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EDITORIAL

Rapid impact of effective chemotherapy on transmission of drug-resistant tuberculosis: pity the guinea pig

Pity the poor guinea pig, called upon so often to prove the basic facts of pathophysiology and clinical medicine. Across the world, its name is synonymous with anyone or anything constrained to suffer an experiment or trial in order to learn something of value to our own species. Seldom have guinea pigs been sacrificed for more important, if confirmatory, knowledge than in studies conducted in a small South African facility, which patients with active pulmonary tuberculosis (TB) share with a colony of guinea pigs hidden in sealed compartments abutting the patients' rooms. These animals breathe only the recirculated air of the patient in the room beside their respective colonies. Most of these patients are sick with drug-resistant strains of *Mycobacterium tuberculosis*, and the point is to explore the impact of treatment on transmission of those strains to those who share the same air. A similar model was used at the outset of the chemotherapeutic era, and has been updated by those practicing at the front lines of an explosive epidemic of multidrug-resistant TB (MDR-TB).

In this issue of the *Journal*, Dharmadhikari and colleagues, reporting from this unique facility, confirm both our hopes and some of our best-founded fears: this mutant, airborne pathogen, although extremely virulent, can still be killed by effective combination chemotherapy.[1] Dead mycobacteria may well be coughed into the air and even into the lungs of exposed guinea pigs, but for the subset of animals whose air is piped directly from the rooms of coughing patients on 'effective' therapy for MDR-TB—a multidrug regimen tailored to match the drug susceptibility of the dominant strain—we are not in the world of zombies: dead is dead. And dead means non-infectious. Good news (at least in the very short term) not only for guinea pigs, but also for the families and care givers of these patients, and indeed for all those who share the air they breathe.

The bad news is that high rates of transmission from patients to guinea pigs (and presumably to exposed humans) occurred whenever treatment regimens were 'ineffective.' If these conclusions seem obvious to some, why is this study newsworthy? Why is it even worthy of an editorial? There are several reasons why this is so, and we would like to underline three of them.

First, the key word here is 'effective.' In this study, which includes data collected during the course of treatment for 109 patients, regimens are ineffective because the dominant infecting strains are classed as 'extensively' drug-resistant, or XDR, strains of *M. tuberculosis*. The unlucky guinea pigs—those infected after brief exposure—were exposed to patients with XDR-TB. Dharmadhikari and his colleagues use the dry language of medical journals: 'It is likely that the current treatment of XDR-TB is often ineffective in rapidly interrupting transmission.' What this really means is that 'the current treatment' is inadequate, as it was based largely on agents to which these patients' infecting strains were resistant. And since the patients were not receiving effective therapy for XDR-TB, there should be no reason for surprise: combination chemotherapy, preferably with well-absorbed, cidal drugs, is what—choose your metaphor—lands the punch, clips the wings, and knocks the bacillus dead. In other words, the medications, long called 'antibiotics', have antibiotic effects, and rapid ones, as long as the basic principles of infectious disease are respected. No one would argue that serious disease due to methicillin-resistant strains of *Staphylococcus aureus* is best treated by methicillin.

Second, this paper has major implications for infection control. Although one might be the rather discouraging conclusion that we spend a lot of time—and sacrifice a lot of guinea pigs—to discover things once known and then forgotten, this paper corroborates, with in vitro studies, epidemiological and clinical studies suggesting the importance of good clinical care for infection control in a region in which the human immunodeficiency virus (HIV) has fanned large and lethal outbreaks of tuberculosis, including those due to drug-resistant strains. Central to good clinical care is rapid diagnosis of active tuberculosis due to drug-resistant strains so that patients can initiate effective treatment.

Third, the study suggests that the one-two punch—more of a five-drug punch—of a regimen to which the infecting strains are susceptible is effective therapy and works to reduce transmissibility very quickly. As shown nearly 40 years ago by Rouillon et al. with drug-susceptible TB, even a few days of effective treatment renders coughing patients significantly less infectious.[2] This was true among all MDR-TB patients in the African study, even though many were both smear- and culture-positive. To repeat the metaphor, the initiation of a multidrug regimen for MDR-TB seems to clip the wings of this airborne pathogen *well before* all viable bacilli are extinguished, as long as one receives drugs to which the infecting strains are susceptible.

