EXTENSIVELY DRUG RESISTANT TUBERCULOSIS (XDR-TB): AN OVERVIEW

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ABSRTACT: Tuberculosis or TB is a common and often deadly infectious disease caused by various strains of mycobacteria, usually Mycobacterium tuberculosis in humans. Tuberculosis usually attacks the lungs but can also affect other parts of the body. It is spread through the air, when people who have the disease cough, sneeze, or spit. Most infections in humans result in anasymptomatic, latent infection, and about one in ten latent infections eventually progresses to active disease, which, if left untreated, kills more than 50% of its victims. Extensively drug-resistant tuberculosis (XDR TB) is a relatively rare type of multi drug-resistant tuberculosis (MDR TB). It is resistant to almost all drugs used to treat TB, including the two best first-line drugs: isoniazid and rifampin. XDR TB is also resistant to the best second-line medications: fluoroquinolones and at least one of three injectable drugs (i.e., amikacin, kanamycin, or capreomycin). One in three people in the world is infected with dormant TB germs (i.e. TB bacteria). 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 four standard, or first-line, anti-TB drugs. If these drugs are misused or mismanaged, multidrug-resistant TB (MDR-TB) can develop. MDR-TB takes longer to treat with second-line drugs, 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. Because XDR-TB is resistant to first- and second-line drugs, treatment options are seriously limited. It is therefore vital that TB control is managed properly. This article presents a brief review of extensively drug-resistant tuberculosis with an emphasis on its various aspects associated i.e. introduction, symptoms, transmission, diagnosis, treatment, vaccines as well as prevention; the article reveals the different approaches in the management of Multi-drug resistant tuberculosis and correlation between XDR-TB as well as HIV/AIDS.

Key words: tuberculosis, drug resistance, isoniazid, rifampicin, fluoroquinolones, extensively drug-resistant tuberculosis, XDR-TB

INTRODUCTION

Tuberculosis (TB) is a bacterial infection caused by a germ called *Mycobacterium tuberculosis*. TB spreads through the air when a person with TB of the lungs or throat coughs, sneezes or talks. TB primarily affects the lungs, but it can also affect organs in the central nervous system, lymphatic system, and circulatory system among others. The disease was called "consumption" in the past because of the way it would consume from within anyone who became infected. Most infections in humans result in an asymptomatic, latent infection, and about one in ten latent infections eventually progresses to active disease, which, if left untreated, kills more than 50% of its victims. The classic symptoms are a chronic cough with blood-tinged sputum, fever, night sweats, and weight loss. Infection of other organs causes a wide range of symptoms. Diagnosis relies on radiology (commonly chest X-rays), a tuberculin skin test, blood tests, as well as microscopic examination and microbiological culture of bodily fluids. Treatment is difficult and requires long courses of multiple antibiotics. Contacts are also screened and treated if necessary. Antibiotic resistance is a growing problem in (extensively) multi-drug-resistant tuberculosis. Prevention relies on screening programs and vaccination, usually with Bacillus Calmette-Guérin vaccine.

A third of the world's population are thought to be infected with *M. tuberculosis*, and new infections occur at a rate of about one per second. The proportion of people who become sick with tuberculosis each year is stable or falling worldwide but, because of population growth, the absolute number of new cases is still increasing. In 2007 there were an estimated 13.7 million chronic active cases, 9.3 million new cases, and 1.8 million deaths, mostly in developing countries. In addition, more people in the developed world are contracting tuberculosis because their immune systems are compromised by immunosuppressive drugs, substance abuse, or AIDS. The distribution of tuberculosis is not uniform across the globe; about 80% of the population in many Asian and African countries test positive in tuberculin tests, while only 5-10% of the US population test positive (Jasmer, RM, et al, 2002).

Tuberculosis outbreaks in the developed world are newsworthy. However, in the developing world, where deaths from tuberculosis are common, it takes something exceptional for an outbreak to attract much attention. In response to a recent report at the 16th international AIDS conference and to increasing South African media reports, the World Health Organization last week expressed concern about extensively drug resistant tuberculosis (also referred to as "XDR tuberculosis")(Watson, JM, et al, 2001). Among 536 culture confirmed cases of tuberculosis at a rural hospital in South Africa, 41% were multidrug resistant, defined as resistance to rifampicin and isoniazid (two key first line drugs). This is cause enough for concern as multidrug resistant tuberculosis has a worse outcome and its management is very difficult even in high resource settings (Mukherjee, JS, et al, 2004).

EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS

Extensively drug-resistant tuberculosis (XDR-TB) is a relatively rare type of multidrug-resistant tuberculosis (MDR TB). It is resistant to almost all drugs used to treat TB, including the two best first-line drugs: isoniazid and rifampin. XDR TB is also resistant to the best second-line medications: fluoroquinolones and at least one of three injectable drugs (i.e., amikacin, kanamycin, or capreomycin).

XDR-TB is a form of TB caused by bacteria that are resistant to the most effective anti-TB drugs. Some contend that XDR-TB strains have emerged from the mismanagement of multidrug-resistant TB (MDR-TB) and once created can spread from one person to another. The exact nature of this mismanagement is not yet known, but origin of XDR-TB may coincide with the institution of new policies to promote drug compliance, such as DOTS (http://www.ncbi.nlm.nih.gov/) .

One in three people in the world is infected with TB bacteria. 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 four standard, or first-line, anti-TB drugs. If these drugs are misused or mismanaged, multidrug-resistant TB (MDR-TB) can develop. MDR-TB takes longer to treat with second-line drugs, 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. XDR-TB raises concerns of a future TB epidemic with restricted treatment options, and jeopardizes the major gains made in TB control and progress on reducing TB deaths among people living with HIV/AIDS. It is therefore vital that TB control is managed properly and new tools developed to prevent, treat and diagnose the disease. 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 have confirmed cases of XDR-TB.

TRANSMISSION OF XDR-TB

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. 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 the disease. The immune system "walls off" the TB bacilli which, protected by a thick waxy coat, can lie dormant for years.

CAUSES OF DRUG RESISTANCE AND SERIOUSNESS OF XDR-TB

Drug resistance to tuberculosis results largely from poorly managed care and control of the disease. Poor prescribing practices, low drug quality (or erratic supply), and suboptimal adherence can all contribute to this. Bacilli are subject to intense drug selection, and exposure to mono-therapy predisposes to an accumulation of mutations that confer resistance. Hence optimal treatment includes four drugs to which the organism is sensitive, and a single drug should never be added to a failing regimen. In much of the world, routine culture and sensitivity testing is not available. Thus, where multidrug resistant tuberculosis emerges, inappropriate treatment regimens may lead to serial acquisition of resistance mutations, with potential for emergence of extensively drug resistant tuberculosis. Widespread use of second line tuberculosis drugs (such as quinolones for respiratory tract infections) may also contribute to the development of resistance. Thus, the emergence of extensively drug resistant tuberculosis should come as no surprise it was entirely predictable in the context of poor control practices. Because XDR TB is resistant to the most powerful first-line and second-line drugs, patients are left with treatment options that are much less effective and often have worse treatment outcomes. XDR TB is of special concern for persons with HIV infection or other conditions that can weaken the immune system. These persons are more likely to develop TB disease once they are infected, and also have a higher risk of death once they develop TB disease.

The havoc that institutional transmission of multidrug resistant tuberculosis can wreak amongst HIV infected people was evident in the US in the early 1990s (Frieden, T, et al, 1993). The very modest actual rise in the incidence of tuberculosis that coincided with these outbreaks has now been reversed (Sweeden, R, et al, 2004), albeit with extraordinary effort and cost. However, the huge potential for extensively drug resistant tuberculosis to further undermine control practices in communities in South Africa and elsewhere in the region is self evident and would be much more difficult to control. In some communities with an antenatal prevalence of HIV of 30%, annual notification rates for tuberculosis have already increased uncontrollably over the past 10 years, reaching 1500/100 000—a rate more than 250 times higher than rates in the US(Lawn, SD, et al, 2006). Extensively drug resistant tuberculosis must now serve as a serious wake-up call. Although the potential consequences may be most grave in settings with a high prevalence of tuberculosis and HIV, extensively drug resistant tuberculosis is nevertheless already a very serious development in many other parts of the world too.

WHAT RESPONSE IS NEEDED?

The global scale and molecular epidemiology of extensively drug resistant tuberculosis require urgent assessment, and laboratory capacity needs to be greatly increased within a network of sentinel sites. Control practices must be rigorously and effectively implemented. Increasing cure rates for tuberculosis through directly observed treatment short course (DOTS) is crucial.

Detection rates for cases of tuberculosis need to be improved, highlighting the need for a new diagnostic test. Technologies that can determine the presences of drug resistance at the point of care are needed, as are new drug treatments. The DOTS-Plus strategy for treatment of multidrug resistant tuberculosis needs to be further developed for areas where the disease is established. Nosocomial transmission of tuberculosis is probably commonplace in the developing world, and simple, effective strategies to reduce such transmission need to be urgently implemented. More fundamentally, the emergence of extensively drug resistant tuberculosis is a reminder that tuberculosis needs massive broader commitment: the incompletely funded Global Plan to Stop TB demands political will and financial action (Farmer, P, et al, 1998).

