MAYO CLINIC

SPECIAL ARTICLE

Extensively Drug-Resistant Tuberculosis: Principles of Resistance, Diagnosis, and Management

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Abstract

Extensively drug-resistant (XDR) tuberculosis (TB) is an unfortunate by-product of mankind's medical and pharmaceutical ingenuity during the past 60 years. Although new drug developments have enabled TB to be more readily curable, inappropriate TB management has led to the emergence of drug-resistant disease. Extensively drug-resistant TB describes *Mycobacterium tuberculosis* that is collectively resistant to isoniazid, rifampin, a fluoroquinolone, and an injectable agent. It proliferates when established case management and infection control procedures are not followed. Optimized treatment outcomes necessitate time-sensitive diagnoses, along with expanded combinations and prolonged durations of antimicrobial drug therapy. The challenges to public health institutions are immense and most noteworthy in underresourced communities and in patients coinfected with human immunodeficiency virus. A comprehensive and multidisciplinary case management approach is required to optimize outcomes. We review the principles of TB drug resistance and the risk factors, diagnosis, and managerial approaches for extensively drug-resistant TB. Treatment outcomes, cost, and unresolved medical issues are also discussed.

 ■ Mayo Clin Proc. 2016;■■(■):1-14

Mycobacterium tuberculosis is an ancient and very successful human pathogen. Through gene sequencing and phylogenic reconstruction, it is estimated that tuberculosis (TB) first emerged approximately 70,000 years ago and followed human migrations out of Africa during the Neolithic period.[1] Indeed, TB has been found in the skeletal remains of a woman and child who lived 9000 years ago in the eastern Mediterranean,[2] in humans living in 3 Saxony-Anhalt (modern Germany) sites dating back to 5400 to 4800 BC,[3] and in other settlements located in modern-day Hungary[4] and Jordan.[5] The assimilation of agricultural food production and animal domestication in the early Neolithic period enabled the development of more permanent settlements, higher populations, and dense communal living and facilitated the spread of communicable infectious diseases, such as TB. From the 17th through the 19th centuries, TB caused 20% of all human deaths in Europe and North America.[6]

Despite the advent of effective antimicrobial drug chemotherapy, TB currently remains the leading killer of humans due to a single pathogen, with an estimated 1.5 million deaths in 2014.[7] One factor that contributes to its resilience in modern times is antibiotic drug resistance. *M tuberculosis* is intrinsically resistant to many common antibiotic agents, due in part to the structure of its mycolic acid–containing cell wall, efflux mechanisms, and the presence of a β-lactamase.[8] The first antibiotic drug effective against TB, streptomycin, was introduced more than 70 years ago,[9,10] and resistance to this drug was encountered shortly thereafter.[11] The addition of a second drug, para-aminosalicylic acid (PAS), reduced the emergence of streptomycin resistance and further suppressed bacterial growth.[12] As additional anti-TB antimicrobial agents were developed, a strategy was devised to overcome the evolution of additional drug resistance by simultaneously treating TB with multiple antibiotic drugs. This combination therapy approach to TB has proved to be very effective and remains the standard of treatment today.[13]

Although the prescribing of combination drug chemotherapy has been a prevailing practice for decades, new and more complex patterns of drug-resistant *M tuberculosis* continue to

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emerge. Isoniazid and rifampin are the 2 most important drugs in the treatment of TB, and resistance to both these drugs defines multidrug-resistant (MDR) TB. Indeed, strains of MDR-TB emerged 1 to 2 decades before clustered MDR-TB outbreaks were reported in the early 1990s.[14] In 2005, a new TB epidemic with near 100% mortality rates was identified in KwaZulu-Natal, South Africa, and was caused by an MDR-TB strain containing additional drug resistance to the fluoroquinolones and injectable agents.[15] This new strain of MDR-TB was labeled extensively drug-resistant (XDR) TB in 2005 by the Centers for Disease Control and Prevention (CDC) and was revised in 2006 to describe *M tuberculosis* collectively resistant to isoniazid, rifampin, a fluoroquinolone, and an injectable agent (including amikacin, kanamycin, and capreomycin).[16]

Through 2015, 105 countries reported cases of XDR-TB to the World Health Organization (WHO), composing just less than 10% of all patients diagnosed as having MDR-TB.[7] The number of cases diagnosed globally seems to be rising, but this may, in part, reflect increased laboratory testing and improved reporting. Countries reporting the highest numbers of patients with XDR-TB in 2014 include India (n=1262), Ukraine (n=657), South Africa (n=562), Belarus (n=431), and Kazakhstan (n=318).[7] In the United States, 15 cases of XDR-TB were reported to the CDC from 2009 through 2014; 11 of these patients were born outside of the United States.[17]

PRINCIPLES OF DRUG RESISTANCE

The development of antimycobacterial drug resistance relies on a Darwinian model of random spontaneous genetic alterations that propagate under selective environmental pressure and subsequently provide selective advantages for mycobacterial growth. These nucleotide transcription errors occurring in select target genes of *M tuberculosis* DNA enable drug resistance through structural changes of drug binding sites, inhibition of prodrug metabolism, and activation of efflux pumps. Resistance to rifampin, for example, involves single nucleotide substitutions in the β subunit of the RNA polymerase (*rpoB*) gene,[18] and isoniazid resistance is most often caused by changes in the catalase peroxidase (*katG*) gene[19] and *inhA* gene[20] involved in mycolic acid synthesis. Stepwise accumulation of gene mutations results in drug resistance to multiple antibiotic agents.

The rate of clinical drug resistance development is proportional to the number of bacteria present in the infected tissue, differs for specific drugs, and can be predictable. For example, the mutation rate to develop spontaneous isoniazid resistance occurs in approximately 1 in 10^6 *M tuberculosis* bacilli present; for rifampin the mutation rate is 1 in 10^8. The average bacillary burden in cavitary pulmonary TB is approximately 10^9 organisms. Therefore, in patients with pulmonary TB receiving suboptimal therapy, the initial infecting strain of *M tuberculosis* predictably will undergo DNA mutagenesis, leading to bacilli acquisition of mutations conferring drug resistance and the evolution of new subpopulations of drug-resistant bacilli.[21]

Although the rate of spontaneous development of *M tuberculosis* that is resistant to both isoniazid and rifampin is much lower at 10^{14}, resistance to multiple anti-TB drugs can be acquired in a sequential manner. Indeed, the lung tissue of a patient with cavitary TB may contain a diverse array of *M tuberculosis* strains with differing drug-resistance capacities. Adding a single new active drug to a drug regimen that is ineffectual (a so-called failing regimen) leads to the development of further drug-resistant TB populations. As this cycle is repeated, *M tuberculosis* strains simultaneously resistant to multiple antimicrobial agents emerge.

Drug-resistant *M tuberculosis* strains can also be transmitted directly from one person to another. This type of primary transmission of drug-resistant TB is especially common in patients with human immunodeficiency virus (HIV) infection and those with other immunomodulatory conditions.[22,23] The current prevalence of drug-resistant TB globally most likely reflects a combination of acquired and transmitted TB drug resistance.[24,25]

RISK FACTORS FOR DRUG-RESISTANT TB

Drug-resistant TB is a human-made problem. Risk factors for the development and perpetuation of drug-resistant TB (including XDR-TB) are listed in Table 1. Patient noncompliance with TB therapy remains a major problem, as second-line and expanded drug therapies are less well tolerated and involve multiple pills consumed daily. The lack of directly observed