SECOND-LINE ANTITUBERCULOSIS DRUGS

Second-line antituberculosis agents are indicated for treatment of drug-resistant TB, for patients who are intolerant or allergic to first-line agents, and when first-line supplemental agents are unavailable.

Fluoroquinolones Fluoroquinolones inhibit mycobacterial DNA gyrase and topoisomerase IV, preventing cell replication and protein synthesis, and are bactericidal. The later-generation fluoroquinolones levofloxacin and moxifloxacin are the most active against *M. tuberculosis* and are recommended for the treatment of MDR-TB. They are also being investigated for their potential to shorten the course of treatment for TB. In a recent trial, gatifloxacin, which had been withdrawn from the market because of significant dysglycemia, was assessed for treatment shortening; although its inclusion in the TB treatment regimen did not shorten the duration of therapy from 6 to 4 months, the drug did not cause dysglycemia in TB patients who took it thrice weekly for 4 months. Ciprofloxacin and ofloxacin are no longer recommended for the treatment of TB because of poor efficacy. Despite the documented resistance of the infecting strains to these and other early-generation fluoroquinolones, use of a later-generation fluoroquinolone in patients with XDR-TB has been associated with favorable outcomes. Fluoroquinolones are also considered safe alternatives for patients who develop treatment-limiting adverse effects due to first-line agents. Levofloxacin and moxifloxacin have both been used effectively in the treatment of MDR-TB. The optimal dose of levofloxacin for this indication is being actively studied, but doses of at least 750 mg are commonly used.

The fluoroquinolones are well absorbed orally, reach high serum levels, and distribute well into body tissues and fluids. Their absorption is decreased by co-ingestion with products containing multivalent cations, such as antacids. Adverse effects are relatively infrequent (0.5–10% of patients) and include gastrointestinal intolerance, rashes, dizziness, and headache. Most studies of fluoroquinolone side effects have been based on relatively short-term administration for bacterial infections, but trials have now shown the relative safety and tolerability of fluoroquinolones administered for months during TB treatment in adults. Although the potential to prolong the QTc interval, leading to cardiac arrhythmias, has been a source of concern with fluoroquinolones, cessation of treatment due to this adverse effect is rare. There is increasing interest in the use of fluoroquinolones in children, which has traditionally been avoided because of the risks of tendon rupture and cartilage damage, because the benefits in treatment of drug-resistant TB may outweigh the risks.

Mycobacterial resistance can develop rapidly when a fluoroquinolone is inadvertently administered alone. Empirical fluoroquinolone therapy for presumed community-acquired pneumonia is associated with increased fluoroquinolone resistance in *M. tuberculosis*. Mutations in the genes encoding for DNA gyrase (*gyrA* and *gyrB*) are implicated in the majority of cases—but not all cases—of clinical resistance to fluoroquinolones.

Injectable Agents • ***CAPREOMYCIN*** Capreomycin, a cyclic peptide antibiotic derived from *Streptomyces capreolus*, is an important first-choice second-line agent used for treatment of MDR-TB, particularly when additional resistance to aminoglycosides is documented. Capreomycin is administered by the IM route; an inhaled preparation is under study. A dose of 15 mg/kg per day is given five to seven times per week (maximal daily dose, 1 g) and results in peak blood levels of 20–40 μg/mL. The dosage may be reduced to 1 g two or three times per week 2–4 months after mycobacterial cultures become negative. For individuals ≥60 years of age, the dose should be reduced to 10 mg/kg per day (maximal daily dose, 750 mg). For patients with renal insufficiency, the drug should be given intermittently and at lower dosage (12–15 mg/kg two or three times per week). A minimal duration of 3 months is recommended for MDR-TB treatment. Penetration of capreomycin into the CSF is believed to be poor.

