an incurable status, and mortality rates are higher with MDR-TB.[6]

Table 1: Estimated global incidence and proportion of MDR among TB cases, 2004

2004	TB cases	MDR cases	%
New Cases	8,897,743	272,906	2.7
Previously treated cases	982,639	181,408	18.5
Total cases	9,880,382	424,203	4.3

The factors presently considered as the cause behind the occurrence of drug resistance.

Drug resistance is largely man-made and is a consequence of suboptimal regimens and treatment interruptions. Table 2 lists the drugs that are used to treat tuberculosis into five groups based on drug efficacy and drug properties (or drug classes) by WHO.[7]

Table 2: Categories of anti-tuberculosis drugs

Category 1	First-line oral drugs: isoniazid, rifampicin, ethambutol, pyrazinamide
Category 2	Fluoroquinolones: ofloxacin, levofloxacin, moxifloxacin [10-15]
Category 3	Injectable agents: streptomycin, kanamycin, amikacin, capreomycin [9,16-17]
Category 4	Oral bacteriostatic second-line agents: ethionamide, cycloserine, para-aminosalicylic acid (PAS), sodium PAS, (protionamide, terizidone)* [9,14]
Category 5	Agents with unclear role in drug resistant treatment (not generally recommended by WHO for routine use in treating patients with drug-resistant tuberculosis)[18]: clarithromycin, clofazimine, high-dose INH (> 10 mg/kg), amoxicillin-clavulanate[19-27], meropenem-clavulanate, linezolid, thioacetazone, rifabutin

*The drugs listed in parentheses are not widely available

Though various patient-related factors, healthcare provider and healthcare system-related factors are invariably cited as the principal reasons, inadequate treatment is indicated to be the key factor behind the problem.[8] Here is a hypothetical example of a patient with a strain that is not MDR to begin with, but is resistant to multiple drugs given in Table 3. In this situation, transformation into an MDR strain can take place very quickly. The baseline tests show resistance to INH and EMB (treating provider was unaware). Although the standard WHO recommended 4-drug regimen is used, rifampicin resistance occurs at two months because the only effective drugs in the regimen at the beginning of treatment are rifampicin and PZA. Unfortunately, PZA does not prevent drug resistance like other companion drugs and rifampicin resistance occurs. In this case, amikacin and a fluoroquinolone (moxifloxacin) and ethionamide were added and by eight months smear and culture conversion occurred.[4]

Table 3: Resistance: Unintended Acquired

Months of Rx	0	2	4	8
INH/RIF/EMB/PZA				
Ami/Moxi/Eti				
Smear	+	+	+	-
Culture	+	+	+	-
Susceptibility				
INH	R*	R	R	No growth
RIF	S*	R	R	No Growth

*Results not known to clinician

The probable clinical errors that commonly lead to the emergence of drug resistance include: failure to provide effective treatment support and assurance of adherence, failure to recognize and address patient nonadherence, inadequate drug regimens, failure to recognize existing drug resistance and adding a single new drug to a failing regimen. In addition, co-morbid conditions associated with reduced serum levels of anti-TB drugs (e.g., mal absorption, diarrhea, HIV infection, or use of antifungal agents) may also lead to the acquisition of drug resistance. The probable programmatic causes of drug resistance are due to drug shortages and stock-outs or administration of poor-quality drugs and lack of appropriate supervision to prevent erratic drug intake.[28,29]

The probable clinical and epidemiologic risk factors that can lead to the development of drug resistance should be assessed. History of prior treatment is the most powerful predictor for MDR TB. A history of prior treatment may be difficult to obtain. Patients may not know that they were treated for TB or may willfully deny prior therapy. In the patient who cannot describe what he/she was treated for, clues can be obtained by asking the duration of treatment (few lung diseases other than TB will be treated for six or more months with antibiotics), the number and color of pills or use of injections (possible streptomycin), or orange-discoloration of urine (rifampicin). It is important to attempt to determine if the patient was adherent to treatment by asking directly and indirectly. If there has been prior treatment, the source of the treatment should be ascertained. Community prevalence of drug resistance: In most situations this is not known. In general one should not assume that a previously untreated patient has drug-resistance based on an assumed prevalence of drug resistance. Exceptions would include certain specific situations in which a high prevalence of drug resistance has been documented such as some refugee-camp settings or documented outbreaks. Exposure to possible drug-resistant sources: Commonly, patients do not know if there has been exposure to a drug-resistant source case. The provider should ask if anyone in the house has had tuberculosis or

any lung disease for which they have been treated for many months repeatedly, or if their treatment for TB was deemed "incurable". HIV infection: In some areas of the world, HIV infection is a risk factor for MDR. HIV is also associated with acquiring rifamycin resistance. Hence, HIV-infected TB patients deserve special attention.

