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Mini Review

Extensively Drug Resistant Tuberculosis - A Global Challenge

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Abstract

Extensively Drug-Resistant (XDR) Tuberculosis (TB) is a major global health problem. With the current pace of globalization, diseases that occur locally can spread rapidly to other parts of the world, threatening national and global health security. In 2013, an estimated 480,000 cases of Multidrug Resistant (MDR) Tuberculosis (TB) were reported; approximately 10% of people with multidrug resistant TB (MDR-TB) have extensively drug-resistant TB (XDR-TB). In countries in Eastern Europe and Southeast Asia, XDR-TB affect up to 15% of persons with MDR-TB. Unfortunately, many of the high TB-burdened countries have large socio-economically vulnerable populations including women and children. Additionally, many countries where TB is endemic do not have adequate laboratory capacity for extensive and rapid drug-susceptibility testing. Furthermore, little success has been achieved in terms of treatment of XDR-TB. These add to the challenge of global TB control in many resource-challenged countries. This article reviews the epidemiology of XDR-TB, common risk factors, current trend and challenges in the management of XDR-TB.

Keywords: Extensively drug resistant tuberculosis; Multidrug resistant tuberculosis; Global health security; Vulnerable populations

Introduction

Extensively Drug-Resistant Tuberculosis (XDR-TB) is a form of multidrug resistant tuberculosis in which Mycobacterium Tuberculosis (Mtb) strains are resistant to the first-line anti-TB drugs, isoniazid and rifampicin, at least one fluoroquinolone, and a second-line injectable such as amikacin, capreomycin, or kanamycin [1]. The emergence of XDR-TB threatens global health security and offsets the progress made in reducing the incidence of TB worldwide [2]. For example, XDR-TB now affects over one hundred countries, compared with 83 countries that were reported by the World Health Organization (WHO) in 2013 [2,3]. The rising prevalence of XDR-TB is primarily due to inappropriate TB treatment [4]. Other risk factors that have been reported in the scientific literature include poor adherence to previous anti-TB regimen, poverty, and HIV coinfection [5,6]. Rapid detection and treatment of XDR-TB is crucial in controlling the spread of the disease. However, TB surveillance coverage is still a challenge especially in many high TB burden countries [2]. Facilities for drug susceptibility testing are not readily available and the development of more efficacious anti-TB drugs is slow. For these reasons, it is important to prioritize strategies that focus on effective TB surveillance, timely diagnosis of drug resistance, rapid development of new antiTB drugs, and strengthening of health systems. This review aims to highlight important aspects of the epidemiology, risk factors, current trend and challenges in the management of XDR-TB.

Epidemiology of drug-resistant tuberculosis

In 2013, an estimated 480,000 new cases of MDR-TB were reported globally, despite the poor TB reporting practice in some countries. Over 50% of these cases occured in the Russian Federation, India, and China [3]. Approximately 10% of people with MDR-TB have XDR-TB, and XDR-TB has affected over 100 countries to date [2]. In European Union countries, XDR-TB accounts for an estimated 10-15% of persons with MDR-TB. Of these, an estimated 70% of MDR-TB cases are not successfully treated including failed treatment and those who stop treatment; hence increasing the risk of XDR-TB emerging [7]. Per economic impact, the 2015 Global Tuberculosis Report showed that the cost of treating XDR-TB per patient ranged from approximately US$ 7,000 in low-income countries (e.g. Uganda, a high TB-burden country with a gross national income per capita of US$ 681.5) to US$ 21,000 in upper middle-income countries (e.g., South Africa, a high TB-burden country with a gross national income per capita of US$ 6,754) [2,8,9].

Although global efforts targeted at reducing the burden of TB has reported some success, mortality from the disease is still a concern. Approximately 210,000 deaths from MDR-TB were reported in 2013. The term XDR-TB was first introduced in 2006 following a global survey by the World Health Organization (WHO) and the Centers for Disease Control (CDC) which found XDR-TB cases had spread to all regions of the world. For instance, while cases are prevalent in Eastern Europe and Southeast Asia, the largest global outbreak of XDR-TB Extensively Drug-Resistant (XDR) Tuberculosis (TB) occurred in Tugela Ferry, a town in KwaZulu-Natal Province, South Africa where HIV is prevalent [10,11]. Data from the outbreak showed that 221 out of the 544 patients studied had MDR-TB. Of these, 53 had XDR-TB; 44 were tested and all had HIV. Within an average of 25days, 52 of the 53 XDR-TB patients died. The high case-fatality rate of the Tugela Ferry-outbreak underscores the need for a comprehensive approach for the prevention, early identification of risk factors and comorbidities, diagnosis, and treatment of persons with XDR-TB, including all form of TB.

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Risk factors and drug-resistance pattern

XDR-TB can occur in the setting of inadequate clinical care or drug management such as the use of inappropriate drug regimen or duration of treatment, prescription of sub therapeutic doses, lack of proper patient support or poor compliance, and the use of poor quality drugs [6,12]. In a recent study, failure to offer standardized treatment regimen to patients with MDR-TB was linked to the evolution of XDR-TB in South Africa [13]. Another epidemiological study found that XDR-TB was associated with inadequate treatment of TB patients in a tertiary health care facility in South Korea [14]. Other risk factors for XDR-TB include presence of bilateral and cavitary lesions among MDR-TB patients, young age, smoking, living in an area with a high prevalence of drug-resistant TB, occupational exposure (e.g. working in a TB clinic), history of incarceration, immigration, alcoholism, HIV coinfection and previous intake of second line injectable drugs have also been reported as risk factors for XDR-TB [5,6,15]. In a study conducted in India, socioeconomic status, concurrent illness and family history of TB were among risk factors associated with occurrence of XDR-TB [16].

