A Review of Drug-resistant Tuberculosis, Risk Factors and TB Epidemiology and Incidence in Sistan and Baluchestan Province

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Abstract: Mycobacterium tuberculosis is known as the most prevalent of mortality due to infection even with tuberculosis (TB) control programs. TB drug resistance has evolved and produced different strains of TB against numerous antimicrobial drugs, which has led to an increase in mortality. Resistant to Isoniazid and Rifampin is called multi-drug resistant TB (MDR-TB). And the resistant isolates to both first- and second-line antimicrobial factors have been recognized as extensively drug-resistant TB (XDR-TB). More than 90% of prevalence TB and its mortality occur in developing countries. Sistani and Baluchistan province has a high TB prevalence due to its proximity to Afghanistan and Pakistan.

The aims of this review are investigating of the drug-resistant tuberculosis and risk factors related to TB. Also, treatment and epidemiology of the XDR-TB as a new challenge in TB control are described. And then epidemiology and incidence of TB are investigated in Sistan and Baluchestan Province.

The main risk factors are previous treatment, age, HIV, male sex, alcoholism, smoking, poor socioeconomic, immigration and diabetes mellitus. To achieve success treatment and prevention of drug-resistant TB following World Health Organization (WHO) treatment guidelines extremely suggest.

Due to the neighborhood of Iran with two countries Afghanistan and Pakistan that are among most polluted countries in the world, the more attention to this disease is strongly needed.

To achieve the goals of the WHO, timely discovery and effective treatment of patients in each country, such as TB screening for exposed people and new methods of diagnosis and treatment of TB are needed.

Keywords: MDR-TB, XDR-TB, Tuberculosis, Risk Factors, Drug-resistant.

1. INTRODUCTION

Mycobacterium tuberculosis is known as the most prevalent of mortality due to infection even with tuberculosis (TB) control programs. About 9 million people die each year from

active infections and about 2 million dies from TB complications and every country is at risk of this disease.[1].

Uni-drug resistant TB has been known. Fortuitously, the common usage of direct treatment and multiple drugs for controlled active infections have a significant effect on reducing mortality [2, 3]. However, drug resistance has evolved and produced different strains of TB against numerous antimicrobial drugs, which has led to an increase in mortality[4].

The disease because of the strains of Mycobacterium tuberculosis that are resistant to Isoniazid and Rifampin is called multi-drug resistant TB(MDR-TB), which causes many deaths annually[5]. The MDR-TB is highly prevalent in many developing countries that lack relevant lab equipment and characteristic sources. Approximately two-thirds of the global duty of MDR-TB is imagined to happen in Russia, China, and India [6]. Since the MDR-TB development in the 1990s, the TB-resistance pattern has proceeded to develop, and resistant isolates to both first- and second-line antimicrobial factors have been recognized as broadly drug-resistant TB (XDR-TB). The XDR-TB was initially announced in November 2005. The US National TB Surveillance System (NTSS) reprinted further accurate information and introductory data from the originally announced reason for XDR-TB in 2006. By October 2006, the WHO convened an Emergency Global Task Force on XDR-TB [6].

Improper use of antimicrobial drugs to treat drug-sensitive tuberculosis as well as uncontrolled tuberculosis programs can lead to drug resistance, according to the Food and Drug Administration (WHO). In other words, inappropriate doses and therapeutic regimens are generally not completed, and generally in cases where TB controls programs are poor [7-9]. MDR-TB and XDR-TB epidemics are able to be created by three mechanisms:

1. Obtained resistance: the transformation of pan-susceptible strain to resistant strain.
2. Amplified resistant: enhancing the progress of resistance of drug-resistant strains caused by unsuitable chemotherapy.
3. Transmitted resistance: transmission of drug-resistant strains[10].

