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The Role of Therapeutic Drug Monitoring in Mycobacterial Infections

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ABSTRACT Tuberculosis (TB) is a leading cause of infectious death. Nontuberculous mycobacteria (NTM) cause a wide variety of difficult-to-treat infections in various human hosts. Therapeutic drug monitoring (TDM) remains a standard clinical technique that uses plasma drug concentrations to determine dose. The reason to do this is simple: drug exposure (that is, the free drug area under the plasma concentration-time curve) relative to the MIC and not the dose *per se* largely determines the outcome of the infections. TDM provides objective information that clinician can use to make informed dosing decisions. The normal plasma concentration ranges provide reasonable guidance for initial target concentrations. Clinicians then combine concentration data with knowledge about the patients, in order to decide how aggressive to be with dosing. With sicker patients, who are closer to a poor outcome, one may be willing to accept an increased risk of potential toxicity in order to secure patient survival. In the clinic, time and resources are limited, so typically only two samples are collected postdose. The 2-h postdose concentrations approach the peak for most TB and NTM drugs. A 6-h sample allows the clinician to distinguish between delayed absorption and malabsorption, because patients with the latter need higher doses in order to gain the benefit associated with standard doses. Plasma concentrations do not account for all of the variability in patient responses to TB or NTM treatment, and concentrations cannot guarantee patient outcomes. However, combined with clinical and bacteriological data, TDM can be a decisive tool, allowing clinicians to look inside of their patients and adjust doses based on objective data. Knowing the dose, rather than guessing at the dose, is the path to shorter and more successful treatment regimens.

The treatment of active tuberculosis (TB) disease began in the 1940s (1). With the introduction of each new drug, different combinations were tried until investigators settled on the current regimen in the 1970s (while this author was still in high school) (2). The regimen of rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE) became the standard regimen for TB in countries with developed economies, while countries with smaller economies continued to use rifampin-sparing regimens in order to save money. Eventually, nearly all countries adopted the RIPE regimen, once it was clearly shown that treatment outcomes were significantly better with rifampin, despite the initial greater cost of the drug (3). This focus on cost remains a major driving force in the treatment of TB.

The focus on cost is very much in contrast to the treatment of other conditions, particularly in countries with developed economies. For example, on average, one heart-lung transplant costs about $2.3 million (4). Since TB treatment in the United States recently was estimated to cost about $17,000, for the price of one heart-lung transplant, approximately 135 TB patients, who have a communicable disease with airborne transmission, could be treated (5). The transplant patient will continue to receive whatever drugs and tests are needed to sustain the transplant, in an effort to protect the initial investment. It is a field where cost considerations are

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secondary, and personalized medicine is the standard of practice. In contrast, especially with prior treatment guidelines, TB treatment is very much standardized, and every effort is made to cut costs by making routine tests such as liver enzyme tests "optional" and extending the interval between doses to 2 doses per week (5, 6). Viewed in this light, it might be considered depersonalized medicine. That is not meant to detract from the very hard work done to control TB worldwide. It is meant to point up the fact that a system has been set up to make treatment as simple and as inexpensive as possible. The system is not set up to maximize treatment outcomes. It is the latter approach that we turn to in this chapter.

With the continued spread of multidrug- and extremely drug-resistant TB (MDR-TB and XDR-TB) globally, many clinicians are reevaluating TB treatment. Perhaps the system has been made too simple. Albert Einstein is often paraphrased as having said "Everything should be as simple as possible, but no simpler," and his words may apply to current TB treatment practices (7). The directly observed treatment, short-course (DOTS), strategy, including engaging local, regional, and national governments while administering directly observed doses, is an important part of improving treatment outcomes. Implementation of DOTS has been uneven, and in many areas it has not stemmed the tide of MDR- and XDR-TB. The standard regimen with the standard drug doses continues to be used, even though patients have become larger, heavier, more frequently diabetic, and often HIV infected (8, 9). Thus, the time seems to be right for a reevaluation of our treatment goals and methods.

TB treatment is guideline driven (6, 8). Yet even guidelines evolve, and the emphasis gradually shifts. Historically, the underlying pharmacology of the TB drugs has not been emphasized in TB treatment guidelines. Drug molecules are very small, and they must make their way from the dosage form swallowed by the patient, through the gut wall, past the liver, through the bloodstream, and to the site of infection. Only a fraction of the dose actually finds this path. At the site of infection, the drug molecules must enter the TB bacillus, locate the pharmacological target, and bind chemically to it. If the drug is not delivered to the site of infection (pharmacokinetics), it cannot produce these desired effects (pharmacodynamics) (10). There simply is no way around this. Compounding the situation is the consistent observation of wide interpatient variability in the pharmacokinetics of most TB drugs (11, 12). Thus, it is highly unlikely that one dose will fit all patients. That is an unreasonable expectation. Yet, it is precisely the expectation made when dosing rifampin and isoniazid in TB patients. Nearly everyone gets rifampin at 600 mg daily and isoniazid at 300 mg daily.

