Dis Mol Med 2013;1: 72-76

disease & molecular medicine

Disease and Molecular Medicine

www.dismolmed.org

OPEN ACCESS

Review Article

Multi Drug Resistant (MDR) and Extensively Drug Resistant (XDR) Tuberculosis

Salih Cesur

Received: August 22, 2013
Accepted: January 06, 2014

Dis Mol Med 2013;1: 72-76
DOI:10.5455/dmm.20140106032100

Key words: *Multidrug resistant (MDR) tuberculosis, extensively drug resistant (XDR) tuberculosis, epidemiology, diagnosis, treatment, prevention*

Abstract

Multi drug resistant tuberculosis (MDR-TB) is defined as tuberculosis that is resistant to at least isoniazid and rifampicin, the two most powerful first-line anti-TB drugs. Extensively drug resistant tuberculosis (XDR-TB) is defined as tuberculosis that is resistant to resistant to isoniazid and rifampin and to any fluoroquinolone and at least one of three injectable second-line drugs (namely, amikacin, kanamicin, or capreomycin). MDR-TB and XDR- TB are great dangers that threaten the public health. XDR-TB has been reported from many countries including the United States. In Turkey, among newly diagnosed cases, it was reported that the number of MDR-TB patients was 101 (3.1%), MDR-TB rate in the retreatment cases was 17.7% (90 patients), and MDR-TB rate in all cases was 5.1 (191 patients) in 2005. The percentages were calculated through the number of patients who were tested in terms of susceptibility for both isoniazide and rifampin. In 2009, it was reported that the number of MDR-TB patients was 99 (2.7%) among newly diagnosed cases, it was 123 (20.5 %) in the retreatment cases and the total number of MDR-TB cases was 222 (5.1%). The first patient with XDR-TB was identified in 2010 in Turkey. Diagnosis of XDR TB takes several weeks by using conventional culture-based methods, although (however) some molecular test can detect it rapidly. Treatment of XDR-TB patients is difficult and usually requiring at least 18-24 months of four to six second-line anti-TB drugs. The success rate with the treatment is about 30-50%, and mortality rate is higher in HIV-infected patients. Prevention of contact to XDR-TB patients is more complicated by the lack of a proven effective preventive treatment for XDR latent tuberculosis infection. Rapid diagnostic tests and new anti-TB drugs are needed to control the spread of this worldwide public health problem.

Introduction

One third of the world population is infected with tubercle bacillus. Almost 9 million new cases of tuberculosis are seen each year (1). There have been two big problems about controlling tuberculosis in recent years. One of them is high prevalence of HIV infection that is seen in tuberculosis patients especially in the specific geographic regions like Saharan Africa, the other one is the increase in anti-tuberculosis (anti-TB) drug resistance. These issues cause failure in treatment of tuberculosis, increased mortality rate, prolonged treatment time and increased treatment costs. In recent years, extensive drug-resistant tuberculosis (XDR-TB) has been reported from many countries and became a global threat. World Health Organization (WHO) reported that about 3.7% of new cases and 20% of previously treated cases have multidrug-resistant tuberculosis. It has been reported that 9-32% of new patients and more than 50% of previously treated patients have MDR-TB in Eastern Europe and Central Asia (2-5)

In South Africa in 2006, it was reported that there

Author affiliation: *Ankara Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey*
Correspondence to: *scesur89@yahoo.com (S.Cesur)*

was XDR-TB epidemic in HIV infected patients. Following this report, 84 countries in the world have been reported at least one case of XDR-TB in 2011 (5). MDR-TB and XDR-TB are very important public health problem that emerges as a result of inadequate treatment of tuberculosis and/or poor airborne infection control in health care facilities and community.

MDR/XDR-TB is a case that needs to be considered vitally in tuberculosis control due to the factors such as the facts that the prognosis is poor, treat cure rates are low, mortality rates are high, patients' adherence to treatment is low, the duration of treatment is long and the cost of treatment is high. As MDR/XDR-TB patients need to take medication for a long time, it undermines patient compliance and raises the rates of drug side effects and toxicity. Therefore, MDR/XDR patients should be closely monitored. There is a need for an urgent action plan for MDR/XDR-TB control (6).

