Medications and Monitoring in Nontuberculous Mycobacteria Infections

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KEYWORDS

• Nontuberculous mycobacteria • *Mycobacterium avium* complex • Macrolides • Ethambutol • Rifamycins • β-Lactams • Pharmacokinetics

KEY POINTS

- In general, multiple drugs are needed to treat nontuberculous mycobacteria (NTM) infections in order to prevent the selection of drug resistance.
- Pharmacokinetic and especially pharmacodynamic indices are not well established for NTM infections.
- Because of the lack of agents specifically developed for NTM, and the lack of pharmacodynamic indices for the currently available drugs, treatment is long and often ineffective.
- Prospective studies are needed to determine appropriate drug regimens for most NTM species.

INTRODUCTION

Nontuberculous mycobacteria (NTM) encompass more than 200 species of bacteria. Of these, only a small number of species are known to cause human disease; most commonly *Mycobacterium avium* complex (MAC), *Mycobacterium kansasii* and the *Mycobacterium abscessus* group. MAC and *M kansasii* are slow-growing mycobacteria. Doubling times for these mycobacteria approach 1 day, and they may take longer than a week to form mature colonies.[1] These infections often are treated with macrolides plus other antimycobacterial drugs, such as ethambutol, rifampin, or rifabutin. Another major group are the rapidly growing mycobacteria, which include *M abscessus* (including *M abscessus* subsp. *bolletii* and *M abscessus* subsp. *abscessus*), *Mycobacterium chelonae*, and *Mycobacterium fortuitum*.[2] Drug regimens for the rapidly growing mycobacteria depart significantly from the treatment of *Mycobacterium tuberculosis* (Mtb) or MAC.

The drugs used for the treatment of these infections were not designed specifically for NTM. The rationale for their use has often been extrapolated from the treatment of tuberculosis. Many of the prospective studies for NTM were conducted in patients with acquired immunodeficiency syndrome (AIDS) with disseminated MAC, before the advent of highly active antiretroviral therapy. It is not known whether the study results from disseminated MAC infections in patients with AIDS can be

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extrapolated to other situations, such as nodular bronchiectatic lung infections in elderly women. Randomized clinical trials for pulmonary NTM are rare in such patients, or those with chronic obstructive pulmonary disease. Understanding of the treatment of pulmonary NTM infections is limited, and is based largely on trial and error: Treatment usually lasts months to years. Long-term monotherapy leads to drug resistance. Drug combinations are needed to prevent resistance.[3]

NTM infections are increasingly common in the elderly, and age-related changes in drug absorption, metabolism, and excretion may lead to decreased efficacy and increased toxicity.[4] The extended durations of treatment often lead to adverse drug reactions, drug interactions, and patient nonadherence or treatment discontinuation. Given these obstacles, it is imperative that clinicians begin to optimize the use of these drugs, and find better drugs.

This issue discusses specific treatment regimens for the slow-growing and rapidly growing mycobacteria, as well as treatment in special populations. This article provides information about the drugs commonly used to treat NTM, the use of therapeutic drug monitoring (TDM), and clinical monitoring for adverse drug reactions.

MACROLIDES

The macrolides (clarithromycin and azithromycin) are the cornerstones of treatment of most slow-growing NTM infections. Some rapidly growing NTM can be treated with macrolides, but *M fortuitum* and *M abscessus* often are macrolide resistant because of the presence of the *erm* gene.[5] Isolates from previously treated patients with NTM also show higher rates of macrolide resistance, making any subsequent treatment far less likely to succeed. Therefore, it is necessary to avoid macrolide monotherapy, and it is necessary to make the initial NTM treatment as effective as possible in order to prevent macrolide resistance.[6]

Macrolides bind to the 50S subunit of bacterial ribosomes and prevent protein synthesis. Typical clarithromycin minimal inhibitory concentrations (MICs) for MAC isolates are 1 to 4 μg/mL.[7] Clarithromycin has been more commonly used than azithromycin because it has been studied more extensively. However, clarithromycin is both a substrate for and inhibitor of cytochrome P (CYP) 3A enzymes, whereas azithromycin is not. Thus, azithromycin often is preferred in order to avoid drug interactions, including with the rifamycins.

