DISEASE REVIEW

DIAGNOSIS AND TREATMENT OF DRUG-RESISTANT TUBERCULOSIS

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Tuberculosis remains one of the leading causes of morbidity and mortality throughout the world. Its management has become more complex because of increased resistance to commonly used antituberculosis drugs.

This article will review the diagnosis and therapy of patients infected with drug-resistant strains of M. tuberculosis. Treatment of drug-resistant tuberculosis can be difficult, and may necessitate the use of second-line drugs or resectional surgery. Therefore, management of patients with resistant disease should only be undertaken by, or in very close consultation with, experts in this area. Good patient outcomes depend upon a rapid and accurate diagnosis, and the institution, administration, and monitoring of proper therapy [1].

Definitions – There are a series of definitions used in describing the different types of drug-resistant tuberculosis:

- The term "drug-resistant tuberculosis" refers to cases of tuberculosis caused by an isolate of Mycobacterium tuberculosis which is resistant to one of the first-line antituberculosis drugs: isoniazid, rifampin, pyrazinamide, ethambutol, or streptomycin.

- Multidrug-resistant tuberculosis (MDR-TB) is caused by an isolate of M. tuberculosis which is resistant to two or more of the first-line chemotherapeutic agents, usually isoniazid and rifampin.

- Primary drug-resistance is said to occur in a patient who has never received antituberculosis therapy.

- Secondary resistance refers to the development of resistance during or following chemotherapy, for what had previously been drug-susceptible tuberculosis.

Diagnosis

The diagnosis of drug-resistant tuberculosis depends upon the collection and processing of adequate specimens for culture prior to the institution of therapy. Sputum cultures are positive in 85 to 90 percent of cases of pulmonary tuberculosis, and every attempt should be made to collect adequate material before treatment is initiated. If a patient cannot produce an expectorated sputum sample, sputum induction should be performed. If an adequate sample is still not produced, bronchoscopy may provide diagnostic material for culture in a significant number of cases, although the risks of nosocomial transmission of potentially drug-resistant tuberculosis must be weighed against the benefits of the procedure [2]. In patients with exclusively extrapulmonary disease, samples of involved tissue (eg, lymph nodes, bone, blood) should be obtained.

Susceptibility testing for first and second-line agents should be performed at a reliable reference laboratory. Improvements in culture techniques and molecular diagnosis (eg, PCR) permit more rapid identification of antibiotic resistance than was possible when solid medium alone was used for mycobacterial growth [3-5].

A careful history must be obtained from every patient with tuberculosis before treatment begins, and while drug susceptibility data are pending. Clinical and radiographic features on presentation are not altered in comparison with drug-susceptible disease, but several demographic and historical features should raise the suspicion of drug-resistant tuberculosis. These include:

- Previous treatment for active tuberculosis, particularly if therapy was self-administered
- HIV infection
- Contact with a case of drug-resistant tuberculosis
- Failure to respond to empiric therapy, particularly if adherence to therapy has been documented

In cases in which prior antituberculosis therapy has been prescribed, the physician must obtain a complete record of all previous cultures, drug susceptibility testing results, and treatment.

Chemotherapy of Monoresistant Disease

If drug-resistant disease is suspected on historical or clinical grounds, therapy should be instituted with at least two new drugs which the patient has not received previously, and to which community isolates are sensitive. Treatment of these infections in HIV-infected patients is discussed in detail elsewhere.

Effective therapy for drug sensitive and isoniazid monoresistant tuberculosis is associated with very high (>95 percent) success rates, defined by bacteriologic and clinical response, and low relapse rates (<5 percent), defined as recurrence of culture-positive disease after completion of therapy. The trials discussed below were all performed in HIV-negative persons; however, similar responses can be expected in HIV-infected patients, although many experts choose to prolong therapy for 3 months in this setting.

Isoniazid monoresistance – Tuberculosis resistant to isoniazid (INH) should be treated with a rifamycin (rifampin or rifabutin), pyrazinamide, and ethambutol for six to nine months, or four months after culture conversion [6]. This recommendation is based upon trials conducted by the Hong Kong Chest Service/British Medical Research Council, which demonstrated success rates of 95 to 98 percent with this type of regimen among 107 patients with INH-resistant disease [7]. Some experts consider continuing isoniazid in the setting of "low-level" INH resistance, ie, resistant to a concentration of 0.2 μg/mL but sensitive to 2.0 μg/mL.

