Archives of Clinical Infectious Diseases. 2012 July; 7(3): 81-4. DOI: 10.5812/archcid.14773

Published Online 2012 July 02. **Review Article**

Extensively Drug-Resistant Tuberculosis: A Review Article

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Received: April 06, 2012; **Revised:** April 28, 2012; **Accepted:** May 04, 2012

Extensively Drug-Resistant Tuberculosis (XDR-TB) is a new challenge for Tuberculosis control programs. Lack of effective drugs and high rate of failure in treatment and mortality is a major threat for public health. Treatment of this serious infection needs well-designed individualized dosage regimen and powerful national TB program. In this review we will describe the XDR-TB definition and its epidemiology and will discuss about the treatment options and future opportunities.

Keywords: Tuberculosis; Extensively Drug-Resistant Tuberculosis; Drug Resistance, Multiple

1. Introduction

Despite tuberculosis (TB) control programs, *Mycobacterium tuberculosis* remains as the most common cause of infection-related mortality, worldwide. In 1997, nearly 2 billion people were estimated to be infected with TB. Every year, 8 - 9 million individuals developing active infection, and at least 2 million people die from TB or related complications (1). In other words, 1 out of 3 people is infected with TB, and 1 of 8 deaths is resulted by TB infection, globally. While nearly every nation faces the burdens and risks of this disease, TB is largely a problem among developing nations, which accounts for 95% of cases and 98% of deaths. Mono drug resistant TB has long been recognized. Fortunately, the controlled use of multiple agents to treat active infections, the efficacy of these drugs, and the common use of directly observed therapy (DOT) have a significant impact on treatment regimens and reduced the mortality rate. Unfortunately, the evolution of drug resistance has led to the recent emergence of TB strains resistant to multiple antimicrobial agents, including those medications used as standard first-line therapies. This has forced considerable alterations in the treatment of TB and is expected to dramatically increased the mortality rate (1). Multi drug-resistant (MDR) Tuberculosis is defined as a disease caused by strains of *Mycobacterium tuberculosis* that are resistant to Isoniazid and Rifampin, Approximately 500000 peoples will develop MDR-TB annually. It has been estimated that MDR-TB had killed 1.5 million people from 2000 to 2009 (2, 3).

The true prevalence of MDR-TB is likely under recognized as many developing countries endemic for TB, lack appropriate lab facilities and diagnostic resources. Nearly two thirds of the global burden of MDR-TB is thought to occur in 3 countries including Russia, China, and India (1). Since the discovery of MDR-TB in 1990s, the resistance pattern of TB has continued to evolve, and resistant isolates to both first- and second-line antimicrobial agents has been identified as extensively drug-resistant TB (XDR-TB). The XDR-TB was first reported in November 2005. The US National TB Surveillance System (NTSS) published a more detailed description and preliminary data from the initially reported cases of XDR-TB in 2006. By October 2006, the WHO convened an Emergency Global Task Force on XDR-TB. This task revised the case definition as resistance to Isoniazid and Rifampin (with or without resistance to other first-line agents), resistance to any Fluoroquinolone, and resistance to at least one second-line injectable antimicrobial medication (Amikacin, Capreomycin, or Kanamycin) (1). Similar to MDR-TB, it has been globally identified and now represents as 2% of all cases of culture-positive TB (1). Even more, in a report in May 2007, WHO reported 2 cases of pan-resistant TB identified in Italy. As with MDR-TB, the true prevalence of pan-resistant/XDR-TB is likely under recognized. In highly endemic regions, the prevalence of XDR-TB may be as high as 10% (1). Given the extreme limitations in the ability to treat this infection has increased the death incidence with 80% to 100% mortality rates (1). It has been estimated that around 10% of MDR-TB cases are XDR-TB (4, 5). According to the WHO, drug resistance is the result of poorly managed TB control programs and improper use of anti-

Implication for health policy/practice/research/medical education:
The study has been conducted for medical purposes.

microbial therapy for the treatment of drug-susceptible TB. This improper use includes administration of inappropriate dosage regimens, failure of DOT, and incomplete adherence to or completion of the entire treatment course. Basically, drug resistance arises in areas with poor TB control programs (1).

