Iranian Journal of Clinical Infectious Diseases
2007;2(1):1-3

EDITORIAL

The emergence and impact of extensively drug-resistant tuberculosis

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Mycobacterium tuberculosis remains the most common cause of infection-related mortality worldwide. In 1997, nearly 2 billion people were estimated to be infected with TB (1-3). Each year, 8-9 million individuals develop active infection, and at least 2 million people die of TB or related complications (1-3). TB is largely a problem among developing nations, which account for 95% of cases and 98% of deaths. Mortality exceeds 50% in parts of Africa where resources are lacking and the prevalence of HIV infection is high (2,3).

The World Health Organization (WHO) declared TB a global public health emergency in 1993. Since then, the incidence of TB and its associated mortality have stabilized. However, despite these relative successes, we have seen the emergence of drug resistance, which now poses a significant worldwide threat.

Resistance to single antimycobacterial agents has long been recognized. Unfortunately, the evolution of drug resistance has led to the recent emergence of TB strains resistant to multiple agents, including those medications used as standard first-line therapies.

Multi-drug-resistant TB (MDR-TB) is defined as a resistance to both isoniazid and rifampin, with or without resistance to other first-line agents. The incidence of MDR-TB is rapidly growing. The estimated global incidence of MDR-TB was 460,000 cases in 2005 (4). The true prevalence of MDR-TB is likely underrecognized as many developing countries endemic for TB lack appropriate lab facilities and diagnostic resources. Nearly two thirds of the global burden of MDR-TB is thought to occur in 3 countries: Russia, China, and India (4). In Iran, the sputum specimens from a total 2030 patients with TB were digested, examined microscopically for acid fast bacilli, and inoculated into Lowenstein-Jensen through a standard procedure. Testing of susceptibility to first-line drugs was performed for 1284 mycobacterium tuberculosis isolates. Subsequently, 113 isolates identified as multi-drug-resistant M. tuberculosis. A total of 12 (10.9%) multi-drug-resistant M. tuberculosis strains were resistant to all 8 second-line tested drug and therefore, were denoted as extensively drug-resistant tuberculosis. In the present study, they described 2 clusters of XDR-TB (6). The XDR M. tuberculosis isolates were resistant to isoniazid and rifampin and to at least 3 of the 9 main classes of second-line drugs (aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine, and para-aminosalicylic acid). They are not only a serious threat for the affected TB patients but also hamper the TB control program. If these extensively resistant pathogens are allowed to develop and spread in society, they will remain a significant public health concern.

Received: 3 August 2006 *Accepted*: 7 December 2006
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Since the discovery of MDR-TB in the 1990s, the resistance pattern of TB has continued to evolve, and isolates resistant to *both* first- and second-line agents, termed extensively drug-resistant TB (XDR-TB), have been identified. XDR-TB was first reported in November 2005. WHO convened an Emergency Global Task Force on XDR-TB. This task force revised the case definition as resistance to isoniazid and rifampin (with or without resistance to other first-line agents), resistance to any fluoroquinolone, and resistance to at least one second-line injectable antimicrobial medication (amikacin, capreomycin, or kanamycin) (7-9). Like MDR-TB, it has been identified worldwide and now represents 2% of all cases of culture-positive TB (8-10). In highly endemic regions, the rates of XDR-TB may be as high as 10% (5,8). Given the extreme limitations in the ability to treat this infection, death is common, with 80% to 100% mortality rates reported (7,11). In 2006, of 544 TB isolates in South Africa, 53 (9.7%) were XDR-TB. Among these, 52 individuals (98%) died within 25 days of diagnosis (11).

Resistance to standard first-line agents requires the use of multiple second-line medications. Second-line medications are, by definition, less effective, more toxic, more expensive, less available, or less convenient, characteristics initially making them secondary or nonpreferred choices. With regard to TB, second-line agents are also not suitable for short courses of therapy and require a longer duration of administration, further adding to their increase in cost and toxicity. Cost and duration of therapy make them extremely difficult to use in the areas (developing nations) that are most in need.

Given the decreased efficacy of second-line agents, treatment failures are more common in drug-resistant TB. In fact, the currently available second-line agents are 5-8 times more likely to fail than first-line agents. Ineffective treatment of MDR-TB, either through poor efficacy of the medications or noncompliance with longer, more toxic therapies, creates a perfect platform for acquiring further resistance and the emergence of XDR-TB. Because XDR-TB is resistant to first- and second-line drugs, treatment options are seriously limited. It is, therefore, vital that TB control programs be managed properly to prevent further progression of MDR-TB and mitigate the emergence of XDR-TB.

Treatment options for drug-resistant TB are limited and often ineffective. There are no clinical trials to guide the choice of agents to treat MDR-TB. In addition, there are no validated studies to direct empirical regimens for presumed drug resistance. As such, the combined American Thoracic Society, Centers for Disease Control, and Infectious Diseases Society of America (ATS-CDC-IDSA) statement on the treatment of drug-resistant TB is based largely on extrapolated data from unrelated trials and expert opinion.

While not confirmed in clinical trials, surgical resection may play an important role in the management of MDR-TB. Surgery has been shown to reduce the bacillary burden, reduce transmissibility, and improve outcomes in MDR-TB (12).

The WHO has issued a statement that early identification and treatment of XDR-TB may confer successful treatment and cure. Unfortunately, the currently available antimicrobials have significant limitations and are often ineffective. Few new agents show promise as reasonable alternatives. Attempts at creating an effective and reliable vaccination have not come to fruition. Given the progressive acquisition of resistance, the lack of efficient treatment options, and the near universal mortality, it appears that the most practical and effective strategy is to minimize further emergence and spread of this disease.

Improved infection control aimed at reducing TB transmission, especially in HIV and other high-risk populations, is paramount in the prevention of further spread of MDR-TB and XDR-TB (13).

In conclusion, drug-resistant TB presents a global threat. Further spread must be prevented to reduce the incidence of MDR-TB and minimize further emergence of XDR-TB.

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