The New York City Department of Health has recommended that a quinolone (ciprofloxacin 750 mg BID or ofloxacin 400 mg BID) be added to this regimen for the duration of therapy [8]. While this approach may be advisable in patients with HIV infection or an unusually high burden of organisms, no randomized, controlled data demonstrate improved outcomes with this approach. It has not been our practice to add a quinolone in this setting.

Rifampin monoresistance – Rifampin monoresistance most often occurs in HIV-positive patients and represents an uncommon but increasingly frequent clinical problem [9-11]. Because rifampin is the cornerstone of all 6-month regimens, resistance to this drug requires prolongation of treatment. Treatment regimens are based on large trials conducted before the introduction of rifampin, in which success rates of greater than 95 percent were documented with prolonged treatment. Acceptable regimens include:

• Streptomycin, isoniazid, and pyrazinamide given together for 9 months. This is the shortest duration regimen with good efficacy for use in rifampin monoresistance, and it is our preferred regimen.

Some experts recommend extending treatment to 12 months for HIV-infected patients who do not convert their sputum cultures and clinically improve during the first 2 months of treatment [6,12].

• Isoniazid and ethambutol given for 18 months, in some cases supplemented by streptomycin for the first 3 to 6 months [13-15]. We prefer to supplement with streptomycin as noted when this regimen is used.

Of the 14 mutant RNA polymerase alleles which confer resistance to rifampin, 9 also confer high level resistance to rifabutin [16]. Approximately 25 percent of rifampin-resistant clinical isolates are sensitive to rifabutin, which appears as effective clinically as rifampin in short-course regimens for patients with drug-sensitive disease [17-19]. However, no data are available regarding short-course, rifabutin-containing regimens in patients with rifabutin-sensitive, but rifampin-resistant disease. Therefore, its use in this setting cannot be recommended at the present time.

Suggested treatment regimens for multidrug-resistant tuberculosis

Resistance pattern	Regimen	Duration*
Isoniazid, ethambutol ± streptomycin	Rifampin or rifabutin Pyrazinamide Quinolone Amikacin or capreomycin	6-12 months
Isoniazid, streptomycin, pyrazinamide	Rifampin or rifabutin Ethambutol Amikacin or capreomycin	6-9 months
Isoniazid, rifampin, ± streptomycin	Pyrazinamide Ethambutol Quinolone Amikacin or capreomycin	18-24 months
Isoniazid, rifampin, ethambutol, ± streptomycin	Pyrazinamide Quinolone Amikacin or capreomycin 2 of 3: ethionamide PAS cycloserine	24 months after sputum culture negative
Isoniazid, rifampin, pyrazinamide, ± streptomycin	Ethambutol Quinolone Amikacin or capreomycin 2 of 3: ethionamide PAS Cycloserine	24 months after sputum negative
Isoniazid, rifampin, pyrazinamide, ethambutol, ± streptomycin	Quinolone Amikacin or capreomycin Ethionamide PAS Cycloserine	24 months after sputum negative

*Treatment duration should generally be longer in patients with HIV infection. Duration of amikacin or capreomycin administration is usually about 6 months, although longer administration (up to a year) is possible with careful monitoring of drug levels, renal function, and eighth cranial nerve function.

Pyrazinamide monoresistance – Single drug-resistance to pyrazinamide requires a nine month regimen of isoniazid and rifampin. This combination is well studied, and has a greater than 96 percent success rate in large trials [20-22].

Monoresistance to other agents – Single drug resistance to ethambutol, streptomycin, or second line agents is of little clinical significance. Patients can still be treated with the standard short course regimen of two months of isoniazid, rifampin, and pyrazinamide followed by four months of isoniazid and rifampin, which yields success rates of around 97 percent [23].