The mechanism of capreomycin's action is not well understood but involves interference with the mycobacterial ribosome and inhibition of protein synthesis. Resistance to capreomycin is associated with mutations that inactivate a ribosomal methylase (*tlyA*) or that encode genes for the 16S ribosomal subunit (*rrs*). Cross-resistance to kanamycin and amikacin is common with *rrs* but not always with *tylA* mutations. However, some strains that are resistant to streptomycin, kanamycin, and amikacin generally remain susceptible to capreomycin.

Adverse effects of capreomycin are relatively common. Significant hypokalemia and hypomagnesemia as well as oto- and renal toxicity have been reported.

AMIKACIN AND KANAMYCIN Amikacin and kanamycin are aminoglycosides that exert mycobactericidal activity by binding to the 16S ribosomal subunit. The spectrum of antibiotic activity for amikacin and kanamycin includes *M. tuberculosis*, several NTM species, and aerobic gram-negative and gram-positive bacteria. Although amikacin is highly active against *M. tuberculosis*, it is used only infrequently because of its significant side effects. The usual daily adult dosage of both amikacin and kanamycin is 15–30 mg/kg given IM or IV (maximal daily dose, 1 g), with a reduction to 10 mg/kg for patients ≥60 years old. For patients with renal insufficiency, the dose and frequency should be reduced (12–15 mg/kg two or three times per week). Mycobacterial resistance is due to mutations in the genes encoding the 16S ribosomal RNA gene. Cross-resistance among kanamycin, amikacin, and capreomycin is common. Isolates resistant to streptomycin are frequently susceptible to amikacin or kanamycin. Adverse effects of amikacin include ototoxicity (in up to 10% of recipients, with auditory dysfunction occurring more commonly than vestibulotoxicity), nephrotoxicity, and neurotoxicity. Kanamycin has a similar side-effects profile, but adverse reactions are thought to be less frequent and less severe.

Other Second-Line Agents • ***ETHIONAMIDE*** Ethionamide is a derivative of isonicotinic acid. Its mechanism of action is through inhibition of the *inhA* gene product enoyl–acyl carrier protein (acp) reductase, which is involved in mycolic acid synthesis. Ethionamide is bacteriostatic against metabolically active *M. tuberculosis* and some NTM. It is used in the treatment of drug-resistant TB, but its use is limited by severe gastrointestinal reactions (including abdominal pain, nausea, and vomiting) as well as significant central and peripheral neurologic side effects, reversible hepatitis (in ~5% of recipients), hypersensitivity reactions, and hypothyroidism. Ethionamide should be taken with food to reduce gastrointestinal effects and with pyridoxine (50–100 mg/d) to limit neuropathic side effects.

CYCLOSERINE Cycloserine is an analog of the amino acid D-alanine and prevents cell wall synthesis. It inhibits the action of enzymes, including alanine racemase, that are involved in the production of peptidoglycans. Cycloserine is active against a range of bacteria, including *M. tuberculosis*. Mechanisms of mycobacterial resistance are not well understood, but overexpression of alanine racemase can confer resistance in *Mycobacterium smegmatis*. Cycloserine is well absorbed after oral administration and is widely distributed throughout body fluids, including CSF. The usual adult dosage is 250 mg two or three times per day. Serious potential side effects include seizures and psychosis (with suicide in some cases), peripheral neuropathy, headache, somnolence, and allergic reactions. Drug levels are monitored to achieve optimal dosing and to reduce the risk of adverse effects, especially in patients with renal failure. Cycloserine should be administered as DOT only with caution and with support from experienced TB physicians to patients with epilepsy, active alcohol abuse, severe renal insufficiency, or a history of depression or psychosis.

PARA-AMINOSALICYLIC ACID Para-aminosalicylic acid (PAS, 4-aminosalicylic acid) is an oral agent used in the treatment of MDR- and XDR-TB. Its bacteriostatic activity is due to inhibition of folate synthesis and of iron uptake. PAS has relatively little activity as an anti-TB agent. Adverse effects may include high-level nausea, vomiting, and diarrhea. PAS may cause hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency. The drug should be taken with acidic foods to improve absorption. Enteric-coated PAS granules (4 g orally