Epidemiology of drug-resistant tuberculosis

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Summary

Multi-drug resistant tuberculosis (MDR-TB) is a man-made phenomenon and represents an important clinical and public health issue. According to the last World Health Organization (WHO) estimates, the global incidence and mortality of MDR-TB were 480,000 and 190,000 in 2014, respectively. The proportion of MDR-TB cases among new and previously treated TB cases is increasing. In particular, the percentage of MDR-TB among new cases is significantly high in some geographical settings, such as Former Soviet Union countries, as a consequence of an elevated transmission of MDR Mycobacterium tuberculosis strains in the community. The emergence and spread of MDR-TB rely on several mechanisms: the ineffective or non-implementation of the DOTS strategy, poor supply of anti-TB drugs (including the administration of poor quality medicines), poor patients’ adherence (psychiatric disorders, toxicity of the prescribed antibiotics, financial issues), pivotal role of an uncontrolled private sector.

In the last decade, more severe drug-resistant patterns have been described. Extensively drug-resistant (XDR) and totally drug-resistant (TDR; not standardized definition) TB are two difficult-to-treat TB forms. The current therapeutic approach of MDR-TB is poorly effective, toxic, and expensive. The duration of drugs’ exposure should range from 20-25 months in order to achieve a treatment success. An individual patient-data meta-analysis showed that the current treatment success rate is about 62%, with a declining rate as number of drug resistances increases (e.g., 40% for XDR-TB). New effective options are needed in the near future. The new antibiotics bedaquiline and delamanid have showed a good efficacy and tolerability profile before their market approval; however, local public health strategies are needed to preserve their long-term susceptibility.

The WHO strategies are aimed at improving the clinical and public health management, addressing all the mechanisms behind the emergence of MDR-TB.

KEY WORDS: epidemiology, tuberculosis, MDR-TB, XDR-TB, directly observed therapy.

Introduction

Tuberculosis (TB) is one of the most important clinical and public health issue worldwide. Along with HIV/AIDS and malaria it is associated with an elevated mortality. According to the estimates of the last World Health Organization (WHO) Global Report published in 2015, the estimated global TB incidence was equal to 9.6 million cases in 2014, whereas the estimated mortality was equal to 1.5 million cases (including 0.4 million deaths in HIV-positive patients) (1).

In order to address this public health threat, particularly for low- and middle-income countries, WHO designed during the last decade of the previous century a global plan named DOTS Strategy aimed at improving the clinical management of the disease and, thus, Mycobacterium tuberculosis transmission and worldwide burden (2). In particular, attention has been focused on both microbiological diagnosis and treatment standardization.

The strategy was successful but not as expected. The emergence and spread of...
HIV/AIDS as well as drug-resistant TB have changed the epidemiologic scenario (3, 4). The cohort of HIV-positive individuals with an impaired immunity represents the sub-population at highest risk of developing TB disease in case of recent or previous Mycobacterium tuberculosis infection. Furthermore, the colliding HIV and TB epidemics in sub-Saharan Africa have increased TB incidence and mortality rates (5, 6). Numerous cases of multi-drug resistant TB (MDR-TB) have been described globally. MDR-TB is a TB form caused by Mycobacterium tuberculosis strains resistant at least two of the most potent anti-TB drugs, i.e. isoniazid and rifampicin (1, 7, 8). Its treatment should rely on second-line anti-TB drugs which are more expensive, more toxic, less effective, and whose exposure should be longer in comparison with first-line anti-TB drugs (9). In order to prevent an evolving and complicated epidemiology, WHO decided to strengthen the DOTS strategy. In 2006 the WHO Stop TB strategy was published to address the new epidemiological threats and to improve the clinical and public health management of TB (3).

The new WHO strategy significantly improved the main epidemiological indicators but in order to meet the final goal of the TB elimination by 2050, the annual incidence rate should decrease more rapidly. On this basis, in 2014 the World Health Assembly approved a new, more comprehensive strategy named End-TB Strategy. According to that, not only the patient-centered clinical approach should be improved, but also more attention should be given to the welfare as well as research and development activities in the fields of diagnosis, treatment and prevention (10).