Clarithromycin generally is dosed at 500 mg twice daily, producing peak concentrations (C_{max}) of 2 to 7 μg/mL 2 to 3 hours after the dose (time of peak [T_{max}]). Azithromycin is dosed at 250 mg or, more often, 500 mg daily, producing C_{max} of 0.2 to 0.7 μg/mL (10-fold lower than clarithromycin) and a T_{max} about 2 hours after the dose. Macrolide tissue concentrations are far greater than serum concentrations: 2-fold to 20-fold greater with clarithromycin and 10-fold to 100-fold greater for azithromycin.[8] As noted, clarithromycin is metabolized by CYP3A4. Its primary metabolite, 14-hydroxy-clarithromycin, is not active against most NTM. Therefore, unlike *Haemophilus influenzae* infections, the clarithromycin metabolite does not seem to contribute to treatment. Combinations with rifamycins, especially rifampin, convert much of clarithromycin to the 14-OH form, and this likely detracts from therapy.

Food has minor effects on absorption of clarithromycin, slightly delaying T_{max}, increasing C_{max} by 24%, and reducing its area under the concentration versus time curve (AUC) by only 11%.[9] Food has similarly minor effects on azithromycin oral tablet absorption, increasing C_{max} by 23% (or by 56% for the azithromycin oral suspension).[10] With either formulation, the azithromycin AUC remains largely unchanged. Note that the azithromycin extended-release oral suspension is not bioequivalent to the immediate-release formulation (83% relative bioavailability), and therefore cannot be used interchangeably.[10]

Gastrointestinal (GI) disturbances are the most common adverse effect seen with the macrolides. Diarrhea, nausea/vomiting, and abdominal pain often are reported.[11] Switching macrolides (from clarithromycin to azithromycin, or vice versa) may be tried, or antiemetics may be tried if that fails. Azithromycin and clarithromycin are both associated with QT prolongation.[12–14] In 2013, the US Food and Drug Administration (FDA) issued a warning regarding azithromycin use and the risk of fatal heart rhythms.[15,16] In 2014, a large observational study of Danish patients showed an increased risk of cardiac death in patients taking clarithromycin compared with those taking penicillin V.[17] Macrolide use should be used with caution in patients with underlying heart disease, electrolyte abnormalities, or those taking other medications that can prolong the QT interval.[18]

RIFAMYCINS (RIFAMPIN/RIFABUTIN)

The rifamycins have broad antimicrobial coverage and are often used in the treatment of NTM infections. Rifamycins inhibit DNA-dependent RNA-polymerase, which prevents transcription of DNA to RNA.[19] The rifamycins show concentration-dependent killing of mycobacteria. Therefore, increasing exposure increases efficacy and reduces

resistance.[20] The current usual rifampin dose is 10 mg/kg. A rifampin oral dose of 600 mg yields a C_{max} of 8 to 24 μg/mL approximately 2 hours after the dose.[21] Food reduces the C_{max} approximately 35%, with little effect on the AUC. Thus, rifampin should be given on an empty stomach.[22] Reduced or delayed absorption may occur with certain disease states, particularly diabetes, human immunodeficiency virus (HIV), and cystic fibrosis.[23,24]

Treatment can be particularly difficult to manage in patients with HIV coinfected with MAC. Rifampin and rifapentine greatly reduce the concentrations of many antiretroviral agents; a less pronounced reduction is seen with rifabutin.[25] The rifamycins are metabolized by esterases to desacetylated derivatives. Although rifampin and rifapentine are not CYP substrates, the rifamycins are capable of autoinduction, showing a reduced AUC with repeated administration.[26]

Rifampin generally is well tolerated. Clinically relevant adverse effects include nausea, rash, and occasional hepatotoxicity. Rifampin-induced hepatitis occurs in up to 2.5% of patients treated with multidrug regimens, and it does not seem to be dose related.[27] The flulike syndrome is uncommon, and occurs most often with higher rifampin doses (1200 mg or more) given once or twice weekly.[28,29] Higher daily doses of rifampin seem to avoid the flulike syndrome. The rifamycins are potent inducers of CYP450 enzymes and several other enzymes and transporters, leading to numerous drug interactions. For example, clarithromycin concentrations are reduced by 50% with rifabutin and 90% by rifampin.[30]

Rifabutin is structurally similar to rifampin, but is more lipid soluble.[31] The increased lipid solubility results in a larger volume of distribution and slower clearance. Rifabutin's terminal half-life is approximately 37 hours. A 300-mg dose of rifabutin produces a C_{max} of 0.3 to 0.9 μg/mL (30-fold lower than rifampin) approximately 3 hours after the dose. Food does not affect rifabutin's C_{max} or AUC, but may cause a delay in absorption.[32]

