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Extensively Drug-Resistant Tuberculosis (XDR –TB): An Overview

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ABSTRACT

On the 20th of November 1944, the first successful anti-tubercular chemotherapy was administered using streptomycin. This was followed by the invention of P-aminosalicylic acid (1949), isoniazid (1952), pyrazinamide (1954), cyclosporine (1955), ethambutol (1962) and rifampicin; 1963. Along the course the capability and power of the tubercle bacteria grew stronger feeding on the host patients, giving birth to XDR-TB. In other words, 1 out of 3 people are infected with TB, and 1 out of 8 deaths are resulted by TB infection, globally. Extensively drug resistant (XDR) TB is a global reality that threatens TB control. CDC and WHO concluded that 20% of the 17,690 strains analyzed world from 2000 to 2004 were multi-drug resistant (MDR), resistant to at least rifampicin (R) and isoniazid (H) and 2% were extensively drug-resistant (XDR-TB), that is, resistant to R and H and resistant to fluoroquinolone and one or more of the following injectable drugs: amikacin (Am), capreomycin (Cm), or kanamycin (Km). Drug resistant TB results largely from poorly managed care of TB. If first-line anti-TB drugs are misused or mismanaged, MDR-TB develops. MDR-TB needs to be treated with SLD and XDR-TB can develop when SLD are also misused or mismanaged, thus becoming ineffective. Duration of treatment for XDR-TB has not been firmly established.

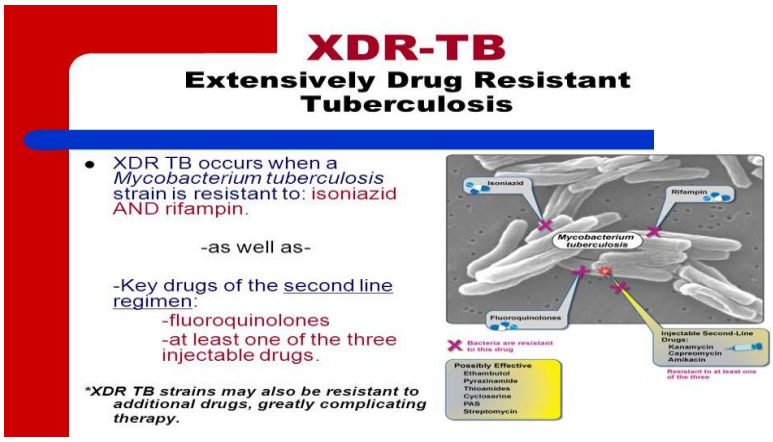
INTRODUCTION

Extensively drug resistant tuberculosis (XDR-TB) is a form of tuberculosis caused by bacteria that are resistant to some of the most effective anti-TB drugs. XDR-TB strains have arisen after the mismanagement of individuals with multi-drug resistant TB (MDR-TB) (1). Extensively drug resistant tuberculosis (XDR TB) was first described in March 2006, following a joint survey of laboratories by WHO, IUATLD, and CDC. The original definition of XDR-TB was revised at WHO Global Task Force on XDR-TB; October 2006 (2). Tuberculosis (TB) remains a major world health problem. Around two billion people are infected with *Mycobacterium tuberculosis*, the causal agent of this disease. This accounts for a third of total world population; it is estimated that nine million people become infected each year (3). One of the three people in the world is infected with TB bacteria (1). Only when the bacteria become active do people become ill with TB. Bacteria become active as a result of anything that can reduce the person's immunity, such as HIV, advancing age, or some medical conditions. TB can usually be treated with a course of standard, or first-line, anti-TB drugs (i.e., isoniazid, rifampin and fluoroquinolone). If these drugs are misused or mismanaged, multidrug-resistant TB (MDR-TB) can develop. MDR-TB takes longer to treat with second-line drugs (i.e., amikacin, kanamycin, or capreomycin), which are more expensive and have more side-effects. XDR-TB can develop when these second-line drugs are also misused or mismanaged and therefore also become ineffective (1).