Definitions

MDR TB is defined as TB caused by Mycobacterium tuberculosis strains (MTB) that is resistant to at least two major anti-TB dry including isoniazid and rifampin . XDR-TB is defined as disease caused by M. tuberculosis with resistance to at least isoniasid and rifampin, any fluoroquinolone, and at least one of three injectable second-line drugs (i.e, amikacin, kanamycin , or capreomycin).

In the beginning of 2000s, Central for Disease Control and Prevention (CDC) has reported that MDR-TB strains were also resistant to several second line anti-TB drugs. About 10 % of MDR-TB strains were also resistant to three classes of second line anti-TB drugs. WHO has also reported that about 9% of MDR-TB cases have resistance to two other classes of tuberculosis drugs, or XDR-TB (5-9).

Epidemiology

The major risk factor for the presence of MDR-TB or XDR-TB is a history of prior anti-tuberculosis treatment. XDR-TB generally occurs due to the inadequate and ineffective treatment of MDR-TB. Drug resistant tuberculosis can be transmitted from a patient to other individuals (2,5,7).

WHO reported that there were at least 1 XDR-TB cases from 77 countries all over the world until the end of 2011. WHO estimates that there are about 650,000 MDR-TB cases in the world. MDR-TB cases consist of % 1.9 of all tuberculosis cases in USA. Almost 9% of XDR-TB cases in the world are XDR-TB. XDR-TB constitutes %3 of MDR-TB cases in the USA. Forty nine XDR-TB cases were reported in US between 1993 and 2006 (2,8). The rate of XDR-tuberculosis cases was notably hight in estern Europe and Asia. The prevalence of XDR tuberculosis cases are 4%, 15% and 19% in USA, South Korea and Latvia, respectively.

The number of tuberculosis cases in sub-Saharan Africa has increased markedly in the past decade, largely as a results of HIV epidemic in this region (8-10). In a study performed by WHO/IUATLP between 1999-2002, MDR-TB rates were found to be %0.8-2.6 in sub-Saharan African region (8).

MDR-TB and XDR-TB in the World

The risk factors associated with MDR-TB are low socioeconomic status, migration and urbanization, poor living conditions (indoor pollution, malnutrition),imprisonment, specific health behavior (tobacco use, alcohol and drug abuse, diabetes), international travel, and HIV infection that are of great concern for most countries , irrespective of their burden of TB (2,5,6).

Eighty-one thousand of the estimated 440,000 primary and acquired MDR-TB cases in the world (18.4% of the global burden) are estimated to be in the WHO European Region. Fifteen of the 27 countries with high burden of MDR-TB worldwide are in this region (Armenia, Azerbaijan, Belarus, Bulgaria, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Republic of Moldova, Russian Federation, Tajikistan, Ukraine and Uzbekistan). Of all newly diagnosed and previously treated TB cases, 15 countries having world's highest rates of MDR-TB rate are located in WHO European Region. To strengthen and promote the studies that will discuss the alarming drug-resistant TB problem in WHO European Region, "The Unified Action Plan to prevent and fight against 2011-2015 WHO European Region Multi-Drug Resistant (MDR) and extensively-drug resistant (XDR) Tuberculosis" has been developed. This plan was prepared as a result of consultations across the region among representatives of 53 European Member States, experts, patients and communities suffering from the disease. The action plan was adopted at the 61st session of the WHO Regional Committee for Europe held in Baku, Azerbaijan in September, 2011. If the action plan successfully implemented; it has been expected that

the emergence of 250,000 new MDR-TB and 13,000 XDR-TB cases will be prevented, an estimated number of 225,000 MDR-TB patients will be diagnosed, at least 127,000 of them will be successfully treated and the contamination of MDR / XDR-TB will be prevented, and 120,000 lives will be saved (2,5,6).

According to the WHO 2013 Global Report, at least one case of XDR-TB was reported in 92 countries in 2012. XDR-TB is estimated to be in 9.6% of MDR-TB cases.

Epidemiology of MDR-TB and XDR-TB in Turkey

In Turkey, among newly diagnosed cases, it was reported that the number of MDR-TB patients was 101 (3.1%), MDR-TB rate in the retreatment cases was 17.7% (90 patients), and MDR-TB rate in all cases was 5.1 (191 patients) in 2005. The percentages were calculated through the number of patients who were tested in terms of susceptibility for both isoniazide and rifampin. In 2009, it was reported that the number of MDR-TB patients was 99 (2.7%) among newly diagnosed cases, it was 123 (20.5 %) in the retreatment cases and the total number of MDR-TB cases was 222 (5.1%). The first patient with XDR-TB was reported in 2010 in Turkey (11).