The approach for most other infectious diseases is to "hit early, hit hard." For some disease states, such as pneumonia, patients receive large doses of broad-spectrum antibiotics as soon as the diagnosis is made (13). TB, which most often presents as a type of pneumonia, currently does not benefit from this approach. However, gradually this is being reevaluated. The 2016 U.S. TB treatment guidelines, Appendix 3, now state the following (8):

> Basic antimicrobial pharmacology is predicated upon achieving adequate drug exposure. This exposure generally is quantified as the area under the curve (AUC) in a plot of unbound (protein-free, *f*) serum drug concentration versus time, divided by the minimal inhibitory concentration (MIC) (i.e., the *f*AUC/MIC). For certain antimicrobials, peak concentration (*f*Cmax/MIC) or time above MIC (*f*%Time>MIC) are more predictive of efficacy in the models or the patients studied. When *f*AUC/MIC or *f*Cmax/MIC are most predictive of microbial killing, antimicrobials are considered "concentration-dependent." Otherwise, when time above MIC (*f*%Time>MIC) is, antimicrobials are considered "time-dependent." The use of such pharmacokinetic/pharmacodynamic (PK/PD) data allow for the most effective employment of antimicrobials, achieving maximum pathogen killing in the shortest time possible. Historically, these measures of drug effect have not been quantified routinely in tuberculosis patients. Drug exposure (i.e., AUC) has been assumed to be "adequate" in all treated patients, regardless of their weight or condition, and this has led to some uncertainties in terms of optimal dosing of first-line drugs. Instead of an MIC, isolates only have been characterized as "susceptible or resistant" at a "critical concentration". In some locations, susceptibility data have not been used at all. Therefore, clinicians generally have not known how close serum drug concentrations were to achieving sub-MIC exposures in their patients. Even with weight adjustment, optimal dosing of PZA, for example, has yet to be determined. In prior guidance, PZA was recommended at 20 mg/kg/day (20-25 mg/kg/day); international guidelines recommend 25 mg/kg/day (20-30 mg/kg), however, the British Medical Research Council (BMRC) short-course clinical trials used PZA at 36 mg/kg/day. Further research is needed to establish the optimal dosing of PZA in terms of efficacy, safety and tolerability.

> Drug exposure is determined by the magnitude and the frequency of the dose. Drug exposure also is determined by the size of the patient, and the patient's ability to clear the drug through the liver and/or kidneys. Inadequate drug exposure has been shown to produce delayed treatment responses and failures, as well as drug resistance. Conversely, high drug exposures have been correlated with more rapid clearance of tuberculosis. Thus, drug exposure is a key driver of efficacy in tuberculosis patients, and fixed doses (INH 300 mg, RIF 600 mg) and "maximum" doses may not be appropriate for heavier patients. This document removes the term "maximum" dose.

It is often stated that TB treatment is 6 months long and over 95% effective. The British Medical Research