Definition:

WHO –XDR-TB Task Force Committee in 2006, gave a much accepted definition of XDR_TB which defines it as "resistant to at least rifampicin and isoniazid among the first line antitubercular drugs in addition to resistant to any fluoroquinolones i.e. ofloxacin, ciprofloxacin and levofloxacin, and at least one of the three injectable second line anti-TB drugs i.e. amikacin, kanamycin and capreomycin (2). The earlier definition of XDR-TB as MDR-TB that is also resistant to three or more of the six classes of second-line drugs, is no longer used, but may be referred to in older publications (1).

Table no: 1(24)

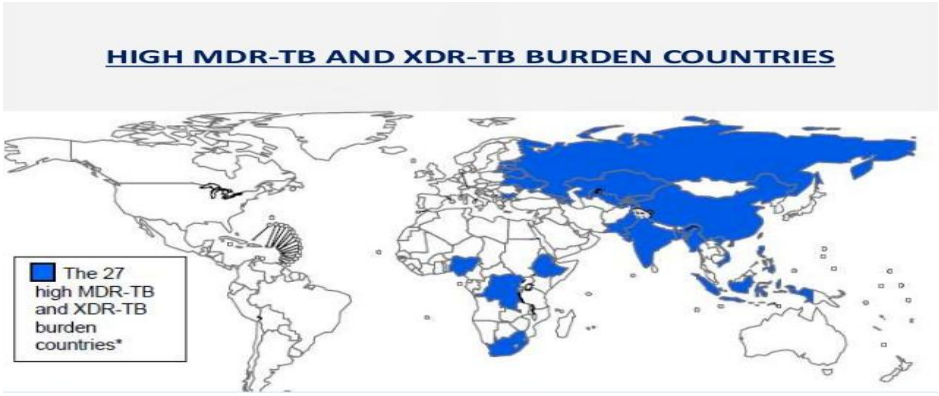


Magnitude of the XDR-TB:

Extensively drug resistant (XDR) TB is a global reality that threatens TB control. CDC and WHO concluded that 20% of the 17,690 strains analyzed world from 2000 to 2004 were multi-drug resistant (MDR), resistant to at least rifampicin (R) and isoniazid(H) and 2% were extensively drug-resistant (XDR-TB), that is, resistant to R and H and resistant to fluoroquinolone and one or more of the following injectable drugs: amikacin (Am), capreomycin (Cm), or kanamycin (Km) (3,4). The stop TB partnership estimates that around 458,000 MDR-TB cases exist. As of November 2007, 41 countries have reported confirming XDR-TB cases to WHO. In addition, population- based data from United States (for 1993-2004), Latvia (for 2000-2002) and South Korea (for 2004) showed that 4%, 19%, and15%, respectively of MDR TB cases, were XDR (4, 5).

The true scale of XDR-TB is unknown as many countries lack the necessary equipment and capacity to accurately diagnose it. It is estimated however that there are around 40,000 cases per year. As of June 2008, 49 countries had confirmed cases of XDR-TB. By 2013, that number had risen to 84 (1). In other words, 1 out of 3 people is infected with TB, and 1 out of 8 deaths is resulted by TB infection, globally (6).

Table no: 2(25)



Risk factors:

Drug resistant TB (XDR) is mainly common in people who:

- ❖ Do not take their TB medicines regularly.
- ❖ Do not take all of their TB medicines as prescribed by their doctor.
- ❖ Develop TB disease again, after having taken TB medicine in the past.
- ❖ Come from areas of the world where drug-resistant TB is common.
- ❖ Have spent time with someone known to have drug resistant TB disease (7).

Studies have found that men have a higher risk of getting XDR-TB than women. One study showed that the male to female ratio was more than three-fold, with statistical relevance ($p<0.05$). Studies done on the effect of age and XDR-TB have revealed that individual who is 65 and up are less likely to get XDR-TB. A study in Japan found that XDR-TB patients are more likely to be younger (1). Demographic and social determinants have also been increasingly identified as major risk factor for XDR-TB development. In a recent prospective study involving 1,278 patients with MDR-TB from eight countries, women were more likely to have XDR-TB. Unemployment, alcohol abuse, and smoking were additional risk factors for resistant for second-line drugs in all countries surveyed (8).