Assessment of the response to treatment in patients with HIV infection is often complicated by the likelihood of other opportunistic lung diseases. Adherence should be assured and intermittent treatment regimens should be avoided if CD-4 counts are low. Early recognition of signs and symptoms for treatment failure in patients currently on TB treatment should also raise clinical suspicion for possible drug-resistant disease. Clinical evidence of failure can include persistence or recurrence of symptoms. A significant proportion of patients with cough improve over the initial few weeks of treatment. An unchanged or worsening cough may be an early clue for treatment failure. Suspicion of treatment failure should prompt further microbiologic evaluation. The official WHO definition for treatment failure is a positive sputum smear at month 5 of treatment. A high percentage of patients usually become smear negative by month 3 and some experts would consider a thorough reevaluation of the patient at this time point. If treatment failure is suspected, the patient should also be assessed for other factors that may contribute to inadequate treatment (non-adherence, mal-absorption, etc) and DOT instituted if not already in use. Substranded and falsified anti-tuberculosis drugs are readily available in the private market place and probably contribute to drug resistance in low-and middle-income countries, making them likely to contribute to drug resistance.[30]

Methodology

Various screening methods for active TB identification of people with suspected active TB in a predetermined target group are available by the application of tests, examinations or other procedures. Among those with suspected TB, diagnosis needs to be established through the application of one or several diagnostic tests and clinical assessment. Screening can be done either as an outreach activity in the general community, among TB contacts and in other specific high- risk groups, or among people seeking care, including those who seek care for reasons other than symptoms compatible with TB. The latter category includes, for example, people attending for regular check-up of conditions that are risk factors for TB, such as HIV and diabetes. Passive case finding (PCF) is defined as the detection of active TB disease among symptom- antic patients who self-present to medical services for the diagnosis of symptoms, with a specific focus on people with typical TB symptoms, such as chronic cough. Active case finding (ACF) implies screening through outreach activities outside health services. Enhanced case finding (ECF) primarily aims to make a population aware of TB symptoms through publicity and education, and encourages self-presentation to medical services, which may be decentralized as part of the intervention. This in effect means that ECF is PCF combined with intensified health information.[31] However, ECF can also include a screening element, for example as part of a chest/health camp, in which case the intervention is a combined ACF/ECF intervention.[32-37] Six studies presented comparable data on cases found through screening and passively, the outcomes for both the cases within each study were very similar, and this was seen in the meta-analysis: RR 1.01 (95%CI 0.99–1.04), with low heterogeneity as shown in Figure 1.[38]

Appropriate diagnosis and timely treatment intervention for MDR-TB is facilitated by recognizing and evaluating risk factors for MDR-TB and properly monitoring for evidence of treatment failure. Developing the appropriate clinical suspicion for drug-resistance is the essential first step. Treatment can then be adjusted based on local guidelines, and case management and monitoring also adjusted accordingly. If laboratory resources are available, timely use of drug-susceptibility testing can confirm the presence of drug resistance and allow the informed tailoring of treatment drugs. If MDR-TB is strongly suspected, consultation with an expert is suggested. If drug resistance is suspected based on the assessment of clinical or epidemiologic risk factors and/or evidence of treatment failure, whenever possible, drug-susceptibility testing (DST) should be obtained to both confirm the diagnosis and pattern of drug resistance and guide treatment choices.[39]