In our experience, rifabutin is not well tolerated by many patients with NTM. Griffith and colleagues[33] noted similar results in patients with MAC treated with a thrice-weekly regimen of clarithromycin, ethambutol, and rifabutin. Twenty-four of 59 patients required a dose decrease or removal of the drug because of adverse effects.[33] In addition, rifabutin is a CYP3A4 substrate, resulting in bidirectional interactions. Important examples include clarithromycin and the azoles.[30,34]

Unlike rifampin, rifabutin is subject to concentration-related adverse effects. The risk of uveitis, leukopenia, and arthralgia increases with increasing concentrations. In general, high rifabutin concentrations are caused by the presence of a CYP inhibitor. For example, in a study of patients with HIV on a multidrug regimen of clarithromycin, rifabutin, and ethambutol, clarithromycin concentrations were decreased by rifabutin's enzyme induction, and rifabutin concentrations were increased because of clarithromycin inhibition.[35] Ritonavir and cobicistat can also increase rifabutin concentrations. Whenever a rifamycin is used, the clinician should examine the patient's maintenance medications, including antihypertensives, antiepileptics, and so forth, for additional drug-drug interactions.[36,37]

Rifapentine, a cyclopentyl derivative of rifampin, is approved for tuberculosis (TB) treatment. To date, it has not been studied for use in patients with NTM.

ETHAMBUTOL

Ethambutol's antimicrobial activity is limited to mycobacteria. It may be used for slow-growing NTM; rapidly growing NTM normally show high levels of resistance. Daily doses typically are 15 to 25 mg/kg, and produce a C_{max} of 2–6 μg/mL 2–3 hours after the dose.[38] For Mtb, intermittent doses (2 times weekly) as high as 50 mg/kg are used.

Optic neuritis is the most common adverse effect seen with ethambutol. Elderly patients and young patients with decreased renal function are at an increased risk because of reduced clearance. Snellen eye charts are used to test for visual acuity, whereas Ishihara color plates are used for red-green color discrimination. Patients should be tested at baseline and periodically during treatment. Increased serum uric acid values are occasionally seen with ethambutol. Drug interactions with ethambutol are uncommon.

FLUOROQUINOLONES

Ciprofloxacin, levofloxacin, and moxifloxacin are sometimes used for NTM infections. However, their role is not well established. For example, it is unclear whether the fluoroquinolones, when combined with macrolides, are able to prevent the selection of macrolide-resistant NTM. The fluoroquinolones show concentration-dependent killing of most bacteria and Mtb.

Ciprofloxacin doses of 500–750 mg (once or twice daily) produce a C_{max} of 4 to 6 μg/mL about 2 hours after the dose. Levofloxacin doses of 750–1000 mg once daily produce a C_{max} range of 8 to 12 μg/mL about 2 hours after the dose. Moxifloxacin doses of 400 mg daily produce a C_{max} of 3 to 5 μg/mL about 2 hours after the dose. Higher

doses (600–800 mg daily) are being studied in patients with TB, but dose escalation must be done cautiously because of the risk of QT prolongation.[39] All 3 fluoroquinolones show extensive tissue penetration. Levofloxacin is renally cleared, whereas ciprofloxacin and moxifloxacin are cleared both renally and hepatically.

QT prolongation is the most serious class of adverse event requiring monitoring. Central nervous system adverse effects (headache, dizziness) and phototoxicity may occur. Tendinopathy also occurs with fluoroquinolone use.[40,41] Fluoroquinolones have a black-box warning regarding tendon rupture.[42] Risk factors for tendon rupture include advanced age (>60 years old), renal insufficiency, steroid use, type II diabetes, and a prior history of musculoskeletal disorders.[40,43] As with many antibiotics, patients should be warned of GI adverse effects such as nausea/vomiting and diarrhea.[44]

Drug interactions are not common with the fluoroquinolones. It is best not to administer fluoroquinolones within 2 hours of drugs, supplements, or foods containing divalent or trivalent cations because this may lead to the formation of insoluble chelating complexes and poor absorption of the fluoroquinolones.[45,46] Rifampin and rifapentine reduce moxifloxacin serum concentrations by 20% to 30%.[47–49] Increasing the moxifloxacin dose from 400 to 600 mg followed by TDM should be considered when moxifloxacin is coadministered with a rifamycin. Diabetic patients prescribed fluoroquinolones should monitor their glucose concentrations. In 2006, gatifloxacin was withdrawn from the market because of concerns over both hypoglycemic and hyperglycemic events.[50] Drug-induced dysglycemia has been associated with many of the remaining fluoroquinolones.[51]