According to 2012 Tuberculosis Control Report in Turkey (TB Department); the rate of new MDR-TB cases was 2.7% (116 people), that of previously treated patients was 24.3% (146 people), and that of all cases of MDR-TB was 5.4% (262 people) in 2011. In 2012, the rate of new MDR-TB cases was 3.2%, that of patients receiving prior treatment was 21.8 % (140 people), and that of all cases was 5.4% (291 people) (11).

Three cases in 2010, one case in 2011, six cases in 2012 with XDR-TB were identified in Turkey. Three of these patients were born in Turkey, while the other three were born outside of Turkey. HIV positivity was not detected in any of these cases (11).

Diagnosis of XDR-TB

The diagnosis of XDR-TB base on testing of Mycobacterium Tuberculosis isolate for susceptibility to anti –TB drug. The gold standard for drug susceptibility test is agar proportion method. A major problem is that conventional methods take at least 3-4 weeks to identify drug resistance. Liquid culture method is more rapid and also reliable for first-line drugs. Besides, drug susceptibility test for fluoroquinolones and second line injectable drugs such as amikacin, kanamycin , or capreomycin are more reliable and practical.

On the other hand, the identification of MDR-TB can be available in hours by using rapid molecular methods. Mutation in the rpoB gene of Mycobacterium Tuberculosis account for greater than 95% rifampin resistance and also these mutations ensure identification of MDR-TB.

For this aim, line-prob assay for rifampin resistance test such as Geno Type MTBDR plus and real time PCR assay for rifampin resistane Gene Xpert MTB/RIF test can be used. Even though mutations in Mycobacterium Tuberculosis genes conferring resistance to many other first line and second – line drugs have been reported, they do not account for all of the drug resistance found by conventional methods (7,10). It is necessary for the quality-assured laboratory testing and laboratory surveillance for XDR-TB such as MDR-TB (12-15).

Treatment

Treatment for MDR and XDR-TB is longer (at least 18-24 months) and includes the use of second-line drugs that are more expensive and toxic, but less effective. The success rate of XDR-TB treatment is quite poor and HIV infected XDR-TB case have very high mortality rates. HIV infected XDR-TB cases should be treated with both highly active antiretroviral therapy and anti-TB drugs. Surgical resection should be considered in XDR TB cases. (5,7,9,10).

Prevention and infection control

Because of the fact that the success rates of treatment of XDR-TB patients are low, secondary protective and control measures are more important than treatment. New drug regimens that will improve compliance of MDR-TB cases should be developed and applied.

For prevention of XDR-TB cases, patients should be diagnosed correctly and treated appropriately. The major strategy for controlling and preventing XDR-TB is rapid diagnosis and early treatment for patients with tuberculosis. MDR/ XDR-TB cases should be taken to services that have proper ventilation. Contact with other patients should be minimized. XDR-TB cases should be isolated longer than drug-susceptible tuberculosis patients. XDR-TB patients must be kept in respiratory isolation until culture of sputum gets negative. For those who do not accept respiratory isolation, necessary legal measures must be taken. There is not any effective regiment for treatment of MDR/ XDR latent tuberculosis infection.

Nevertheless, contacts of patients with XDR-TB can

be evaluated for LTBI by using tuberculin skin test or interferon – gamma release assay such as Quantiferon-TB Gold test and T Spot test. Tuberculosis should be excluded with chest radiograph and symptoms of tuberculosis. Contact persons should be monitored for sign or symptom of progression to TB disease for two years following infection.

Hospitals should have an action plan for control of tuberculosis.

BCG vaccine is not effective in the prevention of XDR-TB. BCG vaccination is recommended in two situations. First, BCG vaccination should be applied for infant or child who is exposed continually to a patient with pulmonary MDR or XDR. Secondly, medical personnel who are at a high risk of contact with XDR-TB cases. WHO is actively advocating for the development of new vaccine.

People have HIV infection is at greater risk of developing TB as well as XDR-TB. Those with HIV infection, treatment with highly active antiretroviral therapy will likely reduce the risk of developing XDR-TB (7,9,10,14,15).