One must realize that current available DST methods are slow. Identification of MDR may take 4–8 weeks, and second-line drug sensitivity testing 6–12 weeks for results. 2–4 weeks for initial culture to become positive, additional 2–4 weeks to get 1st-line susceptibilities and an additional 2–4+ weeks (sent to CDC) to get 2nd-line susceptibilities. With standard culture and DST methods, 4-12 weeks are usually needed to get results (liquid broth methods are faster) from the time of initial sputum collection to the completion of both first- and second-line DST tests. In view of this inherent delay, one should not wait to treat a patient with an augmented regimen if MDR suspicion is high and resistance pattern can be predicted. The only reason not to treat an MDR suspect while waiting for test results is when the disease burden is minimal or if prior MDR treatment was given and it remains unpredictable which drugs will work. In addition to the current methods being slow, there are other common problems with drug susceptibility testing. Substantially more training and experience is required for susceptibility testing than for culture alone. Having a quality assurance program in place is essential, yet few labs are qualified to provide the assessments. Testing of ethambutol and pyrazinamide is unreliable, which may lead to conflicting results in different laboratories.

In MDR-TB suspects, predicting the pattern of resistance is important in determining what drugs you use while waiting for DST results. One should attempt to utilize all available information to make treatment decisions. Carefully obtain a good history of prior TB treatment from

the patient and consider all drugs used previously as potentially ineffective. Early suspicion, diagnosis and appropriate treatment are the critical factors in preventing further progression and transmission of drug-resistant disease. Prior treatments are the most significant predictor for drug resistance, but always learn to recognize all risk factors particularly when the patient is failing standard treatment. Also obtain first- line drug susceptibility testing whenever possible for patients with suspected MDR.

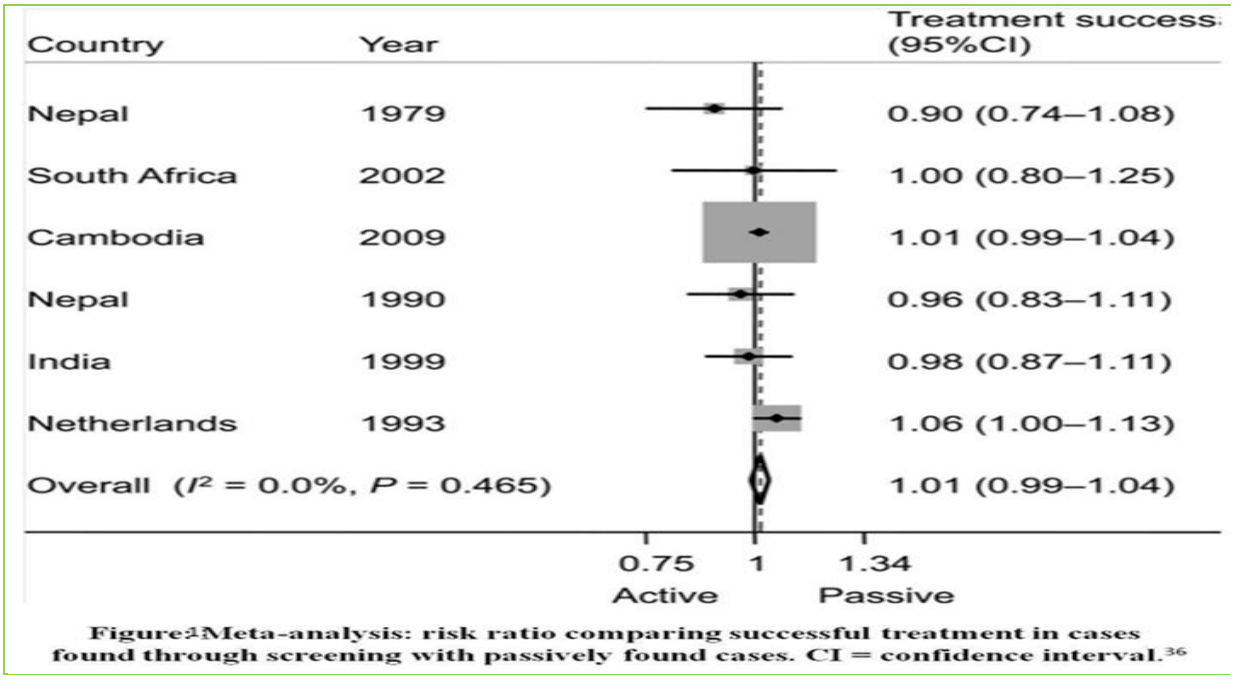

Figure 1 Meta-analysis: risk ratio comparing successful treatment in cases found through screening with passively found cases. CI = confidence interval.[36]