Amongst the discussed mechanisms, transmitted resistance is the main cause of the increase of XDR-TB quantities that has been displayed in Tuberculosis outbreaks [11]. For example 39 (25%) of 46 isolated XDR-TB strains in the Tugela ferry outbreak in South Africa Owned by one strain [12]. Hence in a study in Iran, all XDR-TB cases Owned by 1 of 2 epidemiological bunches include a single-family bunch (4 cases) and a bunch of alike contacts (8 cases) [13]. The transference of drug-resistant TB is related to a virulent organism[14, 15].

Around three decades ago, it had been revealed that INH-mono-drug resistant TB had a low procreative ability, although newly it has been revealed that compensatory deviation had returned the low procreative ability of the microorganism[16, 17]. The prevention of M. tuberculosis transmission-related to a correct and speedy determination, [18] the currently possible diagnostics are the compound of old and new technologies [11] in current years, series of speedy analyses have been introduced to the market. The benefit of speedy analyses is their potential for sputum smear[19, 20].

By utilizing these rapid analyses, the effects of the drug-susceptibility analysis will be reached in less than one week contrasted to the standard way that takes 30 - 60 days to see the outcomes[19, 20].

Additionally, increasing drug resistance TB can be related to migration, poverty, HIV infection, age, ethnic conflict and poor performance of government. These factors may cause TB drug resistance development. Therefore, controlling and identifying of these related factors can help to drug resistance TB treatment.

More than 90% of TB cases and deaths occur in developing countries, according to WHO experts, about 1,000 million people will develop new TB infections and 150 million of them will die. But using of current control method can reduce Patients with TB. To achieve the goals of TB control, activities that lead to timely discovery and effective treatment of patients in each country and province should be incorporated into TB control strategies[21].

The aims of this review are investigating of the drug-resistant tuberculosis and risk factors related to TB. Also, treatment and epidemiology of the XDR-TB as a new challenge in TB control are described. And then epidemiology and incidence of TB are investigated in Sistan and Baluchestan Province.

Causes of TB Drug Resistance

The TB drug resistance can genesis because of lack of access to medication and treatment in some parts of the world, non-awareness of free disease treatment, relatively poor intensive care of patients in some cases, negative attitudes of some communities towards TB and their exclusion in some case cause to hide of the disease and not being treated. Patients' ignorance or lack of knowledge about the disease and its transmission or treatment, Patients' problems with access to clinics and medication and et cetera.

Drug-related factors include inadequate drug quality and supply, or inappropriate drug availability, inadequate drug storage conditions, failure to provide appropriate medication by the unit responsible for treating the patient, and time lag in treatment. In some case dereliction in personnel operation such as not educating the patient and their families about the disease, absence of appropriate national guidelines for treatment, negligence of guidelines by therapists, inadequate education in personnel, lack of monitoring patients, credit problems in controlling tuberculosis, weakness in informing people about diagnosis, transmission, and treatment, can cause to drug resistance TB[22].

Clinical Era

MDR TB patients had stronger clinical results Compared with XDR-TB patients. Mortality was lower in MDR TB patients than in XDR TB patients. Isoniazid, a powerful lethal mycobacterial, effective in early sputum conversion and reduces tuberculosis transmission, is used to treat latent TB infections (LTBI). Rifampin, which prevents relapses and promotes sterilization and is an important factor in the treatment of TB, is a very effective mycobactericidal agent[23].Treatment with resistance to either of these agents is challenging and results in less success with first-line drugs and requires second-line drugs[23].

Second-line drugs are in the second line of treatment because of their lower availability and more toxicity. Second-line drugs are not suitable for short-term treatment because they require longer-term use in addition to those listed above, making them difficult to use in areas where they are most needed [23].

Second-line factors are 5 to 8 times further possible to neglect than first-line factors. Tuberculosis XDR (XDR-TB) appears with ineffective MDR-TB treatment through poor efficacy or longer and more toxic treatments. Proper management of TB control programs is important to prevent the major development of MDR-TB and reduce the appearance of XDR-TB because XDR-TB is resistant to first- and second-line drugs and therapeutic choices are confined [24].