Transmission:

Like other forms of TB, XDR-TB is spread through the air. When a person with infectious TB coughs, sneezes, talks or spits, they propel TB germs, known as bacilli, into the air. XDR-TB

can't be spread by kissing, sharing food or drinks and shaking someone's hand (7, 1). The bacterium has the ability to stay in the air for several hours. A person needs only to inhale a small number of these to be infected. People infected with TB bacilli will not necessarily become sick with disease. The immune system "walls off" the TB bacilli which, protected by thick waxy coat, can lie dormant for years. The risk of spreading increases where there is a high concentration of TB bacteria, such as can occur in closed environments like overcrowded houses, hospitals or prisoners. The risk will be further increased if ventilation is poor. The risk of spread will be reduced and eventually eliminated if infectious patients receive proper treatment (1).

Symptoms:

Symptoms of XDR-TB are no different from ordinary or drug-susceptible TB: a cough with thick, cloudy mucus (or sputum), sometimes with blood, for more than 2 weeks; fever, chills and night sweat; fatigue and muscle weakness; weight loss; and in some cases shortness of breath and chest pain. A person with these symptoms does not necessarily have XDR-TB, but they should see a physician for diagnosis and a treatment plan. TB patients whose symptoms do not improve after a few weeks of treatment TB and are taking treatment should inform their clinician or nurse (1). Symptoms of TB disease in other parts of the body depend on the area affected (7).

Diagnosis:

The definition of XDR-TB relies on two main considerations: the capacity of currently available laboratory tests to reliably detect *in vitro* resistance of *M. tuberculosis* to rifampicin, isoniazid, fluoroquinolones, and injectable drugs, from one side, and the demonstration that patients bearing XDR-TB strains have a prognosis that differs from that of MDR-TB cases (8). Successful diagnosis of XDR-TB depends on the patient's access to quality health-care services. If TB bacteria are found in the sputum, the diagnosis of TB can be made in a day or two, but this finding will not be able to distinguish between drug-susceptible and drug-resistant TB. To evaluate drug susceptibility, the bacteria need to be cultivated and tested in suitable lab. Final diagnosis in this way for TB, and especially for XDR-TB, may take from 6 to 16 weeks (1). The original method used to test for MDR-TB and XDR-TB was the Drug Susceptibility Testing (DST). DST is capable of determining how well four primary anti-TB dugs inhibit the growth of *M. tuberculosis*. The four primary anti-TB drugs are Isoniazid, Rifampin, Ethambutol and

Pyrazinamide (1). XDR-TB is also detected by secondary test, known as Bactec MGIT 960 System. Although Bactec MGIT 960 system was accurate, it was still slow at determining the level of resistance. Some studies have found an in-house assay that could rapidly detect resistance to drugs involved in definition of XDR-TB directly from smear- positive specimens. The assay is called Reverse Line Blot Hybridization Assay also known as RLBH (1).

Reasons for XDR-TB:

- Erratic use of 2nd line drugs moreover poor quality drugs.
- Use of poor quality 2nd line drugs.
- Lack of experience and skill to manage drug resistant TB.
- Factors linked to poor control practices.

Mechanism of resistance in XDR-TB:

1. Conversion of wild type pan-susceptible strains to drug resistant strains during treatment (acquired resistance).
2. Increasing development of resistance in drug-resistant strains because of inappropriate chemotherapy (amplified resistance).
3. Transmission of drug resistant cases (transmitted resistance) (2).

Resistance determinants:

Antibiotic resistance in *M. tuberculosis* develops primarily through mutations in chromosomal genes. *M. tuberculosis* lacks plasmids, has a low recombination rate and contains a unique, impermeable cell wall that prevents horizontal transfer of resistance genes. Rifampin resistance occurs in 95% of cases through nucleotide substitutions in an 81-bp core region of *rpoB,* the beta-subunit of DNA- dependent RNA polymerase. INH resistance is more complicated and can be mediated by mutations in several genes, including *katG* (40-60% of the time), *inhA, ahpC, oxyR, kasA, furA*. The mechanism of INH resistance is unknown in 10-15% cases. High-level FQ resistance occurs in more than 90% of cases via mutations in the quinolones resistance-determining region of the gyrA gene that encodes a DNA gyrase. Low-level FQ resistance in the absence of *gyrA/B* mutations occurs rarely but has been observed (4).