While other factors, such as the use of antimycobacterial agents (especially Rifampin) to treat other nonmycobacterial infections; malabsorptive disorders, antacids, or other medications that prevent the absorption of antimycobacterials; malnutrition; residing in a country or region with a high prevalence of resistance; and HIV infection, contribute to the development of drug resistance, the most powerful predictor for MDR-TB is a history of TB treatment. Prior use of antimycobacterial agents was associated with MDR-TB in a linear fashion (1). The basis of drug resistance in Tuberculosis is to select the bacterial mutant with innate resistance to chemotherapy (5). While host genetic factors and spontaneous mutations (primary resistance) occur, the frequency of these mutations is low and unlikely to produce significant resistance (1).

MDR-TB and XDR-TB epidemics can be generated by three mechanisms:

1) Acquired resistance: transformation of pan-susceptible strain to resistant strain.

2) Amplified resistance: increasing development of resistance of drug resistant strains because of inappropriate chemotherapy.

3) Transmitted resistance: transmission of drug-resistant strains (6-8).

Among the mentioned mechanisms, transmitted resistance is the leading cause of rise of XDR-TB numbers which has been shown in Tuberculosis outbreaks (5). For example 39 (25%) of 46 isolated XDR-TB strains in the Tugela ferry outbreak in South Africa belonged to one strain (9). Elsewhere in a study in Iran, all XDR-TB cases belonged to 1 of 2 epidemiological clusters consisting of a single-family cluster (4 cases) and a cluster of close contacts (8 cases) (10). The transmission of drug-resistant TB is dependent on virulent organism (11, 12). About Three decades ago, it had been shown that INH-mono drug resistant TB had low reproductive ability, but recently it has been shown that compensatory mutation had restored the low reproductive ability of the microorganism(13, 14). The prevention of *M. tuberculosis* transmission depends on an accurate and rapid diagnosis, (15) the current available diagnostics are the combine of old and new technologies (5) in recent years, series of rapid tests have been introduced to the market. The advantage of rapid tests is their potential on sputum smear (16, 17). By using these rapid tests, results of drug-susceptibility test will be obtained in less than one week compared to standard proportional method which takes 4 - 8 weeks to obtain the results(16, 17).

2. Clinical Course

XDR-TB patients had poorer clinical outcomes in comparison with MDR TB patients. Patients with XDR TB had higher rate of mortally compared to MDR TB patients (18, 19). Isoniazid is the drug of choice for the treatment of latent TB infections (LTBI) and active infections. It is a powerful mycobactericidal agent and is effective on early sputum conversion and decreases transmissibility of TB. Rifampin is a highly effective mycobactericidal agent that promotes sterilization and prevents relapses. It is also a cornerstone agent of TB treatment. Resistance to either of these agents makes difficulties on effective therapy. Resistance to both antimicrobial agents caused therapy challenging and less likely to be successful (1). Resistance to standard first-line agents requires the use of multiple second-line medications. Second-line medications are, less effective, more toxic, expensive, less available, or less convenient, characteristics initially making them secondary or non-preferred choices. With regards to TB, second-line agents are also not suitable for short course therapy and require a longer duration of administration, besides to the increased cost and toxicity. Cost and duration of therapy make them extremely difficult to use in the regions (developing nations) that are mostly in need (1).

Given the decreased efficacy of second-line agents, treatment failures are more common in drug-resistant TB. In fact, the currently available second-line agents are 5 - 8 times more likely to fail compared to first-line agents. Ineffective treatment of MDR-TB, either through poor efficacy of the medications or noncompliance with longer, more toxic therapies, has created a suitable platform for further resistance acquisition and the emergence of XDR-TB. Since the XDR-TB is resistant to first- and second-line drugs, the treatment options are seriously limited. It is, therefore, vital to manage TB control programs properly in order to prevent further progression of MDR-TB and mitigate the emergence of XDR-TB [32]. The mortality rate of patient with XDR TB infection is about 14% - 20% (20) which may reach to 98% in HIV co-infected patients (9). In a retrospective study in Iran, successful outcome was observed in 81.2% of MDR-TB patients in comparison with 41.6% of XDR-TB patients (21). These findings indicate that patients with XDR TB have higher probability of treatment failure and mortality (22, 23).