Table 4: Empiric Regimens for MDR-TB

Predicted Resistance Pattern	Suggested Regimen	Minimum duration of treatment	Comments
INH, RIF	Fluoroquinolone, PZA, EMB, Injectable	18- 24 months beyond culture conversion	Extended treatment is necessary to lessen the risk of relapse
INH, RIF, EMB	Fluoroquinolone, PZA, Injectable, CS ± PAS/ETH	18- 24 months beyond culture conversion	Consider surgery. Consider high dose INH treatment if low level resistance is documented
INH, RIF, PZA	Fluoroquinolone, EMB, Injectable, CS ± PAS/ETH	18- 24 months beyond culture conversion	Consider surgery. Consider high dose INH treatment if low level resistance is documented
INH, RIF, PZA, EMB	Fluoroquinolone, Injectable, CS, PAS/ETH ± one more drug	24 months beyond culture conversion	Consider surgery. Consider high dose INH treatment if low level resistance is documented

INH = Isoniazid; RIF = Rifampicin; EMB = Ethambutol, PZA = Pyrazinamide, CS = Cycloserine, PAS = *P*- amino salicylic acid, ETH = Ethionamide.

Therapeutic drug monitoring (TDM) is potentially useful in anti tuberculosis chemotherapy in the optimization of therapy to ensure/improve success in specific clinical settings. TDM enables us to study and manage the pharmacokinetic drug–drug and drug–disease interactions as well as to evaluate new fixed-dose combinations FDC developed for treatment of tuberculosis. TDM is useful in studying the influence of dietary contents and antiulcer drugs on bioavailability of anti tuberculosis drugs. TDM is also very essential in the careful monitoring of anti tuberculosis drug compliance of patients.[40]

DISCUSSION

Patients with tuberculosis caused by drug-resistant (especially MDR) organisms should be treated with specialized regimens containing second-line anti-tuberculosis drugs. At least 4 drugs to which the organisms are known or presumed to be susceptible should be used, and treatment should be given for at least 18 months. Patient-centered measures are required to ensure adherence. Consultation with a provider experienced in treatment of patients with MDR-tuberculosis should be obtained. Three strategic options for treatment of MDR-TB are currently recommended by WHO.[9]

1. *Standardized regimens* are based on information about the drugs used in the country in the past and the results of drug-resistance testing within the population. This information can be used to develop a regimen for use in all previously treated patients or

other patients in whom resistance is strongly suggested.

2. The composition of *empiric regimens* is determined individually based on knowledge of the drugs used previously and local resistance patterns.
3. *Individualized treatment regimens* are based on the history of drugs used previously and the results of drug susceptibility testing. It should be noted that because of the delay in obtaining second-line drug-susceptibility test results, even when such testing is available, most patients are begun on either a standardized or an empiric regimen.

The choice among these three approaches is largely determined by the three factors listed. It should be noted that second-line drug susceptibility testing is not well standardized and that results even between experienced laboratories may vary. Consequently, quality control for these laboratories is very important for the test results to be valid. In standardized treatment, all patients in patient category/group receive same regimen. In standardized treatment followed by individualized treatment, initially all patients receive same treatment then adjusted when individual DST results are available where as in empirical treatment followed by individualized treatment, treatment is designed individually based on history of TB treatment and then adjusted when DST results of individual patient are available.

Management principles

The basic principles on which a second-line drug regimen is designed are described by WHO[7]. At least four drugs highly likely to be effective and drugs from groups 1-5 in a hierarchical order based on potency should be included in the treatment regimen. Drugs for which there is cross-resistance and drugs that are unsafe for the patient should be avoided. Careful prevention, monitoring and management of adverse effects from the drugs selected should be done periodically. These treatment principles are discussed in detail in the subsequent paragraphs.