DIAGNOSIS AND TREATMENT OF XDR-TB

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 a suitable laboratory. Final diagnosis in this way for TB, and especially for XDR-TB, may take from 6 to 16 weeks. To reduce the time needed for diagnosis, new tools for rapid TB diagnosis are urgently needed. 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 and hallucinations. Patients are often hospitalised for long periods, in isolation. In addition, second-line drugs are extremely expensive compared with the cost of drugs for standard TB treatment. XDR-TB is associated with a much higher mortality rate than MDR-TB, because of a reduced number of effective treatment options. Despite early fears that this strain of TB was untreatable, recent studies have shown that XDR-TB can be treated through the use of aggressive regimens. A study in the Tomsk oblast of Russia, reported that 14 out of 29 (48.3%) patients with XDR-TB successfully completed treatment (Keshavjee, S, et al, 2008).

Successful outcomes depend on a number of factors including the extent of the drug resistance, the severity of the disease and whether the patient's immune system is compromised. It also depends on access to laboratories that can provide early and accurate diagnosis so that effective treatment is provided as soon as possible. Effective treatment requires that all six classes of second-line drugs are available to clinicians who have special expertise in treating such cases.

PREVENTION AND TB VACCINES

Countries aim to prevent XDR-TB by ensuring that the work of their national TB control programmes, and all practitioners working with people with TB, is carried out according to the International Standards for TB Care.

These emphasize providing proper diagnosis and treatment to all TB patients, including those with drug-resistant TB; assuring regular, timely supplies of all anti-TB drugs; proper management of anti-TB drugs and providing support to patients to maximize adherence to prescribed regimens; caring for XDR-TB cases in a centre with proper ventilation, and minimizing contact with other patients, particularly those with HIV, especially in the early stages before treatment has had a chance to reduce the infectiousness. Also an effective disease control infrastructure is necessary for the prevention of XDR tuberculosis. Increased funding for research, and strengthened laboratory facilities are much required. Immediate detection through drug susceptibility testing's vital, when trying to stop the spread of XDR tuberculosis. The BCG vaccine prevents severe forms of TB in children, such as TB meningitis. It would be expected that BCG would have the same effect in preventing severe forms of TB in children, even if they were exposed to XDR-TB, but it may be less effective in preventing pulmonary TB in adults, the most common and most infectious form of TB. The effect of BCG against XDR-TB would therefore likely be very limited.

New vaccines are urgently needed, and WHO and members of the Stop TB Partnership are actively working on new vaccines.

XDR-TB AND HIV/AIDS

TB is one of the most common infections in people living with HIV/AIDS. In places where XDR-TB is most common, people living with HIV are at greater risk of becoming infected with XDR-TB, compared with people without HIV, because of their weakened immunity. If there are a lot of HIV-infected people in these places, then there will be a strong link between XDR-TB and HIV. Fortunately, in most of the places with high rates of HIV, XDR-TB is not yet widespread. For this reason, the majority of people with HIV who develop TB will have drug-susceptible or ordinary TB, and can be treated with standard first-line anti-TB drugs. For those with HIV infection, treatment with antiretroviral drugs will likely reduce the risk of becoming infected with XDR-TB, just as it does with ordinary TB.

A research study titled "TB Prevalence Survey and Evaluation of Access to TB Care in HIV-Infected and Uninfected TB Patients in Asembo and Gem, Western Kenya," says that HIV/AIDS is fueling large increases in TB incidence in Africa, and a large proportion of cases are not diagnosed.

SOUTH AFRICAN EPIDEMIC

XDR-TB was first widely publicised following the report of an outbreak in South Africa in 2006. 53 patients in a rural hospital in Tugela Ferry were found to have XDR-TB of whom 52 died. The median survival from sputum specimen collection to death was only 16 days and that the majority of patients had never previously received treatment for tuberculosis suggesting that they had been newly infected by XDR-TB strains, and that resistance did not develop during treatment (Gandhi, NR, et al, 2006).
This was the first epidemic for which the acronym XDR-TB was used, and although TB strains that fulfil the current definition have been identified retrospectively (Shah, NS, 2005).

This was the largest group of linked cases ever found. Since the initial report in September 2006, cases have now been reported in most provinces in South Africa. As of 16 March 2007, there were 314 cases reported, with 215 deaths. It is clear that the spread of this strain of TB is closely associated with a high prevalence of HIV and poor infection control; in other countries where XDR-TB strains have arisen, drug resistance has arisen from mismanagement of cases or poor patient compliance with drug treatment instead of being transmitted from person to person. It is now clear that the problem has been around for much longer than health department officials have suggested, and is far more extensive.

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