**MDR-TB Epidemiology**

The last WHO Global Report on TB highlighted that the estimated MDR-TB incidence is increasing worldwide (1). In 2014 480,000 (range: 360,000-600,000) patients occurred but only 123,000 were diagnosed and reported. About 190,000 MDR-TB patients died in the same year. The proportional distribution of MDR-TB between new and previously treated TB cases is significantly different. It was estimated that 3.3% and 20% of new and previously treated TB cases have MDR-TB, respectively. However, in some Eastern European countries (e.g., Ukraine and Kazakhstan) the proportion of MDR-TB cases among previously treated TB patients is higher than 50% (1). The proportion of MDR-TB among new cases is significantly increased (more frequent transmission of MDR Mycobacterium tuberculosis strains): a survey carried out in Minsk (Belarus) in 2010 showed a proportion of 35.3% (11). The geographical areas where MDR-TB is more prevalent are India, China, and Former Soviet Union countries. Twenty-seven countries were classified as high MDR-TB burden countries (1).

However, more complicated drug-resistant patterns than MDR-TB have been described. In particular, it was described the extensively drug-resistant TB (XDR-TB), which is a TB form caused by MDR Mycobacterium tuberculosis strains with further resistance to any fluoroquinolone and to at least one of the injectable second-line drugs (amikacin, capreomycin, and kanamycin). Only a few and poorly effective anti-TB drugs are available to treat XDR-TB patients (1, 12).

At national level it is crucial to implement and scale-up surveillance or survey systems, in order to adequately assess the burden of the disease and better allocate economic, financial, and human resources. In some geographical settings (e.g., Central Africa) the few available resources does not allow the assessment of the burden of the drug-resistant forms, particularly the performance of the drug-susceptibility testing of second-line drugs or the adoption of rapid molecular tests (1).

**The Emergence of MDR-TB**

The origin of the MDR-TB cases was summarized by Caminero in a previous issue of the JLTLD (13). He described healthcare- and patient-related causes. In particular, the healthcare-related causes can be divided in two groups:

1. non-implementation of DOTS or DOTS expansion strategies;
2. inadequate supply or poor quality of anti-TB drugs.

The first subgroup includes the following conditions: poor education and training of the healthcare workers; absence of or inadequate guidelines on the management of the drug-susceptible and drug-resistant TB; poor organization or funding of the national TB programs; absence of a system which monitors the treatment outcomes and the continuation phase of treatment, particularly when carried out in the community; absence of a standardized treatment.

The subgroup related to the anti-TB drugs includes the following risk categories: inadequate administration of anti-TB drugs (wrong dosage or drug combination); frequent shortages of anti-TB drugs with treatment interruptions; poor quality of anti-TB drugs (e.g., drugs purchased in not officially recognized markets). Another important issue is represented by the interaction between the TB patient and the anti-TB therapy: the poor adherence to the anti-TB drugs can favor the exposure of the patient to sub-therapeutic doses, increasing the probability of selection of drug-resistant strains.
It is straightforward that MDR-TB is a man-made phenomenon.

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The poor adherence can be supported by the occurrence of serious and non-serious adverse events; the current therapeutic approach for MDR-TB, based on second-line drugs which are more toxic and less effective, can increase the probability of treatment interruptions and, then, can allow the selection of mycobacterial strains with a more complicated drug-resistant pattern. Furthermore, the long duration of therapies for drug-susceptible (i.e., 6 months) and –resistant TB (i.e., 20-24 months) reduces the willingness to continue the exposure to the anti-TB drugs, mainly when toxic and after a clinical recovery.

Moreover, stigma and low educational level can reduce adherence. This last has been frequently described in low-income countries, where infectious diseases, such as HIV/AIDS and TB, are associated with social isolation and, then, patients after the diagnosis do not take therapies or attend specialized clinics, with an increase in the probability of Mycobacterium tuberculosis transmission to contacts. Another important factor is the poor economic condition of the patient/family; sometimes the distance between his/her village and the clinic is relevant and money should be spent for public transport; furthermore, patients cannot interrupt their work for a daily clinical evaluation.

Other important causes of generation of MDR-TB include the following: the relevant influence of the private sector where healthcare workers do not follow national and international guidelines on the clinical management of the patients; poor infection control measures in hospitals or ambulatory settings where MDR-TB patients are treated.