Because, often, the second-line regimen represents the patient's last best hope for cure, direct observation of treatment (DOT) is essential. Observation may be necessary also because of the use of injectable agents. Such frequent encounters between patient and healthcare staff can provide the necessary support to get the patient through a difficult treatment regimen, and can serve to quickly identify the frequent adverse reactions that may occur with these drugs. Much of the guidance for treating patients with MDR-TB is based on empiric observation, not clinical trials. However, the principles listed here seem to be reasonably well established. Daily, but not intermittent administration should be followed. The treatment regimen should be continued for a minimum of 18-24 months. Injectable should be continued for at least six months post-culture conversion when possible. At least three oral drugs should be continued for full treatment duration. An assessment of likely effectiveness is an essential part of determining a drug regimen for a patient or suspected MDR-TB supported by a number of factors such as demonstrated susceptibility, history of treatment failure with the drug, contacts with resistance to the drug, resistance found rare in similar patients (surveys) and whether the drug is commonly used in the area or not. The strength of the assumption that a given drug will be effective decreases as one goes down the list. When there is uncertainty about the effectiveness of a four-drug regimen selected in this way, additional two to three drugs may be added to provide a margin of safety.

Confirmation of MDR-TB by DST in all patients enrolled on a standardized Category IV regimen is strongly recommended. Misclassification of patients can occur, which will either deny isoniazid and rifampicin to those patients who would benefit from these drugs, or unnecessarily expose others to potentially toxic first- or second-line drugs. In order to ensure a standardized regimen that will treat the vast majority of patients with four effective drugs, it is often necessary to use five or six drugs to cover all possible patterns of resistance. An injectable agent and a fluoroquinolone form the core of the regimen are preferably used.

Standardized treatment regimen includes intensive phase for a minimum of 6 months with amikacin, ethionamide, pyrazinamide and levofloxacin followed by continuation phase for a minimum of 12 months with ethionamide, levofloxacin and pyrazinamide. Ethambutol is used in both phases of treatment if strains are still susceptible. Empiric regimens for MDR-TB vary depending on the predicted pattern of drug resistance listed in Table 4. The resistance pattern should be predicted based on the prior TB drugs used and all drugs used at the time of treatment failure.[41] Note that whenever possible, any remaining 1st-line agents, fluoroquinolones, or injectable agents (excluding streptomycin) should be included.

Cross-resistance limits the usefulness of some second-line agents. There is high level cross-resistance among all the rifamycins (ex. rifampicin, rifabutin, rifapentene, rifalazil). There is also considerable cross-resistance among the fluoroquinolones, but there may be some efficacy in using the more potent drugs of the class (ex. moxifloxacin) even when there is resistance to the class. Amikacin and kanamycin are generally, but not always, cross-resistant and hence susceptibilities should be tested. Capreomycin is less likely to be cross-resistant, but occasional cross-resistance can occur with amino glycosides.

Drugs that are known to be unsafe to the patient should not be used. Co-morbidities are common in patients with MDR-TB due to the toxicities associated with many of the second line drugs. It is important that patients should be evaluated prior to initiating treatment to avoid unmanageable drug intolerance. A histological and physical examination directed toward identifying possible HIV infection, hepatic or renal disease, psychiatric disorders, and other co-morbid conditions that could

either mask or compound drug toxicities should be evaluated. The use of drugs that have not been quality-assured, an important problem in some areas, may not be more hazardous to the patient but can expose patients to potential risks with, perhaps, no benefit. Providers should always insist on having quality-assured drugs available.

When initiating treatment for MDR/XDR-TB, one should ensure that laboratory services for hematology, biochemistry and audiometry are available. Adverse effects are a major limitation in using second-line drugs. To use the drugs safely and effectively, clinical and laboratory services are essential before starting the regimen. Treatment should be initiated gradually when using drugs that cause gastro-intestinal intolerance and ensure the availability of ancillary drugs to manage adverse effects. Experience and skill are needed in guiding a patient through what may be a very difficult treatment program. Treatment using second line drugs is sufficiently complicated that it is best undertaken by a person who has specific training in management of MDR-TB and again as noted before, DOT is an essential component in the management of MDR/XDR-TB to help ensure adherence, monitor for adverse effects, and support the patient through a long and often difficult treatment course.

