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### Comprehensive Treatment of Extensively Drug-Resistant Tuberculosis

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**Background:** Extensively drug-resistant tuberculosis has been reported in 45 countries, including countries with limited resources and a high burden of tuberculosis. We describe the management of extensively drug-resistant tuberculosis and treatment outcomes among patients who were referred for individualized outpatient therapy in Peru.

**Methods:** A total of 810 patients were referred for free individualized therapy, including drug treatment, resective surgery, adverse-event management, and nutritional and psychosocial support. We tested isolates from 651 patients for extensively drug-resistant

tuberculosis and developed regimens that included five or more drugs to which the infecting isolate was not resistant.

**Results:** Of the 651 patients tested, 48 (7.4%) had extensively drug-resistant tuberculosis; the remaining 603 patients had multidrug-resistant tuberculosis. The patients with extensively drug-resistant tuberculosis had undergone more treatment than the other patients (mean [ $\pm$ SD] number of regimens,  $4.2\pm 1.9$  vs.  $3.2\pm 1.6$ ;  $P<0.001$ ) and had isolates that were resistant to more drugs (number of drugs,  $8.4\pm 1.1$  vs.  $5.3\pm 1.5$ ;  $P<0.001$ ). None of the patients with extensively drug-resistant tuberculosis were coinfecting with the human immunodeficiency virus (HIV). Patients with extensively drug resistant tuberculosis received daily, supervised therapy with an average of  $5.3\pm 1.3$  drugs, including cycloserine, an injectable drug, and a fluoroquinolone. Twenty-nine of these patients (60.4%) completed treatment or were cured, as compared with 400 patients (66.3%) with multidrug-resistant tuberculosis ( $P = 0.36$ ).

**Conclusions:** Extensively drug-resistant tuberculosis can be cured in HIV-negative patients through outpatient treatment, even in those who have received multiple prior courses of therapy for tuberculosis.

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### Comments

Extensively drug-resistant tuberculosis (XDR-TB) has been reported in 45 countries since 2006.<sup>1</sup> A definition of XDR-TB was revised to include the strains

resistant to isoniazid and rifampicin, in association with resistance to both one fluoroquinolone and one second-line intravenous aminoglycoside (capreomycin, kanamycin, or amikacin).<sup>2</sup> XDR-TB strain was found to be 10 percent of the sampled multidrug-resistant (MDR) TB strains<sup>3</sup>, and the incidence of XDR-TB has been increasing reported from all over the world. MDR-TB is more difficult to treat than drug-susceptible TB.<sup>4</sup> Moreover, the optimal treatment strategy for XDR-TB has not been established, because of inability to use fluoroquinolones and injectable aminoglycosides. In this study, the XDR-TB was identified in 48 of 651 patients (7.4%), and MDR-TB was identified in 603 of 651 patients (92.6%). None of the XDR-TB patients were coinfecting with HIV. The strongest prediction of having XDR-TB was the higher number of treatment regimens prescribed to the patients before the enrollment of this study (the mean number of regimens ( $4.2 \pm 1.9$  versus  $3.2 \pm 1.6$  in XDR-TB and non-XDR-TB group, respectively). This finding is in consistent with previous study which showed that the cumulative previous treatment duration remained significantly associated with XDR-TB.<sup>5</sup>

This study showed that an aggressive comprehensive management program could result in a cure in more than 60 percent of XDR-TB patients who were not coinfecting with HIV. However, the frequency of cure or relapse and the risk of death did not differ significantly between XDR-TB and MDR-TB groups. In contrast, previous studies of HIV-negative patients demonstrated that XDR-TB was associated with much higher failure and mortality rates than MDR-TB.<sup>6-8</sup>

This study showed the several principles of management of XDR-TB patients that might have attributed to the high level of treatment success. First, aggressive regimen with a least five drugs and at the highest tolerated dose was used to maximize the therapeutic benefit. Most of the patients, the regimens

contained cycloserine, capreomycin, paraaminosalicylic acid, amoxicillin-clavulanate, and new-generation fluoroquinolones. In addition, the use of the injectable drug was prolonged for up to 15 months, and overall treatment duration was about two years.

Second, the resective surgery was indicated for patients with high-grade resistant organism, relatively localized disease, and lack of initial response.

Third, the strict treatment supervision was enforced. This ensured a treatment adherence, psychological support, financial incentive, nutritional support, and a prompt identification of circumstance requiring additional attention.

Fourth, the bacteriologic assessment and clinical monitoring were integral to the strategy. The drug susceptibility tests were repeated, and the regimens were adjusted for patients who did not have a response to treatment.

Nevertheless, this study has several limitations. The study was the retrospective design. In addition, this study may have selection bias; the patients referred to the treatment centers could be the less severely illness and more likely to be regularly follow-up. Moreover, the drug susceptibility testing for some of the second-line drugs was hampered by the standardization problem.<sup>9</sup> The results could be not entirely correct.

In conclusion, the strategies of management of XDR-TB that might result in the better outcome should be the aggressive therapy with at least five drugs with the highest tolerated dose, prolonged use of the injectable drug for at least 15 months, strict treatment supervision, intensive bacteriologic assessment, and clinical monitoring.

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