Chemotherapy of Multidrug-Resistant Disease

There have been few controlled trials of the therapy of multidrug-resistant tuberculosis; treatment recommendations are based upon experience in patients who had been previously treated and relapsed, as well as prevailing practices at referral centers for MDR cases [24]. The key principle underlying treatment of multidrug-resistant tuberculosis is to always add at least two additional drugs to which the isolate is susceptible. Suggested treatment regimens are listed in Table 1, and the dosages of second-line agents are given in Table 2.

Dosages and Minimal Inhibitory Concentrations of Injectable and Second-line Agents for Tuberculosis

Drug	Usual adult daily dose†	Usual MIC (μg/mL)
Injectable agents		
Streptomycin	15 mg/kg	0.25-2.0
Amikacin	15 mg/kg	0.5-1.0
Kanamycin	15 mg/kg	1.5-3.0
Capreomycin	15 mg/kg	1.25-3.5
Second-line drugs		
Ciprofloxacin	750 mg BID	0.25-2.0
Ofloxacin	400 mg BID	0.25-2.0
Ethionamide	250 mg BID to TID	0.3-1.2
Cycloserine	250 mg BID to TID	Not established
PAS	3 gm QID	Not established

†The dosage for the injectable aminoglycosides when given 2 or 3 times per week is the same as the daily dosage listed.

When resistance is present to two or more of the four first-line oral drugs, most experts recommend that a parenteral aminoglycoside (streptomycin, kanamycin, amikacin, or capreomycin) and a quinolone (ciprofloxacin, ofloxacin, levofloxacin, or sparfloxacin) be added. Treatment with parenteral agents is usually given for six months, and cures rates are high (in the 85 percent range) for MDR-TB regimens that include these two classes of drugs. Treatment in HIV-positive patients should be continued until 24 months after culture conversion; follow-up visits every four months for an additional 24 months are recommended to monitor for relapse [6].

Aminoglycosides – The injectable aminoglycosides may all cause nephrotoxicity and eighth cranial nerve damage; renal function should be assessed regularly, and audiometry performed on a monthly basis. The aminoglycoside is usually given daily or either two or three times per week. Cross-resistance between kanamycin and amikacin is common, but is rarely observed among the other agents in this class. Patients who cannot tolerate repeated intramuscular injections may receive intravenous therapy through an indwelling catheter.

Quinolones – None of the quinolones is approved by the Food and Drug Administration for use against tuberculosis, but some authors attribute the improved prognosis of MDR-TB over the past decade largely to the administration of these agents [25,26]. Quinolone antibiotics have considerable in vitro activity against M. tuberculosis and have become widely used in the treatment of MDR-TB [27]. However, there are few useful data from controlled trials to define the exact role of these drugs in the treatment of tuberculosis.

Sparfloxacin is the most active quinolone against M. tuberculosis in vitro, followed by levofloxacin, ofloxacin, and ciprofloxacin. Complete cross-resistance within this class of drugs is generally present, so that resistance to one quinolone implies resistance to all. As a group, the quinolones are usually well tolerated, with few treatment-limiting adverse effects except photosensitivity reactions (reported in up to 8 percent of patients taking sparfloxacin) [28,29].

Other second-line agents – A number of second-line drugs are less active against tuberculosis and have considerable adverse effects, making them difficult to use.

- Ethionamide is a nicotinic acid derivative with structural similarities to isoniazid. It can cause significant

gastrointestinal upset, hepatitis, neurologic reactions, and hypothyroidism. One mechanism of isoniazid resistance, mutations in the inhA gene, also is associated with ethionamide resistance.

• Para-aminosalicylic acid (PAS) is one of the oldest antituberculosis drugs, and inhibits the growth of M. tuberculosis by interfering with folate metabolism. It is difficult to tolerate secondary to nausea, vomiting, and diarrhea, but a recently approved enteric-coated formulation may have fewer gastrointestinal side effects.

• Cycloserine has been associated with a variety of adverse psychological effects, including psychosis, anxiety, and severe depression. Pyridoxine (vitamin B6) should be co-administered (at a dose of 50 mg for every 250 mg of cycloserine) to reduce the risk of neurotoxicity.