While chemotherapy using antituberculosis drugs constitutes the primary treatment for pulmonary tuberculosis, emergence of MDR and XDR tuberculosis has indicated to adjunctive surgery to improve the chance of cure in some patients in these drug-resistant scenarios. There are three basic criteria for the selection of adjunctive surgery in MDR tuberculosis patients. The first preference should be given is 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, followed by when the disease is sufficiently localized that the great preponderance of radio graphically discernible disease can be resected with an expectation of adequate cardiopulmonary capacity after surgery and lastly when the drug activity is sufficient to diminish the mycobacterial burden to facilitate healing of bronchial stump after lung resection.[42] Patients should receive chemotherapy prior to surgery for ≥ 3 months.[43]

Prevention and control

To prevent the spread of MDR/XDR-TB, patients should be isolated until three consecutive sputa AFB smears are negative and there has been a good response to treatment. Hospitalization is often helpful when initiating MDR-TB treatment as drug toxicities can occur frequently. Severe anorexia and nausea is very common with ethionamide, diarrhea with PAS, and altered mental status with cycloserine. These three drugs, in particular should be increased to full dose slowly over a course of a week to minimize side effects. Toxicity monitoring should be tailored to each drug employed in the regimen. For example, hypothyroidism can occur with both ethionamide and PAS; renal dysfunction and ototoxicity with all injectable agents. It is essential that the provider understands the side effects of specific drugs used in the treatment.[42] Patient-centered DOT ensures adherence to treatment; addresses social issues that creates barriers to treatment and enables effective clinical monitoring. Good documentation with case management tools to follow serial changes in drugs, bacteriology, radiographic findings, and toxicities helps minimize errors. These tools also help to keep track of the patient's progress (or lack of progress) during treatment. Last but not least, nutritional status and management of underlying medical conditions are essential in the recovery of patients with MDR-TB.

The difficulty of MDR-TB treatment requires tremendous support of the patient. Self-imposed stigma and depression are not uncommon. DOT is a support system that enables the completion of the long, difficult course of MDR-TB treatment. The goal of patient-centered DOT is to inspire and empower patient via a relationship of trust and support. Data in Table 5 supports the use of DOT in drug-resistant disease as a means of reducing further drug resistance and relapse. In the study whose data is shown here, a total of 407 episodes in which patients in the U.S. county of Tarrant, Texas received traditional treatment for TB were compared with 581 episodes in which therapy was directly observed. Despite higher rates of intravenous drug use and homelessness and an increasing rate of TB during this period of study, the relapse rate decreased from 20.9 percent to 5.5 percent (P<0.001), and the number of relapses with multidrug-resistant organisms decreased from 25 to 5 (P<0.001).[44]

Table 5: Effect of resistance and relapse on DOT

	Self-RX N=407 (pre 1987)	DOT N=581 (1987 +)
Primary R	13.0%	6.7%
Secondary R	10.3%	1.4%
Relapse	20.9%	5.5%
MDR relapse	6.1%	0.9%

*P < 0.001

As resources permit, an optimal monitoring plan for the monthly collection of sputum specimens during treatment should be obtained until smears and cultures have converted positive. Additional sputum specimen collection for smear and culture should be obtained at the end-of-treatment to document cure. Periodic chest radiographs during treatment and at the end of treatment (provides further evidence of the effectiveness of treatment) should be performed. Periodic sputum collection and clinical evaluation for a period two years after treatment ends (quarterly during first year, every six months during second year) should be monitored to detect possible relapse. The diagnosis of MDR-TB is confirmed by drug-susceptibility testing. Second-line drug susceptibility testing (resources permitting) should be expedited as soon as an isolate is known to be resistant to isoniazid and rifampicin is established. Susceptibility

testing should be repeated if cultures or sputum smears remain positive after two to three months of treatment.

A substantial number of patients TB and MDR-TB are being undetected, for whom diagnostics and drugs are not purchased, budgeted, manufactured, or even projected. Although the number of invisible patients is uncertain, recent estimates are that up to a third of global TB cases are not notified and therefore would lack access to appropriate diagnosis and care, even if universal DST for notified cases were implemented[45]. These invisible patients will continue to transmit TB (and MDR-TB) to their families and communities until their disease resolves spontaneously or they die. The World Health Organization, and several of the authors cited in the article by Royce *et al*.[46] are among those actively working to improve TB surveillance within countries.[47]

