every 8 h) appear to be better tolerated than other formulations and produce higher therapeutic blood levels. PAS has a short half-life (1 h), and 80% of the dose is excreted in the urine.

***CLOFAZIMINE*** Clofazimine is a fat-soluble riminophenazine dye used primarily in the treatment of leprosy worldwide. It is currently gaining popularity in the management of MDR- and XDR-TB because of its low cost and intracellular and extracellular activity. By increasing reactive oxygen species and causing membrane destabilization, clofazimine may promote killing of antibiotic-tolerant *M. tuberculosis* persister organisms. In addition to antimicrobial activity, the drug has other pharmacologic properties—e.g., anti-inflammatory, pro-oxidative, and immunopharmacologic. Clofazimine has a half-life of ~70 days in humans, and average steady-state concentrations are achieved at ~1 month. Ingestion with fatty meals can improve its low and variable rates of absorption (45–62%). Common side effects include gastrointestinal intolerance and reversible orange-to-brownish discoloration of the skin, bodily fluids, and secretions. Dose adjustment may be necessary in patients with severe hepatic impairment. Clofazimine is being studied as part of a regimen developed in Bangladesh for potential shortening of the MDR-TB treatment course. A recent meta-analysis suggested that inclusion of clofazimine in a multidrug regimen for treatment of MDR-TB was associated with a favorable outcome. Newer analogues with improved pharmacokinetics and alternative formulations of clofazimine (liposomal, nanosuspension, inhalational) are being studied.

## NEWER ANTITUBERCULOSIS DRUGS

**Oxazolidinones** Linezolid is an oxazolidinone used primarily for the treatment of drug-resistant gram-positive bacterial infections. However, this drug is active in vitro against *M. tuberculosis* and NTM. Several case series have suggested that linezolid may help clear mycobacteria relatively rapidly when included in a regimen for the treatment of complex cases of MDR- and XDR-TB. Linezolid's mechanism of action is disruption of protein synthesis by binding to the 50S bacterial ribosome. Linezolid has nearly 100% oral bioavailability, with good penetration into tissues and fluids, including CSF. Clinical resistance to linezolid has been reported, but the mechanism is unclear. Adverse effects may include optic and peripheral neuropathy, pancytopenia, and lactic acidosis. Linezolid is a weak monoamine oxidase inhibitor and can be associated with the serotonin syndrome when given concomitantly with serotonergic drugs (primarily antidepressants such as selective serotonin-reuptake inhibitors). A recent meta-analysis showed that ~80% of patients with MDR- or XDR-TB can be successfully treated with linezolid-containing anti-TB regimens; however, significant adverse events attributed to linezolid were reported. For MDR-TB treatment, linezolid is usually administered at a dose of 600 mg (or less in some cases) once daily, which appears to be effective. The single daily dose is associated with fewer adverse events than twice-a-day dosing.

PNU 100480 and AZD 5847, modified versions of oxazolidinones and protein synthesis inhibitors, are undergoing phase 1 trials and appear to have greater efficacy than linezolid against *M. tuberculosis*. However, the adverse effect profiles of these compounds compared with that of linezolid need further investigation.

**Amoxicillin-Clavulanate and Carbapenems** β-Lactam agents are largely ineffective for the treatment of *M. tuberculosis* because of resistance conferred by a hydrolyzing class A β-lactamase. Because clavulanate may theoretically inhibit the β-lactamase, amoxicillin-clavulanate has been used in the treatment of MDR-TB; however, it is a comparatively weak agent. Carbapenems are poor substrates for class A β-lactamases found in *M. tuberculosis*. Accordingly, meropenem and imipenem have in vitro activity against *M. tuberculosis*, and their use to treat MDR- and XDR-TB has been reported anecdotally. Nevertheless, the need to administer carbapenems by the IV route and lack of information on the drugs' long-term side effects have restricted their use to certain severe cases only.