AMINOGLYCOSIDES

Aminoglycosides show concentration-dependent killing of bacteria and mycobacteria. As a class, the aminoglycosides have similar pharmacokinetic profiles.[52] Amikacin and streptomycin are administered either intravenously or by intramuscular injection. Intravenous infusions can be given over 30 minutes.[53] Intramuscular injections typically are absorbed between 30 to 90 minutes. Typical aminoglycosides doses are 15 mg/kg daily, or 25 mg/kg when administered twice or thrice weekly. Smaller doses reduce the C_{max}, and may reduce efficacy. Linear regression is used to back-calculate to the end of the infusion and determine the C_{max}. As an alternative, Bayesian pharmacokinetic programs may be used. Daily doses produce a calculated C_{max} of 35 to 45 μg/mL (back-calculated to 1 hour after intramuscular doses, or to the end of the intravenous infusion), whereas intermittent dosing produces a C_{max} of 65 to 80 μg/mL.[21] Elimination is by glomerular filtration, and doses need to be adjusted in patients with renal insufficiency. Elimination half-lives are 2 to 4 hours, depending on renal function. No metabolites have been identified thus far.

The primary clinical concerns with the aminoglycosides are auditory, vestibular, or nephrotoxicity. In a prospective study by Peloquin and colleagues,[54] toxicity was not related to either the size of the dose or the frequency of administration. An increased risk of ototoxicity was associated with older age and a larger cumulative dose.[54] It is common practice at some centers to reduce the dose to 10 mg/kg in older patients. However, this may be counterproductive. It may reduce efficacy without changing toxicity, which could prolong treatment, leading to a higher risk of toxicity in the longer term.

Drug interactions are minimal, because the aminoglycosides are not substrates or inducers/inhibitors of CYP enzymes. However, concurrent use with other potential nephrotoxins (eg, amphotericin B) may lead to additive nephrotoxicity.

CLOFAZIMINE

Clofazimine is best known for its role in the treatment of leprosy (caused by *Mycobacterium leprae* and possibly *Mycobacterium lepromatosis*). It has been used occasionally in the treatment of NTM infections. MICs range from 0.06 to 2 μg/mL, with many of the rapidly growing mycobacteria showing MICs of less than or equal to 1 μg/mL.[55,56] Its mechanism of action is not completely known. It may inhibit mycobacterial replication by binding to the guanine base of DNA.[57]

Clofazimine became less favored for NTM when a clinical study found that clofazimine plus clarithromycin and ethambutol was associated with increased mortality in disseminated MAC infections in patients with AIDS.[58] Clofazimine's use for other NTM infections remains poorly documented. In vitro studies show evidence that clofazimine may act synergistically with amikacin against rapidly growing NTM species.[56] However, this action remains to be demonstrated clinically. In addition, clofazimine can be difficult to obtain. In the United States, clinicians must submit an individual investigational new drug application to the FDA. In addition, cross-resistance between bedaquiline and clofazimine has been reported.[59] In vitro tests indicate that bedaquiline could be a potent NTM antibiotic, although that also remains to be demonstrated clinically.

Clofazimine is highly lipophilic, and it displays a long terminal half-life. Clofazimine is administered orally, most often at 100 mg daily. T_{max} normally is observed at 2 to 3 hours, but may be highly variable. Typical serum concentrations range from 0.5 to 2 μg/mL. Absorption is increased with food.

The most common adverse effect with clofazimine is a dose-related hyperpigmentation of body tissues.[60] This discoloration is visible within the first month of therapy, resulting in a tanning or bronzing effect seen in most individuals. Patients should be counseled that this bronze discoloration can last for a year following discontinuation of the drug. Drying of the skin may occur, but usually responds to the use of skin moisturizers. Photosensitivity may occur, so patients should use sunscreen and hats, and should avoid sun exposure when possible. Discoloration of the eye caused by crystalline deposits within the cornea and conjunctiva also can occur.[61] Crystal deposition may cause severe GI effects, necessitating discontinuation of the drug.[62] Drug interactions are uncommon.