The strengths of the fight against MDR/XDR-TB in Turkey

Turkey has revealed strong political commitment in addressing the problem of tuberculosis by international cooperation such as the endorsement of the decisions of the Berlin Declaration and the World Health Assembly. A plan to prevent and combat MDR/XDR-TB has been created. Anti-TB drug resistance surveillance was initiated in 25 cities including Ankara, İstanbul, İzmir and Samsun. Qualified health personnel working in the field of TB prevention and control are available. Ministry of Health publishes and distributes guidelines for the diagnosis and treatment of TB.

The weaknesses of the fight against MDR/XDR-TB in Turkey

There is a limited participation of non-governmental organization including private health sector and social services. Health care workers have insufficient knowledge on tuberculosis. The coordination between TB and other programs is poor in terms of common activities (such as HIV, alcohol, drug users, etc.). Patients with TB have no financial return in terms of inpatient treatment institutions. A lack of case detection and follow-up exists in health institutions. Directly observed therapy is not applied in an effective manner. There are no policies in relation to a multidisciplinary approach to the problems of the patients (socio-economic status and poverty, unemployment, psychiatric disorders, alcoholism, and drug addiction).

Conclusion

There is a need for new approaches all over the world to be successful in the fight against drug resistant tuberculosis. Fast diagnostic tests and new anti-TB drugs should be developed. The fact that rapid and reliable tests detecting rifampin resistance have been developed is an important stage. Similar tests should be developed for fluoroquinolones and for injectable minor anti-TB, as well. Also, effective vaccines for protection should be developed. Due importance should be given to strategies for controlling and preventing tuberculosis until the new developments happen.

References

1. Nachega JB, Chaisson RE. Tuberculosis Drug Resistance: A Global Threat. Clinical Infectious Dis. 2003;36(Sup. 1):S24-S30.
2. World Health Organization. Multidrug and extensively drug-resistant TB: 2010 global report on surveillance and response. WHO/HTM/TB/2010.
3. White VLC, Moore-Gillon J. Resource implications of patients with multidrug resistant tuberculosis. Thorax. 2000;55:962-3.
4. Mahmoudi A, Iseman MD. Pitfalls in the care of patients with tuberculosis. Common errors and their association with the acquisition of drug resistance. JAMA. 1993;270:65-8.
5. Abubakar I, Zignol M, Falzon D, Raviglione M, Ditiu L, Masham S, et al. Drug-resistant tuberculosis: time for visionary political leadership. Lancet Infect Dis. 2013;13:529-39.
6. Stoffels K, Be´guec CA, Groenen G, Wanlin M, Berkvens D, Mathys V, et al. From multidrug- to extensively drug-resistant tuberculosis:upward trends as seen from a 15-year nationwide study. PLoS One. 2013;8:e63128.
7. Jassal M, Bishai WR. Extensively drug-resistant tuberculosis. Lancet Infectious Dis. 2009;9:19-30.
8. World Health Organization. Multidrug-resistant tuberculosis (MDR-TB) 2013 Update. www.who.int/tb/challenges/mdr.
9. Sharma SK, Mohan A. Tuberculosis. From an incurable scourge to a curable disease-journey over a millennium. Indian J Med Res. 2013;137:455-93.
10. LoBue P. Extensively drug-resistant tuberculosis. Curr Opin Infect Dis. 2009;22:167-73.

11. The 2012 report of fighting tuberculosis in Turkey. TC. Ministry of Health, Department of Tuberculosis, Ankara 2013. p 66-67.
12. Alanbayı Ü, Arslantürk A, Karagöz A, Şimşek H, Tarhan G, Durmaz R. Çok ilaca dirençli Mycobacterium tuberculosis izolatlarında yaygın ilaç direncinin araştırılması, 28. ANKEM Kongesi, 22-26 Mayıs , Antalya, Kongre Özet Kitabı, p.45 (Turkish)
13. Bektöre B, Haznedaroğlu T, Baylan O, Ozyurt M, Ozkütük N, Satana D, et al. Investigation of extensive drug resistance in multidrug resistance Tuberculosis isolates. Mikrobiyol Bul. 2013;47:59-70.
14. World Health Organization. Guidance on ethics of tuberculosis prevention, care and control WHO/HTM/2010.16 Geneva, World Health Organisation, 2010 www.who.int/tb/xdr12.pdf
15. Centers for Disease Control and Prevention (CDC). Emergence of M. tuberculosis with extensive resistance to second line drugs worldwide, 2000-2004. MMWR Morb Mortal Wkly Rep. 2006;55:301-5.