**Diarylquinolines** Bedaquiline (TMC207 or R207910) is a new diarylquinoline with a novel mechanism of action: inhibition of the mycobacterial ATP synthetase proton pump. TMC207 is bactericidal for drug-susceptible and MDR strains of *M. tuberculosis*. Resistance has been reported and is due to point mutations in the *atpE* gene encoding for subunit c of ATP synthetase. A phase 2 randomized controlled clinical trial in MDR-TB patients demonstrated substantial improvement in 2-month culture-conversion rates as well as a reduction in acquired resistance to companion drugs. This drug is metabolized by the hepatic cytochrome CYP3A4. Rifampin lowers TMC207 levels by 50%, and protease inhibitors also interact significantly with this drug. The oral bioavailability of TMC207 appears to be excellent. The dosage is 400 mg/d for the first 2 weeks and then 200 mg thrice weekly. The elimination half-life is long (>14 days). A single dose of this drug can inhibit the growth of *M. tuberculosis* for up to 1 week through a combination of long plasma half-life, high-level tissue penetration, and long tissue half-life. Bedaquiline added to a background regimen improved the 2-month sputum culture conversion rate in multicenter, randomized placebo-controlled trials, and these results led to approval by the U.S. Food and Drug Administration (FDA). However, a higher death rate in one trial was observed in the bedaquiline arm than in the control arm (11.4% vs 2.5%); the result was a "black box" warning from the FDA, which also included QT prolongation. The Centers for Disease Control and Prevention has made a provisional recommendation for the use of bedaquiline for 24 weeks in adults with laboratory-confirmed pulmonary MDR-TB when no other effective treatment regimen can be provided.

**Nitroimidazoles** The prodrugs delamanid (OPC-67683) and PA 824 are novel nitro-dihydro-imidazooxazole derivatives that are activated by *M. tuberculosis*–specific flavin-dependent nitroreductases whose antimycobacterial activity is attributable to inhibition of mycolic acid biosynthesis. These drugs are currently in phase 2 clinical trials and show potential in shortening treatment duration through their activity against nonreplicating drug-susceptible and drug-resistant mycobacteria. Delamanid was shown in a randomized, placebo-controlled, multinational clinical trial to significantly improve the culture conversion rate at 2 months. QT prolongation occurred significantly more often in delamanid-treated patients, but no clinically relevant events were reported.

**Diamines** SQ109, an ethambutol analogue with a 1,2-diamine pharmacophore, is the most promising of the diamines for TB treatment. It is activated by mycobacterial cytochrome enzymes and inhibits mycobacterial cell-wall synthesis by an unknown mechanism. It has a high tissue protein-binding capacity with a very long half-life (~61 h) in humans. In vitro studies have demonstrated that SQ109 has low MICs against both susceptible and resistant *M. tuberculosis* strains as well as a synergistic effect when administered with isoniazid and rifampin. The drug is under study in clinical trials for TB treatment.

**Pyrroles** LL3858, a pyrrole derivative, has entered clinical trials examining its utility in the treatment of drug-susceptible and drug-resistant TB. The drug's mechanism of action is unknown. However, because it is active against *M. tuberculosis* strains that are resistant to available anti-TB drugs, its target is thought to differ from those of currently used agents.

## NONTUBERCULOUS MYCOBACTERIA

More than 150 species of NTM have been identified. Only a minority of these environmental organisms, which are found in soil and water, are important human pathogens. NTM cause extensive disease, primarily in persons with preexisting pulmonary disease or immunocompromise, but also can cause nodular/bronchiectatic disease in otherwise seemingly healthy hosts. NTM are also important causes of infections in surgical settings. The two major classes of NTM are the slow-growing and rapidly growing species; subcultures of the latter grow within 1 week. The growth characteristics of NTM have diagnostic, therapeutic, and prognostic implications. The rate of growth can provide useful preliminary information within a specific clinical context, in that growth within 2–3 weeks is much more likely to indicate an NTM than *M. tuberculosis*. When NTM do grow from cultures, colonization should be distinguished from active disease in order to optimize the