LINEZOLID

An oxazolididione, linezolid, has activity against a large number of gram-positive bacteria, including many mycobacteria, such as Mtb and NTM.[63] Linezolid binds to the 23S subunit of a bacterium's ribosome to prevent protein synthesis.[64] MIC values range from 0.5 to 4 μg/mL for Mtb and most gram-positive cocci.[64,65] MICs are variable for NTM species.[64] In vitro testing of 53 clinical isolates showed that *M abscessus* and *Mycobacterium intracellulare* were the least susceptible to linezolid, whereas *M avium* and *Mycobacterium gordonae* were the most susceptible.[66] However, data are limited regarding linezolid's clinical efficacy.

Oral linezolid is completely absorbed, with bioavailability close to 100%. The dose for mycobacteria has not been established clearly. Empirical, once-daily dosing has been tried. The standard dose for gram-positive bacteria is 600 mg twice daily, and this produces C_{max} of 12 to 26 μg/mL 1 to 2 hours after the dose. C_{max} decreases approximately 17% when linezolid is taken with food, but AUC is unaffected.[67] Linezolid has good tissue penetration, producing concentrations higher than the MIC.[68] The drug has an elimination half-life of about 4 to 6 hours.

Linezolid may be considered for NTM infections, especially in cases in which organisms are resistant to primary choices.[69] Linezolid use is limited by its long-term adverse effects, including myelosuppression, ocular and peripheral neuropathy, and lactic acidosis. In a review by Narita and colleagues,[70] optic neuropathy resolved in those patients who stopped linezolid, but those experiencing peripheral neuropathy did not fully recover. The exact mechanisms through which these toxicities occur is not certain, but mitochondrial damage is strongly suspected.[71]

Linezolid is a weak monoamine oxidase inhibitor and increases the risk of serotonin toxicity (serotonin syndrome) when combined with additional serotonergic agents.[72] Although the incidence is small, clinicians should be aware of the potential interaction. Concurrent use of linezolid with rifampin may reduce linezolid serum concentrations. Two other oxazolidinones, AZD-5847 and PNU-100480 (sutezolid), are currently being investigated for use in TB treatment. Their roles for NTM infections currently are not known.

ISONIAZID

Aside from Mtb, isoniazid's (INH) coverage of mycobacteria is limited. Isoniazid's MIC range is 0.01 to 0.25 μg/mL for Mtb.[73,74] Among the NTM, *Mycobacterium xenopi* and *M kansasii* are susceptible, but *M kansasii* typically requires higher INH concentrations.

Isoniazid is a prodrug, converted by the enzyme katG within mycobacteria to its active form. The INH intermediates that are formed interfere with mycolic acid synthesis, disrupting the bacterial cell wall.[75] Organisms without katG display INH resistance. A C_{max} of 3 to 5 μg/mL is seen with 300 mg oral doses, whereas a C_{max} of 9 to 15 μg/mL is achieved with intermittent (2–3 times weekly) 900-mg doses. Isoniazid generally is well absorbed, although high-fat meals reduce isoniazid's C_{max} by 50%.[76] T_{max} typically is 1 to 2 hours after the dose, but may be delayed with a high-fat meal.[76] Isoniazid is widely distributed with a volume of distribution around 0.7 L/kg.[76] Isoniazid is metabolized by the liver to inactive metabolites, primarily by acetylation via *N*-acetyl transferase 2. Isoniazid's half-life in slow acetylators is between 3 and 4 hours, whereas for fast acetylators the half-life is less than 2 hours. Hepatotoxicity occurs in a small percentage of patients taking isoniazid. Chronic alcohol intake, age greater than 35 years, preexisting hepatic disease, and the concurrent use of other hepatotoxins are all considered risk factors. Isoniazid inhibits CYP450 enzymes, including CYP3A4 and CYP2C19, and may inhibit or induce CYP2E1.[77,78] In particular, the antiepileptics carbamazepine and phenytoin may have significant increases in plasma concentrations.[79,80] Clinicians should monitor patients for

signs of toxicity (eg, ataxia, nystagmus) and routinely measure drug concentrations if concurrent use cannot be avoided.[80]