One of the main reasons why DOT is necessary in treatment of MDR-TB is the need to monitor for side effects. Providers who are treating patients with MDR-TB must be aware of these adverse effects in order to detect them early and be prepared to take proper steps when they occur. Gastrointestinal complaints are common with ethionamide, cycloserine, PAS, clofazimine and fluoroquinolones. Split-dosing, starting with small doses and gradually increasing the doses may minimize the GI complaints. Where available, some patients may require or benefit from pre-medication with and/or pre use of H2 blockers, proton pump inhibitors, anti emetics, or motility agents. Hepatotoxicity is the most common severe toxicity (early symptoms are anorexia and malaise, then abdominal pain, vomiting, jaundice) observed with ethionamide, PZA, PAS and fluoroquinolones. If hepatotoxicity occurs, all possibly hepatotoxic drugs should be stopped. Depending on the severity of both the TB and the hepatotoxicity, liver function should be retested and when normal or returning toward normal, the drugs should be reintroduced one at a time while monitoring liver function.

Peripheral neuropathy can be a serious adverse effect with ethionamide, cycloserine and linezolid. It is more likely to occur in patients with conditions that predispose to neuropathy, such as, HIV/AIDS, diabetes, renal insufficiency, malnutrition, etc. It can be avoided by co-administration of pyridoxine (25-50 mg/day). Skin rash may be mild or very severe (Stevens-Johnson syndrome) observed with anti-TB drugs. Often with a mild rash, treatment can be continued. Where available, some patients may require or benefit from pre-medication with and/or pre use of H1 blockers and/or topical corticosteroids. Headache is commonly observed with the use of cycloserine, ethionamide, ethambutol and fluoroquinolones, can often be managed with pain medication. However, persistent or severe headache occurring in a patient with TB or with HIV/AIDS should prompt an evaluation. Seizures have been known to occur with the use of cycloserine. Hypothyroidism may be a subtle adverse effect observed with ethionamide and PAS, presenting with fatigue, depression, etc. and can be diagnosed by checking thyroid function tests. It can be treated with thyroxin, and is reversible with discontinuation of the offending drug.

Hearing loss and vestibular toxicity if occurs with the use of Capreomycin and amino glycosides, it may be permanent and is an indication to discontinue the drug. Behavioral changes may also be subtle, especially with isoniazid. Cycloserine on the other hand may cause dramatic behavioral changes including psychosis and depression. Where available, some patients with mood depression due to cycloserine may benefit from use of antidepressants (e.g., SSRIs). Ethambutol is the drug most likely to cause visual changes, although this is uncommon with doses of 15 mg/kg. Renal failure is obviously a very serious adverse effect. Renal function should be determined as part of the baseline evaluation and monitored at regular intervals while injectable agents are being used. This is a very superficial discussion of this potentially serious adverse effects.[48] A few examples of interventions to counter some of the common clinical/programmatic causes that contribute to the development of drug resistance are given in Table 6.

Table 6: Strategies to Prevent MDR

Common Causes	Interventions
Non adherence, default	Patient-centered DOT, education, support, incentives
Management errors, lack of expertise	Consultation with experts, vigilant patient monitoring for treatment failure, provider training
Inadequate regimen in presence of drug resistance	Improved access to drugs and susceptibility testing

CONCLUSION

Among the various patient-related, healthcare-provider and -system related factors that can possibly be the reasons for the development of anti-TB drug resistance, most of the issues related to this typical problem is the inadequate treatment of TB. It is important to emphasize that treatment of MDR-TB is complex and costly, and that of XDR-TB is even more difficult. Expert consultation or referral is often necessary and recommended when MDR-TB is suspected. Either a standardized or an empiric regimen will be necessary at the outset until drug-susceptibility test results are known. At least four drugs to which isolate is known or presumed susceptible should be included in the treatment regimen for a minimum of 18-24 months. Careful monitoring of the adverse effects of second-line drugs is essential to detect them early before significant damage has been done. Patients with MDR-TB should be treated with specialized regimens containing second-line anti-TB drugs. Treatment using second line drugs is sufficiently complicated that it is best undertaken by a person who has specific training in management of MDR-TB. Patient-centered DOT ensures adherence to treatment; addresses social issues that creates barriers to treatment and enables effective clinical monitoring.

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