Drug resistance pattern studies suggest a higher likelihood of resistance to the first-line drugs isoniazid, streptomycin, and rifampicin. For instance, a study assessing pattern of drug resistance in isolates of Mtb obtained from persons with TB in northeastern China found the highest resistance was to Isoniazid (18.2%) followed by streptomycin (13.9%) and rifampicin (11.3%), ofloxacin (7.7%), ethambutol (7.1%), and kanamycin (4.2%) [17]. The result of this study is similar to those conducted in Ethiopia (East Africa), India (Southeast Asia), and other parts of the world [10,18]. Knowledge of the risk factors and drug resistance pattern of TB are particularly useful in the management of XDR-TB especially in resource-challenged settings where TB testing facilities are limited. Despite the challenges of TB testing in many countries, however, early detection of drug resistant TB is crucial for proper treatment and prevention of the spread of XDR-TB.

Drug-resistant tuberculosis testing

Antimicrobial drug susceptibility testing is required to confirm the diagnosis of XDR-TB. WHO recommends that all patients with MDR-TB should be tested for susceptibility to fluoroquinolones and second-line injectable agents in order to determine if they have XDR-TB. However, conventional laboratory tests for determining drug susceptibility require extensive laboratory procedures that are often time consuming. Because conventional testing can take weeks to months, there is a shift towards faster molecular tests such as Xpert MTB/RIF and line probe assays [19]. While these tests are able to detect isoniazid and rifampicin resistance with a higher accuracy within a short time, usually two hours, they produce inconsistent susceptibility results for other first-line anti-TB agents (i.e. streptomycin, ethambutol and pyrazinamide) [19].

This unique challenge underscores the importance of epidemiological information on TB drug resistance pattern in the management of XDR-TB. It is worth noting that Mtb strains that are resistant to rifampicin are likely to also be to isoniazid; hence, rifampicin resistance suggests MDR-TB. Overall, it is recommended that national programs on TB should have the ability to perform sensitivity tests for isoniazid and rifampicin and use epidemiological data to inform clinical decision-making regarding second-line anti-Tb agents [20].

Treatment

The treatment of XDR-TB remains a challenge and clinical outcomes are often poor. In the 2015 Global Tuberculosis Report, only 26% of 2,685 patients with XDR-TB globally completed treatment; 30% died and 19% had failed treatment. Current therapeutic options for the treatment of XDR-TB are usually individualized and mostly given as part of a trial or under research conditions. Each treatment often involves combining a number of antiTB drugs which are sometimes given for longer periods in some patients. This approach unfortunately increases the likelihood of adverse drug effects despite minimal treatment success. According to a recent meta-analysis, treatment success in patients with XDR-TB was highest with at least six drug combination in the intensive phase and four in the continuation phase. The odds of treatment peaked when total treatment duration was 20.1-25.0 months [21]. In 2012, the United States Food and Drug Administration (FDA) approved Bedaquiline, an antimycobacterial drug that inhibits mycobacterial ATP synthetase and depletes cellular energy stores, for the treatment of adults with MDR-TB [22]. However, there was no available evidence for the use of Bedaquiline in the treatment of patients with XDR-TB. Its use in these group of patients is therefore experimental [23]. Delamanid is another novel drug registered for the treatment of drug-resistant TB. It acts by blocking the synthesis of mycobacterial cell wall components, methoxy-mycolic and keto-mycolic acid. Though little evidence is available to support delamanid-based regimens in XDR-TB, its use may be beneficial in the absence of an alternative. Delamanid may lower the need to use more toxic unproven antiTBdrug combinations in those with XDR-TB. However, caution should be taken especially when delamanid is combined with other drugs due to possible adverse effects [24]. Higher-generation fluoroquinolones such as gatifloxacin and moxifloxacin also play a role in the management of XDR-TB. Empiric evidence from a systematic review showed that the use of higher-generation fluoroquinolones was associated with significant improvement in treatment outcomes for those with XDR-TB, even though drug-susceptibility testing demonstrated resistance to a representative fluoroquinolone [25].

As part of the global effort to improve TB control, the TB Alliance in South Africa started the NiX-TB (New Investigational Drugs for XDR-TB) study in April 2015 [26]. The aim of the study was to investigate the efficacy and safety profile of bedaquiline, linezolid, and pretomanid for the treatment of patients with XDR-TB. Upon completing treatment, patients will be followed up to determine the incidence of bacteriologic failure or relapse or clinical failure [26]. The TB-PRACTECAL study funded by Medicines Sans Frontieres (Doctors without Borders) is another cutting-edge multicenter trial which will be conducted in Uzbekistan and Swaziland. TB-PRACTECAL will investigate the safety and efficacy profile of bedaquiline, pretomanid and linezolid with or without the fluoroquinolone, moxifloxacin, or clofazimine, a FDA-approved drug for the treatment of Leprosy. Overall, the less toxic a XDR-TB agent is, the more likely that patients will complete treatment. Further, novel drug regimens including new or re-purposed drugs are also being investigated. These new drugs belong to several chemical classes including nitroimidazole,

oxazolidinone, rifamycin, benzothiazinone, and diarylquinoline [27,28].

Conclusion

In summary, the fight against XDR-TB require combination tactics including effective TB surveillance systems, efficient laboratory capacity for drug susceptibility testing for early and accurate diagnosis, and the availability of less toxic, shorter duration, and affordable drugs. In addition, better approaches to manage disease in vulnerable populations especially children, should be encouraged [18]. Investment in the development of XDR-TB drug, easy access to appropriate XDR-TB care including sufficient supply of quality drugs should also be encouraged especially because TB is perceived to be rare and of lesser concern in developed countries.

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