3. Treatment

Treatment of drug resistant TB is based on two strategies:

1) Standardized treatment

2) Individualized treatment

Standardized treatment will be designed on representative drug susceptibility test of community. But individualized treatment is based on patient's DST results

(5, 24) individualized treatment needs DST result to first and second line drugs and require sufficient drug supply (25, 26). Several studies have showed that standardized regimen has low potency for treatment of XDR TB patients (21, 23) successful outcome was observed only is 41.6% of XDR-TB patient undergone standardized regiment (22, 23). In contrast success rate of about 60% have been seen in patients undergone individualized regiment (26, 27). Hence, based on these studies, individualized treatment based on patients history of treatment and drug susceptibility pattern is recommended (5, 23). Rules of designing regimen for these patients are same as MDR-TB treatment (24). Choosing an effective Floroquinolon is mandatory. Administration of later generation of Quinolon such as Moxifloxacin and Levefloxacin are recommended. Suitable injectable agents must be considered in regimen. Cross-resistance between Kanamycin and Amikacin must be considered (5, 23, 24). Drugs such as Cyclocerine, Prothionamide and PAS must be included in regimen based on DST (5, 23, 24). For treatment of these patients, drugs such as Clofazimin, Linezolide and Co-Amoxiclave are proper choices, ultimately we must have at last four effective drugs (5, 23, 24). For regimen with less than four effective drugs, consider adding two drugs from group 5 (Table 1).

Table 1. Rational Classification of Anti-TB Drugs (23)

Group 1: First-Line Oral Agents	Group 2: Injectable Agents	Group 3: Fluoroquinolones	Group 4: Oral Bacteriostatic Second-Line Agents	Group 5: Agents With Unclear Efficacy
Isoniazid (H)	Kanamycin (Km)	Ofloxacin (Ofx)	Ethionamide (Eto)/Protionamide (Pto)	CLOFAZIMINE (Cfz)
Rifampicin (R)	Amikacin (Am)	Moxifloxacin (Mfx)	Cycloserine (Cs)/Terizidone (Trd)	Linezolid (Lzd)
Ethambutol (E)	Capreomycin (Cm)	Levofloxacin (Lfx)	P-aminosalicylin acid(PAS)	Amoxicillin /Clavulanate (Amx/Clv)
Pyrazinamide (Z)	Streptomycin (S)			Thioacetazone (Thz)
				Imipenem/Cilastatin (Ipm/Cin)
				High-dose isoniazid (high-dose H)
				Clarithromycin (Clr)

The total number of drugs will depend on the degree of uncertainty and regimens which often contain five to seven drugs (23, 24, 26).

4. Conclusions

Based on mathematical models, MDR TB patients have shown three times higher transmission rate compared with susceptible TB patients (8). Hence, the annual incident may increase even with intensive efforts to control the disease (28). Also rate of XDR-TB will increase as a result of synergistic interaction of acquired resistance due to MDR-TB treatment and transmitted resistance (23, 29). MDR and XDR TB is clearly an emerging problem. Rapid diagnostic tests have facilitated early diagnosis of drug-resistant TB. Drugs such as Linezolid and Clofazimin may play more important role in treatment of drug resistant TB in future (30). Optimizing current tools and strengthen primary healthcare system and dots program could improve or reduce the rise of MDR/XDR TB epidemics. At the end it must be emphasized that emerge of new stains of totally drug resistant (TDR) *M tuberculosis* would be a new challenge for clinicians in near future (31).

Acknowledgements

There is no acknowledgment.

Authors' Contribution

Masoud Mardani came up with the idea of the study. He also designed and edited the manuscript. Payam Tabarsi wrote the manuscript and helped with the draft design.

Financial Disclosure

The authors have no conflicts of interest.

Funding/Support

The Authors did not receive any financial support.

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