Latin American Guidelines for the Diagnosis and Management of Drug-Resistant Tuberculosis

To the Editor: Throughout the current year, at the request of the Latin American Thoracic Association (ALAT), a group of 38 experts in drug-resistant tuberculosis have been preparing a consensus statement for Latin America on the diagnosis and treatment of drug-resistant tuberculosis. The full document is available from www.alatorax.org. The occurrence of drug-resistant tuberculosis in Latin America is due to limited treatment supervision, nonstandard regimens, poor adherence to treatment, an insufficient supply of drugs, limited institutional monitoring of infections, and human immunodeficiency virus (HIV) coinfection. According to data from the World Health Organization, the most affected countries are Ecuador, Guatemala, Peru, and the Dominican Republic. The most dangerous forms of drug-resistant tuberculosis are multiresistant tuberculosis, with resistance to isoniazid and rifampicin at least, and extensively resistant tuberculosis, which is also resistant to fluoroquinolones and second-line injectables. Resistance in patients with no prior treatment reflects a dangerous epidemiological situation and implies that transmission of drug-resistant tuberculosis is occurring in the community. Given that drug resistance is usually detected after treatment failure (persistence of positive culture after 4 months of standard therapy), the transmission period is extended and initial resistance may be amplified. The essential determining factor of drug-resistant tuberculosis is real or masked monotherapy, and the main element that can signal its existence is treatment failure in standard treatment regimens. The best form of prevention is treatment supervision, along with case-finding and treatment of existing cases with second-line drugs.

Diagnosis involves carefully recording the patient's treatment history, which is important information for the empirical selection of drugs and especially for the laboratory. Determining susceptibility to first-line drugs (isoniazid, rifampicin, ethambutol, and streptomycin) is reliable and is undertaken in Latin America according to the method of proportions (taking 30 to 60 days). Several laboratories also use quick methods validated by the World Health Organization. Examples include those methods that use BACTEC and MGIT equipment (10 to 15 days). Resistance to rifampicin is highly predictive of multidrug resistance and can be detected more quickly by using molecular probes or less expensive techniques, such as phages or nitrate reductase. The validity of testing for susceptibility to second-line drugs is less clear, and results must be assessed within the clinical context. An antibiogram should be performed in cases of treatment failure, operational failure, relapse, discontinuation of treatment, contact with a case of drug-resistant tuberculosis, and patients with HIV infection.

Treatment of drug-resistant tuberculosis must be strictly observed and administered daily. Options include first-line drugs that can preserve susceptibility plus second-line drugs (injectables such as kanamycin, amikacin, capreomycin; fluoroquinolones such as ofloxacin, levofloxacin, and moxifloxacin; thioamides such as ethionamide and protionamide; cyclical antibiotics: cycloserine, terizidone, and *p*-aminosalicylic acid [PAS]), and experimental or restricted drugs. Treatment regimens can be standardized (before the results of the antibiogram or in countries with few microbiological resources) or customized according to susceptibility testing. The initial stage will always include an injectable drug (6 months or until 2 negative monthly cultures are obtained), combined with at least 3 oral drugs, for example, a fluoroquinolone, cycloserine/terizidone, and ethionamide/protionamide, supplemented or replaced by first-line drugs that are still effective, and/or PAS. The initial stage (with an injectable drug) is followed by a maintenance stage (of 12 to 18 months) with oral drugs. The patient who presents 5 negative cultures spread over the final year of treatment is considered cured.

Both first-line and second-line drugs have specific adverse effects, and combined treatment can cause digestive disorders, hepatoxicity, and skin reactions that require careful study of the causative agent.

Surgery may be necessary for localized lesions with poor therapeutic response or in the treatment of sequelae and complications.

Admission criteria are similar to those for pan-susceptible tuberculosis, and patients may initially be admitted to assess tolerance to treatment. The use of biosafety measures (administrative, environmental, and personal respiratory protection) is essential to prevent the spread of drug-resistant tuberculosis in hospitals.

Special situations include patients with HIV infection who suffer immune reconstitution inflammatory syndrome when antiretroviral treatment is combined with antituberculous treatment, and the danger of outbreaks of multidrug-resistant tuberculosis such as those reported in Latin America. Pregnancy should be avoided in patients receiving treatment for drug-resistant tuberculosis. However, in the event of pregnancy, drugs like ethionamide and injectables are contraindicated. Fluoroquinolones can be used in the absence of alternatives.

Prevention of transmission from the index case, particularly among the inner circle of contacts, is essential. Unfortunately, there are no chemoprophylaxis regimens of proven efficacy in most cases of drug-resistant tuberculosis. Accordingly, infected contacts (identified by a tuberculin test with 2 tuberculin units of purified protein derivative) must be closely monitored for at least 2 years.

Epidemiological surveillance of the transmission of *Mycobacterium tuberculosis* strains using molecular biological techniques such as restriction fragment length polymorphism, spoligotyping, and mycobacterial interspersed repetitive unit-variable-number tandem repeat analysis is important, particularly in institutions like hospitals, prisons, and nursing or retirement homes, where epidemic outbreaks have been reported.

Domingo J. Palmero,[a]
Rafael Laniado Laborín,[a]
and José A. Caminero Luna[b]
[a]Departamento de Tuberculosis,
Asociación Latinoamericana de Tórax
[b]International Union Against Tuberculosis
and Lung Disease