The same logic must hold for XDR-TB, and it is also this logic that makes us reluctant to define strains

as 'totally' drug-resistant. Since we finally have, for the first time in 40 years, promising new drugs that are likely effective against drug-resistant strains, prudent stewardship of these drugs requires prompt diagnosis with accompanying rapid susceptibility testing, and their inclusion in multidrug regimens assiduously administered in a manner convenient to patients. The South African study helps make the case not only for prompt diagnosis but also for prompt initiation of care using the right delivery system, which is often a community-based one. This is true not only in regions with the highest rates of HIV co-infection: it was true in the New York epidemic, which also affected HIV-negative contacts in households, hospitals, prisons, and shelters.[3] It was true in Russia, where Keshavjee and colleagues, including Edward Nardell, have worked in collaboration with public authorities in both the prison and civilian sectors on aggressive efforts to diagnose drug-resistant strains, to speed up initiation of proper therapy, to improve both administrative and other measures of infection control, and to use, whenever possible, the community-based model of care, which has resulted in both better clinical outcomes and less nosocomial transmission.[4] In Tomsk Oblast, where these complementary measures have had their greatest uptake over the past decade, this has resulted in a contraction of the TB epidemic that exploded, first in prisons and then beyond bars, after 1991.[5]

As both of us are infectious disease doctors, we would like to close by again sounding the alarm: there is a 'crisis in antibiotic resistance', as Harold Neu, writing of several classes of serious pathogens treated by antibiotics, warned at the outset of the New York epidemic.[6] Dharmadhikari and Nardell, along with their partners from South Africa and the United States, are to be commended for this assiduous effort to update Koch's postulates. For decades, we have known three things: TB is airborne, it is treatable with multidrug regimens to which the infecting strain is susceptible, and prompt initiation of effective therapy renders patients non-infectious even when viable mycobacteria can still be cultured from sputum or tissue. Although that was never their intent, it is important to recall the contrary claims—and wishful thinking—of the closing years of the twentieth century and of those much debated in these very pages (for example, claims that drug-resistant strains were untreatable, less transmissible, less virulent, less of a priority, drew attention away from other ranking concerns, etc.[7]). Both the guinea pig study and the review that follows remind us that we had better get moving. The burden of disease due to drug-resistant strains of *M. tuberculosis* continues to challenge good care and control; the BRICS countries (Brazil, Russia, India, China, and South Africa) harbor some two-thirds of all patients with MDR-TB worldwide, yet less than a quarter of them are being effectively diagnosed and treated.[8] Similarly, progress in other parts of the world has been too slow. Recognizing this threat, the World Health Assembly in its May 2014 meeting approved a new, post-2015 Global TB Strategy, endorsing three pillars for future approaches to TB care, control, and prevention. The pillars support, and are supported by, principles of government stewardship, engagement of civil society, and respect of human rights, equity, and ethics. These pillars incorporate what is most important for addressing drug resistance: rapid diagnosis, universal drug susceptibility testing, proper treatment, community participation, and strong policies for infection control and rational use of medicines. Importantly, responding to the need to avoid catastrophic expenditures faced by poor people affected by drug-resistant tuberculosis, the Strategy calls not only for universal health coverage to address medical costs, but also for social protection for patients obliged to stop working due to the long months of treatment.[9]

In conclusion, even though this is a small study, and an animal model, it has required many years of patient (and ethical) study design, to say nothing of transnational collaboration and the consent of grievously ill patients. Let us honor them, rather than the guinea pigs, by drawing the most important conclusions arising from the study. In settings in which drug-resistant tuberculosis is common, and everywhere else in the world, strengthening the basic interventions for TB care and control and the prompt initiation of effective therapy, combined with rapid detection of drug resistance, will allow us to turn off the tap of rising resistance to commonly used antibiotics. Linking this imperative of good care to long overdue infection control measures is the only means to face MDR-TB everywhere in the world. It is a clinical and programmatic imperative for all.

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