TIGECYCLINE

Tigecycline is a glycylcycline, specifically designed to avoid the resistance seen with the tetracyclines.[81] As with the tetracyclines, tigecycline binds to the bacterium's 30S ribosomal subunit and prevents protein synthesis.[82] Tigecycline is FDA approved for skin/soft tissue infections, as well as complicated intra-abdominal infections.[83] It has shown promise against the rapidly growing mycobacteria. Tigecycline has a reported MIC range between 0.06 and 0.25 μg/mL for *M chelonae* and *M fortuitum*, and 0.06 to 1 μg/mL for *M abscessus*.[84] Wallace and colleagues[85] reported favorable results when tigecycline was used as salvage treatment in patients with *M abscessus* and *M chelonae*. However, 90% of the patients experienced significant GI effects (nausea and vomiting), and less than half of the patients received the recommended dose of 100 mg daily. The average dose was not described. In this study, the use of antiemetic drugs became routine. Even though the manufacturer's recommended dose is 50 mg, in our experience some patients cannot tolerate even 25 mg of tigecycline daily without pretreatment with an antiemetic. The requirement for intravenous dosing also limits its appeal. Dosing for bacterial infections is every 12 hours. The frequency of dosing for NTM is less certain but, in the recent study described earlier, many patients improved on once-daily dosing.

Tigecycline is extensively distributed, with a volume of distribution between 7 and 10 L/kg.[86] The half-life has a wide range, caused by variability in the volume of distribution.[87] This variability may reflect nonlinear binding in the plasma or tissue.[87] C_{max} following a 1-hour infusion is about 1 μg/mL.

As noted, GI adverse effects are the primary complaint of most patients.[85] Tolerability may be improved by slowly increasing the dose and the use of antiemetics. Other adverse effects include photosensitivity, drug-induced hepatitis, risk of pancreatitis, and tooth discoloration in young children (as seen with other tetracyclines). In addition, the FDA reported an increased risk of death with tigecycline compared with other drugs used to treat serious skin and intra-abdominal infections. It carries a black-box warning for this reason.[16] However, there are conflicting studies regarding this warning statement.[88–90] Drug interactions with tigecycline are rare. Concurrent use of tigecycline with warfarin showed an increase in warfarin's AUC, but did not have a significant impact on International Normalized Ratio (INR).[83]

CEFOXITIN

Cefoxitin occasionally is used for treating NTM infections, particularly rapidly growing NTM.[91] Cefoxitin works by binding to penicillin-binding proteins (PBPs) that interfere with bacterial cell wall synthesis. Cefoxitin usually is administered intravenously to patients with NTM. Specific dosing for NTM species has not been established. Some clinicians recommend 1 to 2 g every 6 hours.[92] Cefoxitin has a half-life of about 45 minutes. Cefoxitin is renally eliminated, and dosage should be adjusted in patients with renal dysfunction.[91] Cefoxitin generally is well tolerated. GI adverse effects and local injection site reactions are the most common toxicities. High doses of β-lactams can, rarely, cause seizures.[91,93] Drug interactions with cefoxitin are rare. Probenecid increases cefoxitin serum concentrations through competitively inhibiting tubular secretion.[91] Patients taking warfarin may experience an increase in INR when used concurrently with cefoxitin.[91]

IMIPENEM

Like cefoxitin, imipenem occasionally is used to treat NTM infections. For *M chelonae*, imipenem is preferred because *M chelonae* is resistant to cefoxitin.[94,95] Imipenem binds to PBPs and interferes with bacterial cell wall synthesis. Imipenem is administered intravenously. Specific dosing for NTM species has not been established. Some clinicians recommend 500 mg 2 to 4 times daily.[96] Imipenem has a half-life of about 1 hour.[97] Adverse effects include GI and injection site reactions. In addition, imipenem has the potential for causing seizures that exceeds that of other β-lactams.[98] Drug interactions are rare. Similar to cefoxitin, imipenem may interact with probenecid and warfarin.[97] In addition, imipenem should be used cautiously with cyclosporine, ganciclovir, theophylline, and valproic acid.[97]

MONITORING DRUG TOXICITY DURING TREATMENT

As discussed by van Ingen and colleagues elsewhere in this issue, sputum microbiology remains the gold standard for monitoring the response to treatment of pulmonary NTM infections. However, many patients with NTM cannot produce an adequate sputum specimen for the initial diagnosis, and most stop producing sputum at some

point during the course of effective treatment. TDM can help clinicians determine the best doses for drugs by revealing poor or delayed drug absorption or lack of adherence, and by untangling serious drug interactions. When tested (primarily with Mtb), antimycobacterial drug efficacy clearly is concentration dependent. Some adverse effects, such as ethambutol ocular toxicity, are also concentration dependent, so a clear rationale can be set forth for measuring and adjusting doses based on serum concentrations (**Table 1**). Otherwise, clinicians lack direct control over the drug therapy. In practice, obtaining TDM can be challenging, including issues related to preauthorization and medical insurance coverage, and related to logistical issues for patients who may need to travel considerable distances to have the samples collected.