On this basis, it is straightforward that MDR-TB is a man-made phenomenon. Few years ago, the European Centre for Disease Control and Prevention (ECDC) in Stockholm decided to carry out a survey in order to better understand the clinical management of drug-susceptible and –resistant cases in the most relevant TB reference centers in the European Union/European Economic Area (14). After the development of a standardized tool (15), based on the most relevant international guidelines on TB and on the International Standards for TB Care, to assess all the clinical and public health features of TB management, more than 100 medical files were analyzed in four referral national centers. Several shortcomings were detected: from the poor management of the household and hospital contacts to the poor management of patients with comorbidity (HIV/AIDS: choice of adequate anti-retroviral drugs), duration of anti-TB therapies, drug dosages, nosocomial infection control measures (i.e., administrative and environmental measures, personal protective equipment, training of the healthcare workers) (14, 16). According to the findings of this survey, the ECDC and the European Respiratory Society (ERS) decided to prepare the European Standards for TB Care, which is an adaptation of the International ones to the European setting (17).

**Treatment outcomes**

As previously mentioned, the long duration of the anti-MDR-TB treatment and its toxicity are relevant clinical problems, which should be addressed introducing new effective anti-TB drugs. A systematic review and individual patient data meta-analysis carried out on a retrospective cohort of 9,153 MDR-TB patients clarified the importance of the drug-resistance patterns for treatment success (12, 18, 19). In particular, it was demonstrated that the overall treatment success in MDR-TB patients is 62%, with a lower (40%) and higher (64%) percentage in XDR-TB patients and MDR-TB patients with susceptibility to fluoroquinolones and second-line injectables, respectively. A similar trend was showed for the outcome failure/relapse, where the proportion is 22% for XDR-TB cases and 8% for those MDR-TB patients with susceptibility to fluoroquinolones and second-line injectables.

The logistic regression performed on the data collected from this cohort of patients underscored that in order to get a treatment success it is crucial to treat XDR-TB patients with more than six drugs during the intensive phase; four effective drugs are needed for MDR-TB patients with susceptibility to fluoroquinolones and second-line injectables. The same categories of patients need four and three drugs during the continuation phase, respectively.

Furthermore, it was proved that the total duration of treatment should be 20-25 months, whereas the intensive phase should last 6.6-9 months.

**Conclusions**

MDR-TB is a life-threatening event which has an increasing global impact. The new anti-TB drugs bedaquiline and delamanid have shown their efficacy in the treatment of the MDR-TB patients (20, 21). However, more therapeutic options are needed. The solution of re-purposed antibiotics [(e.g., linezolid, meropenem, imipenem (22, 23)) can be helpful but not definitive. From a strategic perspective it is crucial to detect rapidly all cases: economic resources to implement and scale-up the new molecular techniques are necessary particularly in low-income/high MDR-TB burden countries. Immediate isolation and appropriate treatment can reduce the Mycobacterium tuberculosis transmission and, then, the emergence of new cases, as well as to reduce the MDR-TB-related mortality.

However, the availability of financial resources for the new/conventional diagnostic techniques should be associated with the availability of economic and financial resources for the anti-TB drugs (24). New models of clinical management are needed: to better allocate the financial resources (new diagnostics/drugs) it is crucial to implement healthcare models based on short hospitalizations and ambulatory/community care with...
the involvement of social workers and civil society organizations. Current diagnostic and therapeutic tools need to be improved; the third pillar of the WHO TB Elimination Strategy, focused on research and development activities, should be the starting point. A new deal between governments, private industry, and universities could help to revitalize the antibiotic system which has reduced its productivity since the 80s. The introduction of new tools should be accompanied by an improvement of the skills of the healthcare workers in the management of the antibiotics: evidence-based policies should be immediately implemented in order to save the few available therapeutic options. Prevention activities should be one of the cornerstones in the fight against MDR-TB. The recent release of the WHO guidelines on the programmatic management of the latent TB infection could support all the stakeholders for the reduction of the pool of individuals who could develop the disease. However, more scientific evidence is needed on how to manage the contacts of the MDR-TB cases which currently represents an open issue.

References

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