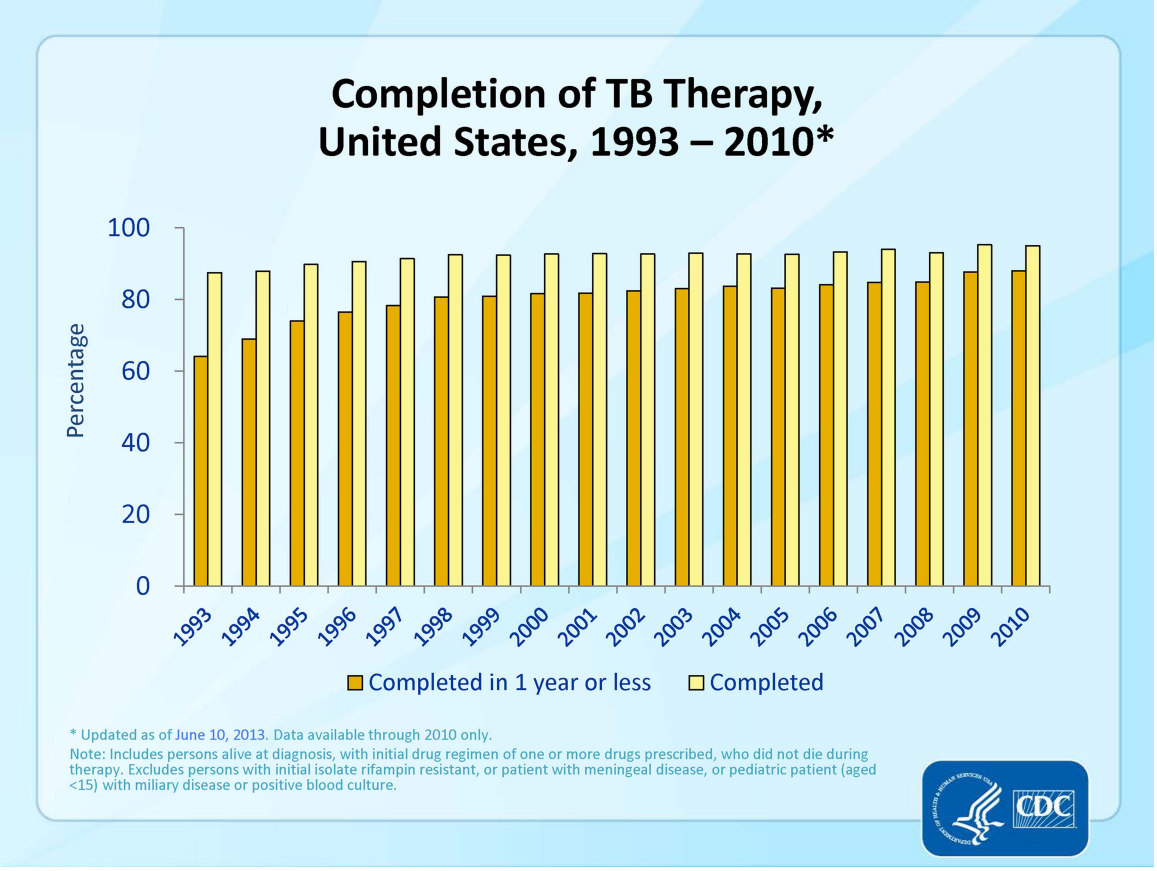

FIGURE 1 CDC slide showing that 88% of U.S. TB patients complete treatment at 12 months, not 6 months.

Council and the British Thoracic Association/Society clearly showed that is true, under certain conditions (2, 8). Those conditions were associated with prospective randomized clinical trials using per-protocol analyses. The 95% figure excludes the patients that did not qualify for the study, the patients that did not complete enrollment, and the patients that did not complete the treatment according to the protocol. The combination of excluded and dropped patients ran from 10% to 20% in these trials. In practical, clinical terms, the effectiveness may be closer to 75 to 80%. To achieve ≥95% efficacy in one's clinic assumes that the per-protocol situation will occur under routine programmatic conditions. That too is an unreasonable expectation, since one cannot exclude any patients from one's clinic. This probably explains the results shown in the annual TB slide set available at CDC.gov (Fig. 1) (14). In the United States, "cure," which requires 6 to 18 months of posttreatment follow-up, is not tracked, because U.S. TB treatment centers are not staffed or funded to do that. Instead, "completion" of drug therapy is tracked. According to the CDC, in 2010 the United States had an 88% completion rate over 12 months (not 6 months). Upon request, the CDC provided additional details: only 18% of patients completed treatment at 6 months, and only 45% of patients completed treatment at 7 months (Surveillance, Epidemiology, and Outbreak Investigations Branch, Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, personal communication). There are many reasons for this, and one that can be changed easily is that we are not using the right doses of the TB drugs.

For decades, the term "maximum dose" was added to prior treatment guidelines, even though that was not the original intent of the studies and despite the fact that the patients have continued to get much larger (6). The average weight of the East African and Hong Kong TB patients, who were predominantly male, in the published British Medical Research Council trials was around 48 kg (2, 10, 15, 16). Thus, the average rifampin dose was 12.50 mg/kg (of body weight), and the average isoniazid dose was 6.25 mg/kg. In many countries, TB patients may weigh twice as much. In the United States, the average male weighs 88.7 kg and the average

female 75.5 kg (17). For these average U.S. patients, the average rifampin dose in males is 6.76 mg/kg, and the average INH dose was 3.38 mg/kg. These drugs show concentration-dependent activity. By declaring "maximum doses" and by failing to adjust the doses for weight, we nearly have cut the doses and subsequent serum concentrations in half. In fact, the "maximum dose" of a drug is the dose that produces the desired effect while simultaneously producing an acceptable level of adverse effects. Thus, a very strong argument can be made to give the highest tolerated dose to each patient, for the shortest duration possible. Given the wide interpatient variability in drug exposure following fixed doses, therapeutic drug monitoring (TDM) allows one to know right away if the target is being hit (10, 18).

