

Extensively Drug-Resistant *Mycobacterium tuberculosis*: Charles Darwin Would Understand

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(See the article by Pillay and Sturm on pages 1409–14)

In this issue of *Clinical Infectious Diseases*, Pillay and Sturm [1] document the evolution over a decade of an extensively drug-resistant strain of *Mycobacterium tuberculosis* (XDR-TB) in the KwaZulu-Natal region of South Africa. This is the latest iteration in the on-going struggle between the tubercle bacillus and *Homo sapiens*.

In the most profound single insight in the history of biology, Darwin's *The Origin of Species* laid out the simple tenets of evolution: diversity among progeny and factors in the environment that favored the survival and replication of certain of those progeny. This is the modern story of tuberculosis (TB).

Consumption was rampant in Europe and North America in the past 400 years, estimated to take the life of 1 in 5 adults in Europe at the turn of the 19th century. However, with the discovery of para-aminosalicylic acid (PAS; in 1944), streptomycin (in 1944), and isoniazid (in 1951), the long-sought cure seemed at hand. An early study by the British Medical Research Council found that the combination treat-

ment with PAS and streptomycin was more effective than treatment with either agent alone. By use of the novel technology of in vitro drug susceptibility testing, it was observed that 2-drug therapy delayed or inhibited the appearance of drug-resistant strains of *M. tuberculosis*.

Extraordinary researchers, such as Canello, Grosset, and Mitchison, demonstrated that resistance occurred in response to spontaneous but rare chromosomal mutations. The mutations were seen in the range of 1 mutation per 100,000–10,000,000 replications, depending on the drug or class, and the mutations were not linked (i.e., each mutation conferred resistance to a single drug or class). Such mutants did not become the dominant strain unless selected by exposure to antimicrobials.

These observations were consonant with the developing practice of 3-drug therapy with isoniazid, PAS, and streptomycin: mutants resistant to one of the drugs would be killed by the other agents. The imperative for multidrug therapy was greatest early in the course of therapy, especially in the context of cavitary disease, wherein the population of rapidly multiplying bacilli (and the likelihood of drug-resistance mutations) was greatest.

As a result of the administration of inadequate regimens and/or patient non-adherence to therapy, treatment failures were seen early in the TB chemotherapy

era. Resistance to the most important agent, isoniazid, was associated with high rates of treatment failure, chronic illness, and death. However, Middlebrook, among others, noted that the strains with high-level isoniazid resistance had lost catalase activity, grew slowly in vitro, and were far less virulent in the guinea pig model. Clinical observations and the epidemiology of drug-resistant diseases in the United States then indicated that there was very limited spread of these highly isoniazid-resistant strains of *M. tuberculosis*, suggesting reduced transmissibility and/or impaired virulence.

By stark contrast, epidemics of TB due to bacilli that were resistant to isoniazid and rifampin (i.e., multidrug-resistant TB [MDR-TB]) appeared in the early 1990s in New York City, New York; Miami, Florida; Buenos Aires, Argentina; and elsewhere. These outbreaks clearly involved high transmissibility and virulence. In multiple sites, the primary MDR-TB strain was the Beijing strain, with "strain W" being dominant in New York City. For unclear reasons, these organisms bore the cost of acquired drug resistance with little or no loss of pathogenicity.

AIDS abetted these epidemics by providing large populations of persons who were exquisitely vulnerable to TB. Also, the practice of cohorting patients who were hospitalized frequently in this era (for opportunistic infections or other

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complications of HIV infection) fostered the wholesale transmission of MDR-TB.

The World Health Organization has worked arduously to expand and improve services for treatment of routine TB cases, implementing their Directly Observed Therapy, Short-Course (DOTS), program widely over the past decade. DOTS programs made therapy available to many additional patients during this period and have doubtlessly had a substantial, positive impact. It should be noted, however, that the “directly observed therapy” element of this model did not have the same implications elsewhere that it has had in the United States. DOTS programs in the United States emphasize supervised administration of all or the great majority of doses of anti-TB medications during the 6-month standard regimen. Owing to inadequate resources and/or skepticism about the need for use of such a model, actual oversight of treatment has been rare elsewhere. Furthermore, given the universal propensity of a certain portion of patients to not take their medications consistently, we may be sure that an unwanted by-product of the expanded treatment program was the generation of new cases of drug-resistant TB. That is not to be second-guess DOTS; if we never had treated TB, there would be no drug resistance.

In response to the increasing prevalence of MDR-TB throughout the globe, the World Health Organization, national public health programs, and nongovernmental organizations joined forces to make second-line medications, including the fluoroquinolones, more available and affordable. The World Health Organization Green Light Committee made a functional DOTS program a prerequisite for access to the discounted second-line drugs.

Given the widened use of the fluoroquinolones and other second-line medications, including the injectable agents, the appearance of XDR-TB was inevitable. Clinicians who treated patients with presumed MDR-TB did not have access to in vitro susceptibility test data to guide their regimen selections, and despite the admonition that such cases be given highest priority for DOTS, true supervision was understandably rare.

With XDR-TB, we are seeing the appearance of cases of TB that are essentially incurable. In a study of 205 patients treated for MDR-TB between during the period 1983–1998 at the National Jewish Medical and Research Center (Denver), the most important variables associated with favorable outcome were fluoroquinolone use and resectional surgery. In settings where comprehensive mycobacterial laboratory services, full access to all anti-TB drugs, pharmacokinetic monitoring, and sophisticated surgical support are not available—and where many patients have AIDS—we may anticipate dismal cure rates.

In roughly 55 years, we have squandered our precious legacy of chemotherapy for these XDR-TB cases. Darwin, though, would understand.

Suggested Reading List

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Acknowledgments

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Reference

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