The mortality rate of an XDR-TB patient infection is reported to be around 14% - 20% percent [25].

TB Treatment

The methods of treating drug-resistant TB are as follows:

1. Standard treatment

2. Individual treatment

The standard treatment will be created by representative drug susceptibility analyses of society. Yet the individual treatment is according to patient's DST results[11, 26] the individual treatment requires DST outcome to first and second-line drugs and need satisfactory drug stocks[27, 28].

Various studies have shown that the standard regimen for the treatment of XDR-TB patients is less potent than the individual regimen [29, 30] and its success rate is only 41%, while the success rate of patients on the individual regimen is above 60%[28]. Therefore, individual treatment based on patients' history and drug sensitivity pattern is proposed. The planning rules regimen for these patients is equal to MDR-TB treatment[26].

Selecting a useful Floroquinolon is necessary. Prescription of later generations of Quinolone like Moxifloxacin and Levofloxacin is suggested. Proper injectable factors requirement be considered in the regimen. Cross-resistance among Kanamycin and Amikacin must be considered. Drugs such as Cyclocerine, Proth-ionamide, and PAS necessity be involved in regimen according to DST[26, 28, 30]. To treat these patients, drugs like Clofazimin, Linezolid and Co-Amoxiclave are usual options; conclusively we should have at last four practical drugs.

Be sure to consider two drugs in group five of **Table 1** for a regimen with less than four effective drugs. The entire drug quantity will depend on the level of doubt and regimens that frequently include 5 – 7 drugs[26, 28, 30].

Table 1: Rational Classification of Anti-TB Drugs[30]

Group 1: First-Line Oral Agents	**Group 2: Injectable Agents**	**Group 3: Fluoro quinolones**	**Group 4: Oral Bacteriostatic Second-Line Agents**	**Group 5: Agents With Unclear Efficacy**
Isoniazid (H)	Kanamycin (Km)	Ofloxacin (Ofx)	Ethionamide (Eto)/Protion- amide (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)

Risk Factors Influencing Development of Drug Resistance

1. Previous Treatment

Previous treatment is a significant risk factor for drug resistance to induce (especially MDR-TB). [31, 32] Frequently, High resistance rates are seen among previously treated cases because drug resistance is a powerful risk factor for repeated TB.[31]

The WHO/IUATLD working group for anti-TB drug resistance reported a prevalence of initial MDR of 1.4% and obtained resistance of 13% in previously treated patients[33]. Accordingly, the currency of MDR-TB is higher in patients who have already been treated. The midpoint combined currency of MDR-TB is 2.2%.[33]

The high rate of obtained resistance is confirmed with previous ineffectual treatment. There are a number of reasons for inadequate treatment, including Irregular or inadequate treatment, Lack of infection control in the hospital, unsupervised treatment, and inappropriate treatment regimens [31, 34, 35].

Immigration

In some countries, migration has been recognized as one of the factors contributing to the increase in TB resistance, including inadequate access to health care and poor working and housing conditions[36-38].

In specific studies,[39, 40] risk of resistance to anti-TB drugs has been published to be Three to ten times higher in foreigners than non-immigrant communities. In a different study,[41] 50% of TB cases in the immigrant community had isolates that were resistant to the minimum one of the standard five drugs, and almost 17% were MDR-TB.

Age

Age is associated with drug resistance separately. People between the ages of 45 to 65 are suffering from MDR-TB. [32]

Faustini et al. discovered that MDR-TB was more probable in patients under 65 years, but the relationship was weak and more independent in patients under 45.[42] Another study managed by Espinal et al. detected that MDR-TB was more common amongst the age group 35 - 64 years old.[43]

Gender

There is no clear relationship between sex and tuberculosis. However, some studies have examined this relationship and have come to conclusions. It has been suggested that women are more in line with treatment.[42] some studies have revealed that male sex may act as a notable risk factor for MDR.[44]

Unlike MDR-TB patients, the female gender has been determined as a vital risk factor in XDR- TB patients; This is due to the late arrival of female patients to the hospital due to some specific social factors.[45]

Additional studies are suggested to completely recognize the role of gender in drug-resistant TB.

