risk and benefit of prolonged treatment with multiple medications. According to the recommendations of the American Thoracic Society and the Infectious Diseases Society of America, significant clinical manifestations and/or sputum radiographic evidence of progressive disease consistent with NTM infection as well as either reproducible sputum culture results or a single positive culture are required for the diagnosis of NTM pulmonary disease. Isolation of NTM from blood or from an infected-appearing extrapulmonary site, such as soft tissue or bone, is usually indicative of disseminated or local NTM infection (Chap. 204). Treatment of NTM disease is prolonged and requires multiple medications. Side effects of the regimens employed are common, and intermittent therapy is often used to mitigate these adverse events. Treatment regimens depend on the NTM species, the extent or type of disease, and—to some degree—drug susceptibility test results. The nodular bronchiectatic form of MAC infection is generally treated three times per week, whereas fibrocavitary or disseminated MAC infection is treated daily.

THERAPEUTIC CONSIDERATIONS FOR SPECIFIC NTM

***M. avium* Complex** Among the NTM, MAC organisms most commonly cause human disease. In immunocompetent hosts, MAC species are most often found in conjunction with underlying significant lung disease, such as chronic obstructive pulmonary disease or bronchiectasis. For patients with nodular or bronchiectatic MAC lung disease, an initial regimen consisting of clarithromycin or azithromycin, rifampin or rifabutin, and ethambutol is given three times per week. Routine initial testing for macrolide resistance is recommended, as is testing at 6 months with a failing regimen (i.e., with cultures persistently positive for NTM).

In immunocompromised individuals, disseminated MAC infection is generally treated with clarithromycin, ethambutol, and rifabutin. Azithromycin may be substituted in patients unable to tolerate clarithromycin. Amikacin and fluoroquinolones are often used in salvage regimens. Treatment for disseminated MAC infection in AIDS patients may be lifelong in the absence of immune reconstitution. At least 12 months of MAC therapy and 6 months of effective immune reconstitution may be adequate.

M. kansasii *M. kansasii* is the second most common NTM causing human disease. It is also the second most common cause of NTM pulmonary disease in the United States, where it is most often reported in the southeastern region. *M. kansasii* infection can be treated with isoniazid, rifampin, and ethambutol; therapy continues for 12 months after culture conversion. Rifampin-resistant *M. kansasii* has been treated with clarithromycin, trimethoprim-sulfamethoxazole, and streptomycin.

Rapidly Growing Mycobacteria Rapidly growing mycobacteria causing human disease include *Mycobacterium abscessus, Mycobacterium fortuitum*, and *Mycobacterium chelonae*. Treatment of these mycobacteria is complex and should be undertaken with input from experienced clinicians. Testing for macrolide resistance is recommended. However, in rapidly growing mycobacteria, an inducible *erm* gene may confer in vivo macrolide resistance to isolates that are susceptible in vitro.

M. marinum *M. marinum* is an NTM found in salt water and freshwater, including swimming pools and fish tanks. It is a cause of localized soft-tissue infections, which may require surgical management. Combination regimens include clarithromycin and either ethambutol or rifampin. Other agents with activity against *M. marinum* include doxycycline, minocycline, and trimethoprim-sulfamethoxazole.

DRUGS FOR THE TREATMENT OF NTM

Clarithromycin

Clarithromycin is a macrolide antibiotic with broad activity against many gram-positive and gram-negative bacteria as well as NTM. This drug is active against MAC organisms and many other NTM species, inhibiting protein synthesis by binding to the 50S mycobacterial ribosomal subunit. NTM resistance to macrolides is probably caused by overexpression of the gene *ermB*, with consequent methylation of the binding site. Clarithromycin is well absorbed orally and distributes well to tissues. It is cleared both hepatically and renally; the dosage should be reduced in renal insufficiency. Clarithromycin is a substrate for and inhibits cytochrome 3A4 and should not be administered with cisapride, pimozide, or terfenadine because cardiac arrhythmias may occur. Numerous drugs interact with clarithromycin through the CYP3A4 metabolic pathway. Rifampin lowers clarithromycin levels; conversely, rifampin levels are increased by clarithromycin. However, the clinical relevance of this interaction does not appear to be great.

For patients with nodular/bronchiectatic MAC infection, the dosage of clarithromycin is 500 mg, given morning and evening three times a week. For the treatment of fibrocavitary or severe nodular/bronchiectatic MAC infection, a dose of 500–1000 mg is given daily. Disseminated MAC infection is treated with 1000 mg daily. Clarithromycin is used in combination regimens that typically include ethambutol and a rifamycin in order to avoid the development of macrolide resistance. Adverse effects include frequent gastrointestinal intolerance, hepatotoxicity, headache, rash, and rare instances of hypoglycemia. Clarithromycin is contraindicated during pregnancy because of its teratogenicity in animal models.

Azithromycin Azithromycin is a derivative of erythromycin. Although technically an azalide and not a macrolide, it works similarly to macrolides, inhibiting protein synthesis through binding to the 50S ribosomal subunit. Resistance to azithromycin is almost always associated with complete cross-resistance to clarithromycin. Azithromycin is well absorbed orally, with good tissue penetration and a prolonged half-life (~48 h). The usual dosage for treatment of MAC infection is 250 mg/d or 500 mg three times per week. Azithromycin is used in combination with other agents to avoid the development of resistance. For prophylaxis against disseminated MAC infection in immunocompromised individuals, a dose of 1200 mg once per week is given. Because azithromycin is not metabolized by cytochrome P450, it interacts with few drugs. Adjustment of the dosage on the basis of renal function is not necessary.

Cefoxitin Cefoxitin is a second-generation parenteral cephalosporin with activity against rapidly growing NTM, particularly *M. abscessus, M. marinum*, and *M. chelonae*. Its mechanism of action against NTM is unknown but may involve inactivation of cell wall synthesis enzymes. High doses are used for treatment of NTM: 200 mg/kg IV three or four times per day, with a maximal daily dose of 12 g. The half-life of cefoxitin is ~1 h, with primarily renal clearance that requires adjustment in renal insufficiency. Adverse effects are uncommon but include gastrointestinal manifestations, rash, eosinophilia, fever, and neutropenia.

CONCLUSION

Treatment of mycobacterial infections requires multiple-drug regimens that often exert significant side effects with the potential to limit tolerability. The prolonged duration of treatment has vastly improved results over those obtained in past decades, but drugs and regimens that will shorten treatment duration and limit adverse drug effects and interactions are needed.