• Aerosolized interferon-gamma has been used as ancillary treatment in patients with MDR-TB who are failing multiple agent chemotherapy. One open label trial consisted of five patients with smears and cultures positive for pulmonary MDR-TB despite at least five months of observed appropriate therapy; the patients were treated with recombinant human interferon-gamma (500 μg via aerosol given three times per week for one month) [30]. Two months after ending treatment, which was well tolerated, acid-fast bacilli were cleared from the sputum, body weight stabilized or increased, and the size of cavitary lesions was reduced. Interferon-gamma is normally produced by CD4+ T lymphocytes and serves to activate alveolar macrophages; it may be a useful adjunctive therapy in patients with MDR-TB who are otherwise not responding to treatment.

Adherence to Therapy

Compliance with therapy is crucial, but is particularly difficult for patients with MDR-TB because regimens are prolonged and employ drugs with considerable adverse effects. For these reasons, directly observed therapy (DOT) is mandatory for all patients with drug-resistant tuberculosis. It insures compliance, thereby eliminating the major cause of treatment failure [31]. Regular observation also allows collection of sputum samples, which can be used to provide an objective assessment of clinical response.

Serum drug levels – Therapeutic drug level monitoring is not routinely performed. However, low serum levels of antituberculosis drugs have been reported in patients with overt malabsorption and in some patients with HIV infection even in the absence of clinical malabsorption [32,33]. For this reason, monitoring serum drug levels may be useful in patients who do not respond clinically to a directly observed, seemingly appropriate regimen [34].

Surgical Therapy

Most patients with MDR-TB respond to appropriate chemotherapy. However, patients with sputum cultures positive for longer than three months despite appropriate therapy or with isolates resistant to all of the first-line oral agents have a worse prognosis. These patients may benefit from surgical intervention[35].

Patients with localized pulmonary disease which can be completely removed at operation are most likely to benefit from surgery [35,36]. Drug therapy is often given for 1 to 3 months before surgery to try to reduce the bacteriologic burden, but there are no firm guidelines or data about this issue. Resection alone should not be considered curative; patients with MDR-TB should continue the best possible drug regimen for 18 months after surgery.

Prevemtive Therapy for Contacts of Drug-Resistant Tuberculosis

There is obviously no way to determine whether or not a person with a positive tuberculin test has been exposed to a case of drug-resistant tuberculosis without a careful contact investigation, and the role of the health department is vital in this regard. After a thorough contact investigation, an estimate should be made both of the likelihood of recent infection with a resistant strain and the risk of the contact developing active tuberculosis. These factors should then be weighed against the risks of preventive regimens of unknown benefit before therapy is prescribed [37].

Exposure to isoniazid monoresistant tuberculosis – Contacts of INH mono-resistant tuberculosis can be treated for two months with the combination of a rifamycin (rifampin or rifabutin) plus pyrazinamide [6]. A four to six month regimen of a rifamycin alone is acceptable in patients who cannot tolerate pyrazinamide; we favor six months of therapy in this setting.

Exposure to rifampin monoresistant tuberculosis – Contacts of patients with rifampin monoresistant tuberculosis can be treated with the usual isoniazid regimen given to patients with exposure to drug-sensitive organisms.

Exposure to multidrug-resistant tuberculosis – Treatment of contacts to MDR cases is difficult because there are no published data concerning the composition, duration, or efficacy of preventive regimens for MDR-TB. Potential regimens which have been suggested (based primarily on animal studies) include pyrazinamide and ethambutol, or pyrazinamide and a quinolone, with drugs given in the doses to treat active disease, for 6 to 12 months.

Prevention of Multidrug-Resistant Tuberculosis

The best way to prevent MDR-TB is by prompt institution of appropriate therapy with efforts to guarantee adherence to therapy. Proper infection control will also limit spread to others. However, there may be instances in which ongoing contact with cases of multidrug-resistant tuberculosis on a regular basis is unavoidable. This may the case for selected health care workers in facilities which treat significant numbers

of MDR-TB patients. In these instances, consideration may be given to vaccination with Bacille Calmette-Guérin [38]. This vaccine is felt to be roughly 50 percent protective when given to children, and is most useful in preventing meningitis and disseminated disease. It should be stressed that the use of BCG vaccine in the prevention of MDR-TB is not well established and should be employed only as a measure of last resort, since the ability to perform screening tuberculin examinations will be lost after the vaccine is administered.

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