HIV

HIV infection is not an objective risk factor for the progress of MDR-TB.[32, 46] Nevertheless, HIV infection has been presented to authorities MDR-TB by supporting the risk of transmission of multidrug-resistant strains of MTB.[47-51].

Alcoholism

It has been known to heighten neglect and failure rates amongst new TB cases. Therefore, it raises the rate of MDR-TB cases.[34, 52].

Diabetes Mellitus (DM)

DM patients are likely to a higher prevalence of TB drug-resistance.[52-54]

Prevalence and Drug Resistance of TB in Sistan and Baluchestan Province

More than 90% of TB and its mortality occur in developing countries. According to WHO experts, if the current control measures are not strengthened, about 1,000 million people will develop new TB infections, and 36 million will die. To achieve the goals of TB control, activities that lead to timely discovery and effective treatment of patients in each country need to be incorporated into TB control strategies[55].

In Iran Over the past 45 years, the incidence of TB has been decreased. The studies in 2006 showed the incidence of positive sputum tuberculosis was 13% in the whole country. In 2008 incidence rate about tuberculosis, pulmonary tuberculosis, positive and negative smears was estimated 13.4, 6.7, 2.7 and 3.6% respectively. But recently investigation indicated increasing of TB prevalence[56].

Sistani and Baluchistan province has a high TB prevalence due to its proximity to Afghanistan and Pakistan. Based on the latest statistics of the health ministry, the incidence of TB in this province was 48.5%.

During the last ten years, there has been researching on the epidemiology of tuberculosis in this area done. In a five-year study in Zahedan, among 1798 patients with tuberculosis 23.2% of them have Extrapulmonary TB. Similar to most studies the lymph nodes, pleural and bone TB were the most common, respectively. Extrapulmonary tuberculosis was more common in young people (15-24 years). Out of 417 extrapulmonary TB, 33 were genital TB and the prevalence of genital TB was 4.5 times higher in men. [57, 58].

In a study of the prevalence of TB in patients less than 18 years old in 2006, extrapulmonary TB included 23% of TB cases, the most prevalent being lymph node TB, and the least prevalent being tuberculosis pericarditis. 9.7% of TB was meningoencephalitis [59, 60].

In another study, 107 patients with TB osteomyelitis were evaluated, that 86 patients had pulmonary TB concurrently and it was concluded that vertebral tuberculosis is common in south-eastern Iran and has serious complications[61]. The highest incidence of TB regardless of the nationality of patients in the Sistan and Baluchistan province, reported in Zabul[62].

According to a report of the TB and Leprosy Department of the of Health and Medical Education in 2009, the incidence of recurrence of tuberculosis was 2.4, while in 2007 it was 1.4 per 100,000. There are no exact statistics of resistant TB cases in the province, but in a study in 2009, 88 Mycobacterium tuberculosis patients were studied in Zahedan and they have evaluated for drug resistance.12% of the isolates were multidrug-resistant (MDR). However, no case of mycobacterium tuberculosis was reported.[63].

2. CONCLUSION

Considering of challenges growing about TB especially drug-resistant TB, the recognition of these challenges is very important. Also, the association between drug-resistant TB and HIV has strongly complexity effect. Therefore, to make sure success in TB treatment and resistant strains limitation, following WHO treatment guidelines extremely suggest. Development of new drug-resistant TB needs to control and prevention. This demand requiring to diagnosing risk factors and their association with drug-resistant TB.

Due to the neighborhood of Iran with two countries Afghanistan and Pakistan that are among most polluted countries in the world, the more attention to this disease is strongly needed.

To achieve the goals of the WHO, timely discovery and effective treatment of patients in each country, such as TB screening for exposed people and new methods of diagnosis and treatment of TB are needed.

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