Parameters for the clinical monitoring of adverse drug effects are shown in **Table 2**. The current ATS-IDSA guidelines on the management of NTM infections recommend monitoring for adverse drug reactions periodically, routinely, or at repeat intervals.[96] The exception is monitoring for ethambutol-induced optic neuritis, with monthly testing of visual acuity and color vision. This recommendation seems to be borrowed from guidelines for managing TB.[90] Some TB guidelines suggest monitoring for hepatotoxicity monthly; every 2 months; or at months 1, 3, and 6. However, those guidelines also review the lack of clinical trial evidence showing a benefit from such monitoring.[99] There is no definitive study regarding the optimal frequency of monitoring of patients with NTM for adverse drug reactions. Unlike patients with TB, patients with NTM do not receive directly observed therapy, and patients with NTM tend to be treated for much long periods of time. Our compromise in the University of Florida NTM Clinic has been to monitor blood tests (eg, cell blood count, liver function tests) every 3 months in patients without symptoms of adverse reactions. We also suggest this period for monitoring of visual acuity and color vision, or a professional eye examination if patients have no visual symptoms. This approach seems to be logistically feasible and tolerable for most patients. However, we also educate patients at each visit to report any new symptoms that may be adverse events; adverse events can occur during the intervals of monitoring tests.

Table 1
Targeted maximum drug concentrations for TDM

Drug	Dose	Concentration Target Range (μg/mL)
Clarithromycin	500 mg	2–7
Azithromycin	500 mg	0.2–0.7
Amikacin (daily)	15 mg/kg	35–45[a]
Streptomycin (daily)	15 mg/kg	34–45[a]
Rifampin	600 mg	8–24
Rifabutin	300 mg	0.3–0.9
Ciprofloxacin	750 mg	4–6
Levofloxacin	750–1000 mg	8–12
Moxifloxacin	400 mg	3–5
Ethambutol	20 mg/kg	2–6
Linezolid	600 mg	12–26
Isoniazid (daily)	300 mg	3–5
Tigecycline	25–50 mg	1

[a] Back-calculated to end of infusion or 1 hour after intramuscular dose.

Common serious adverse drug reactions include ototoxicity from the aminoglycosides. Amikacin often is added for cavitary MAC infections, or for *M abscessus* group infections. Unlike streptomycin, amikacin serum concentrations are easy to obtain. Peripherally inserted central catheters are well used in patients with NTM, given the long durations of treatment. Baseline serum blood urea nitrogen (BUN) and serum creatinine levels can be checked as often as weekly to observe for nephrotoxicity. Serum amikacin concentrations are described earlier. Baseline and periodic audiology evaluations are advisable on all patients who receive either systemic or inhaled amikacin. Many patients with NTM are elderly, and they frequently have mild baseline hearing loss or tinnitus. Such patients may require more frequent audiometry. Patients should be instructed to call their clinicians immediately with any symptoms of increasing tinnitus, decreased hearing, unsteadiness of gait, vertigo, or lightheadedness. We aim to obtain audiometry at baseline and after 2 weeks of intravenous amikacin. If it is stable and there are no other symptoms, monthly audiometry is reasonable. Testing for vestibular toxicity can be performed with a Romberg test, ideally while the patient is standing on compliant foam. Additional tests are available.[100,101]

Optic neuritis caused by ethambutol is a toxicity that many clinicians and patients seem to fear out of proportion to its true incidence. Current NTM guidelines suggest monitoring for toxicity at monthly visits. Although it may seem intuitive that monitoring monthly would be more sensitive in detecting toxicity, we are not aware of data to support that practice. We ask our patients to have their

