Drug-Resistant Tuberculosis

Challenges and Progress

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KEYWORDS

• *Mycobacterium tuberculosis* • Drug-resistant tuberculosis • Antimicrobial resistance

KEY POINTS

- Antimicrobial resistance is a natural evolutionary process, which in the case of *Mycobacterium tuberculosis* is based on spontaneous chromosomal mutations, meaning that well-designed combination drug regimens provided under supervised therapy will prevent the emergence of drug-resistant strains.
- Unfortunately, limited resources, poverty, and neglect have led to the emergence of drug-resistant tuberculosis (DR-TB) throughout the world, particularly in the most vulnerable populations.
- The international community has responded with financial and scientific support, leading to new rapid diagnostics, new drugs and regimens in advanced clinical development, and an increasingly sophisticated understanding of resistance mechanisms and their application to all aspects of tuberculosis (TB) control and treatment.
- Although the obstacles are enormous, it is an exciting time based on optimism for substantial improvements for patients with DR-TB.
- Ultimately, for long-range success, the patient must remain in sight, for all new drugs and scientific advancements will be for naught if TB patients do not receive adequate, well-supervised care.

BACKGROUND

Treatment of drug-susceptible tuberculosis (TB) conducted under strong national TB programs (NTPs) using standard 4-drug therapy and directly observed therapy has led to relapse-free cure rates greater than 95% and dramatic national declines in TB

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incidence. This success has required consistent allocation of substantial money and resources. Conversely, poorly organized and underfunded NTPs result in unsupervised and inappropriate treatment, leading to treatment failure and the development of drug resistance, which is then spread to others.[1] The management of drug-resistant TB (DR-TB) is much more difficult than drug-susceptible TB, leading to epidemic spread of DR-TB in several countries. Drug resistance represents a major threat to global TB control with potential disastrous consequences[2]; this section explores new drugs and treatment regimens that are being developed to treat this deadly, communicable disease.[2]

Multidrug-resistant TB (MDR-TB) is defined as TB that is resistant to isoniazid (INH) and rifampin.[3] According to the Centers for Disease Control and Prevention (CDC), in 2014 there were 96 new cases of confirmed MDR-TB in the United States, representing 1.4% of the total 9421 new TB cases reported, and 88% of the MDR-TB patients were foreign-born.[4] Per the World Health Organization (WHO) Global Tuberculosis Report, there were an estimated 480,000 new cases of MDR-TB in the world in 2013, accounting for 3.5% of the total estimated 9 million TB cases.[3] Estimates are used because many of the countries with high MDR-TB incidence lack the resources and investment to accurately diagnose drug resistance on a national scale. Actual notifications were received for 136,412 people with MDR-TB or rifampicin-resistant TB, and of these, 96,617 (71%) were started on treatment. Treatment outcomes are available for 52,206 patients from 2011 with 48% reported as having successfully completed treatment. The WHO estimates that 210,000 of the 480,000 MDR-TB patients died. Although these numbers represent improvement, global control of MDR-TB remains dismal: less than one-third are diagnosed; about one-fifth are treated, and about 5% successfully complete treatment. The overwhelming majority of MDR-TB patients in the world are likely to have poor outcomes, causing great suffering and continued transmission.

A small subset, estimated at 9% of people with MDR-TB, have extensively drug-resistant TB (XDR-TB). XDR-TB is defined as MDR-TB with additional resistance to any fluoroquinolone and to at least 1 of 3 injectable agents (kanamycin, amikacin, or capreomycin). One hundred countries reported a case of XDR-TB in 2013, and of the 1269 patients reported in the 2011 cohort, only 284 (22%) completed their treatment successfully and 438 (35%) patients died.[3]

RESISTANCE MECHANISMS AND CURRENT APPROACHES TO TREATMENT

Soon after the discovery and initial use of streptomycin to treat TB in the 1940s, it became clear that single-drug treatment led to the rapid development of drug resistance, resulting in high failure rates.[5,6] This recognition led to the development of combination therapy using at least 2 active drugs to prevent resistance.[7] It was also noted that extension of therapy beyond seemingly successful treatment, with resolution of symptoms and microbiological clearance, was necessary to avoid relapse. The addition of INH, an agent with potent early bactericidal activity, led to effective combination therapy with high success rates after treatment for 18 to 24 months.[8] The introduction of rifampicin allowed a dramatic shortening of the treatment course to 6 to 9 months.[9] Ethambutol, an oral agent with relatively low toxicity, offered protection when drug resistance to INH or rifampicin was present. Finally, the addition of pyrazinamide (PZA) reliably allowed for shortening of treatment course to 6 months for most cases (for review, see Ref.[10]).

Although the phenomenon of drug resistance was quickly recognized, the underlying biological mechanisms were only recently elucidated. This scientific advancement