Management:

Drug resistant TB results largely from poorly managed care of TB. If first-line anti-TB drugs are misused or mismanaged, MDR-TB develops. MDR-TB needs to be treated with SLD and XDR-TB can develop when SLD are also misused or mismanaged, thus becoming ineffective (5). Duration of treatment for XDR-TB has not been firmly established. Treatment of XDR-TB should include agents that the strains of *M. tuberculosis* have proven to be susceptible to any first line agents. It is also necessary to get a surgical treatment if clinically significant parenchymal lung disease is localized and high-grade resistance is present (2). Promising new compounds with high potency against *M. tuberculosis* include a diarylquinoline compound (R207910 also called TMC207) and two nitroimidazole compounds (PA-824 and OPC-67683). Tuberculosis vaccines are also currently being tested which might serve immunotherapeutic agents to accompany TB drug regimens (2). For second line therapy, many basic facts regarding drug-drug interactions, toxicities, achievable drug levels, and drug metabolism remain to be determined in HIV co-infected individuals to ensure that the treatment options currently available are applied optimally and provide acceptable efficacy (9).

Treatment of XDR-TB:

The principles of treatment for MDR-TB and for XDR-TB are the same. Treatment requires extensive chemotherapy for up to two years. Second-line drugs are more toxic than the standard anti-TB regimen and can cause a range of serious side-effects including hepatitis, depression, etc. Patients are often hospitalized for long periods, in isolation. In addition, second-line drugs are extremely expensive compared with the cost of drugs for standard TB treatment (10,1). Successful outcomes depend on a number of factors including the extent of drug resistance, the severity of the disease and whether the patient's immune system is compromised. It also depends on access to labs that can provide early and accurate diagnosis so that effective treatment is provided as soon as possible (1).

TB prevention and adjuncts to therapy:

The largest potential impact on TB control would come from effective vaccines to prevent all forms of TB. Combining chemotherapy with various with various vaccines has the theoretical

potential to contribute to the increased effectiveness of drug regimens, to provide alternative strategies for limiting the duration of infectiousness of patients with TB (9).

Steps to control XDR-TB: (Global XDR TB Task Force Meeting. Oct 9, 2006.)

- ✓ Strengthen basic TB and HIV/AIDS control, to avoid creation of MDR-TB and XDR-TB.
- ✓ Scale up programmatic management of MDR-TB and XDR-TB.
- ✓ Strengthen laboratory services for adequate and timely diagnosis of MDR-TB and XDR-TB.
- ✓ Expand MDR-TB and XDR-TB surveillance.
- ✓ Introduce infection control, especially in high HIV prevalence settings.
- ✓ Strengthen advocacy, communication and social mobilization.
- ✓ Pursue resource mobilization at global, regional and country levels (11).

XDR –TB in India:

WHO has recognized 58 countries, including India, in which XDR-TB has been detected (12, 13). The number of XDR-TB formally reported by India's Revised National TB Control Programme (RNTCP) to WHO is just one. That particular case was actually detected sometime between 1999 and 2003 in Chennai (Tamil Nadu State) (12, 14). Treatment of TB by community-based medical practitioners often do not conform the recommended regimen; also many patients interrupt or discontinue treatment. This sets the stage for emergence of MDR-TB and XDR-TB in India (12, 15). Addressing XDR-TB in India will be formidable challenge. Many patients with MDR-TB have been documented to have non-standard treatment regimen in the past (16, 20) or had repeatedly defaulted on treatment (12). The strategy of RNTCP has been minimized the development of MDR-TB by standardized drug regimens and consequently reduce the emergence of XDR bacilli. Guidelines to fully integrate DOTS and DOTS-Plus (diagnosis and treatment of MDR-TB) have already been brought out by RNTCP (12-23).

CONCLUSION

By referencing the sources mentioned below and reviewing papers, we come across to the fact that Extensively Drug Resistant Tuberculosis is still increasing at very high rate. Till today, many reviews on tuberculosis drug resistance in *M. tuberculosis* were published. Extensively Drug Resistant Tuberculosis is major global concern. We should apply the latest techniques and

findings related to XDR-TB in order to decrease the mortality rate. Overall, the emergence of XDR TB is reminder that TB control globally needs a massive commitment by scientific, political and financial authorities. If new TB drugs and rapid diagnostics are not developed and implemented shortly, XDR –TB will be an expanding fraction of TB cases. Core TB control measures include consistent use of DOTS, isolation of infectious XDR patients and use of timely and effective treatment regimens.

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