Table 2
Monitoring parameters

Drug	Adverse Events	Monitoring Parameters	Comment
Clarithromycin	GI, QT prolongation	EKG, LFTs Baseline audiogram	CYP3A4 inhibitor
Azithromycin	GI, QT prolongation	EKG, LFTs Baseline audiogram	—
Aminoglycosides	Vestibular/auditory, renal	BUN, SCr Audiometry Romberg test	Caution when using with other potential nephrotoxins. Monitor renal function. Monitor for auditory and vestibular toxicity
Rifampin	Hepatotoxicity, flulike syndrome	CBC, LFTs	Potent enzyme inducer May monitor renal function
Rifabutin	Uveitis	CBC, LFTs	—
Ciprofloxacin	GI, tendonitis, QT prolongation	EKG	—
Levofloxacin	GI, tendonitis, QT prolongation	EKG	—
Moxifloxacin	GI, tendonitis, QT prolongation	EKG	—
Ethambutol	Optic neuritis	Baseline eye examination Snellen eye chart Ishihara color plates	Baseline color vision and visual acuity should be conducted at initial visit and each month thereafter
Linezolid	Neuropathy Thrombocytopenia, myelosuppression Optic neuritis	Symptoms CBC Eye examinations Snellen eye chart, Ishihara color plates	—
Isoniazid	Liver, peripheral neuropathy	LFTs	Administer with pyridoxine
Tigecycline	GI	LFTs Amylase, lipase	—
Cefoxitin	GI, seizures	CBC, LFTs, renal function	Cannot replace with other cephalosporins
Imipenem	GI, seizures	CBC, LFTs, renal function	—

Abbreviations: BUN, blood urea nitrogen; CBC, complete blood count; EKG, electrocardiogram; LFTs, liver function tests; SCr, serum creatinine.

vision checked with at least a Snellen vision chart and Ishihara color plates at least every 3 months. This testing can be done with their primary care physicians or with their eye care specialists, as they choose, and usually results in patients being seen about every 6 to 8 weeks. We educate patients about optic neuritis and ask that they stop the ethambutol and call us, or their eye clinician, if there is any question of a change in vision, and we review this at every visit. This practice has usually resulted in the detection of eye diseases other than optic neuritis. The 3-month interval also seems to be an appropriate frequency to monitor the complete blood count for rifampin, imipenem or tigecycline toxicity, and liver function tests to detect drug-induced hepatitis from rifampin, the macrolides, imipenem, or tigecycline. Serum BUN and creatinine levels can be used to assess renal function, as needed. Although uncommon, renal function changes induced by rifampin or β-lactam can occur. We also test amylase and lipase levels for patients on tigecycline and renal function for patients on imipenem. This interval is also the frequency at which we prefer to follow our patients in the clinic, so logistically they are reminded to have their monitoring done before the clinic visit.

Although we are not aware of clinically significant QT prolongation causing life-threatening

arrhythmias in a patient with NTM, there has been increasing concern about QT prolongation with macrolides and we are now being more attentive to this risk.[15,102] We generally ask patients to provide us with a recent electrocardiogram (EKG); if not available then we obtain a baseline EKG. We then repeat the EKG 1 to 2 weeks after initiation of macrolide therapy to rule out significant QT prolongation.

We have found that the best way to avoid drug-drug interactions with both rifabutin and clarithromycin is simply to avoid using those drugs. We concur with the NTM guidelines that most patients with NTM, especially elderly women, do not tolerate rifabutin. Azithromycin generally is well tolerated, and its serum concentrations are less affected by rifampin than are those of clarithromycin. Some patients who tolerate clarithromycin better than azithromycin do so because they have very low drug concentrations, because of the interaction with rifampin. The macrolides also have been associated rarely with hearing loss, so we prefer to obtain a baseline audiology consultation given the anticipated long duration of treatment. We only repeat the audiometry if there are new symptoms suggesting ototoxicity.

There is a need for evidence to support specific monitoring of drug toxicities, and we suggest that this be studied in future clinical trials. Operational research also could evaluate the use of self-monitoring. In the modern age of smart phones, there are new applications for testing of both vision and hearing that could be used as screening tools by patients.

SUMMARY/DISCUSSION

The treatment of NTM infections is long, challenging, and sometimes ineffective. Data specific to the treatment of NTM infections, including detailed pharmacokinetic/pharmacodynamic data, are lacking. The drugs used are borrowed from the treatments of other types of infections, and data from large, prospective randomized trials to guide treatments are lacking. Thus, the data presented here can only be seen as suggestions based on current empirical evidence and clinical experience. It is hoped that in the future NTM-specific drugs will be dosed based on clinical trial data.

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