Drug exposure is the key to effective treatment. This has been shown in 3 CDC Tuberculosis Trials Consortium clinical trials: study 22, study 23, and study 29X (11, 19, 20). If there is too little drug exposure, the patient is at much greater risk of failure, relapse, or acquired rifamycin resistance (ARR). One has to get the exposure right, and the dose needed will vary from patient to patient. There is no right dose for all patients. There are only right exposures. There has never been a prospective, randomized trial of TDM versus no TDM in TB patients. As stated above, drug exposure is only 1 factor that determines the outcome of treatment (8, 10, 11, 18). Therefore, such a study would have to be very large to achieve statistical significance, since other factors also would be at play (21, 22). However, especially as proven in study 29X, drug exposure (specifically rifamycin drug exposure in that study) clearly drives treatment outcome (11). There was no association between outcome and the dose (11). It was only after drug exposure was considered that outcomes easily could be stratified. Therefore, outcomes can be predicted going forward.

Many clinicians in the United States and in Europe are experienced in using TDM (10, 18, 21–26). TDM is not "convenient" compared to no TDM, but it is not difficult. It is like drawing a serum chemistry panel twice on one day. It is "expensive" (in hundreds of dollars—not thousands) compared to no TDM. But it does allow one to quickly establish the right dose for a patient based on actual drug exposure. The benefits of appropriate drug exposure are clear. Thus, there is a cost and there is a benefit. There are insufficient data to state what percentage of patients will have the duration of treatment shortened by TDM. It is clear that drug exposure varies widely, and it is clear that exposure can be modified to the desired amount using TDM. Finally, low drug exposures that have been proven to be associated with treatment failure, relapse, and the selection of ARR can be identified early, and these poor outcomes easily can be averted (11, 19, 20). Table 1 lists one approach to prioritizing TDM if one is not able to perform TDM on every patient.

TABLE 1 Patients who especially may benefit from TDM

Critically ill patients
Meningitis patients
Osteomyelitis patients
HIV-coinfected patients
Diabetic patients
Patients with a history of gastrointestinal disease or gastrointestinal surgery
Renal failure patients
Hepatic disease patients
Patients receiving multiple interacting drugs

It has been well known for a long time that rifamycins are sterilizing drugs (that is, they prevent posttreatment relapses) (2, 8, 10–12). Rifamycins are one of two classes, along with pyrazinamide, proven to have sterilizing activity (2, 8, 10–12). Also well-established is the fact that sterilizing activity is concentration dependent (10–12). Higher concentrations produce more sterilizing activity. Verbist and Gyselen showed this as early as 1968, using a murine model and rifampin doses from 5 to 40 mg/kg (27). Since that time, several investigators have asked, "What is the right dose for rifampin?" (28–31) The answer is not 600 mg. Two studies with high-dose rifamycin are under way, with results to date showing improved mycobacterial killing with higher doses of rifampin (12, 32). PHS TB trials 22 and 23, using intermittent rifamycin treatments, clearly showed that poor drug absorption, particularly in HIV-coinfected patients, was associated with treatment failures, posttreatment relapses, and the selection of ARR (19, 20). Several other reports show that intermittent rifabutin (lower weekly exposures to rifabutin) is dangerous in HIV-coinfected patients (33–35). Study 29X has proven that better treatment outcomes correlate with higher rifamycin exposures (11). It is time to accept these very consistent results, which prove that drug exposure drives clinical outcome, and act on behalf of TB patients. Give the patients the drug exposure that they need to succeed.

Logistically, TDM is quite easy. As noted above, it is the same as collecting a serum chemistry panel. The main differences are that (i) one needs to record the time of the observed dose and (ii) one needs to record the times of the blood draws. At least in our laboratory,

this is facilitated by the laboratory order form. One just has to fill in the boxes as one goes. As noted previously (18):

> Since the trough concentrations for many of the TB drugs are below the limit of detection for the assays, and because the peak concentrations may be more important for several of these drugs, 2-hour post-dose samples can be collected to estimate the peak concentrations. For certain drugs, such as rifabutin, 3-hour samples approximate the peak concentrations better. Given the variability of oral drug absorption, single time points may miss the actual peak concentrations. Therefore, second samples, typically 6-hours post-dose (7 hours for rifabutin), allow one to capture information on the rate and completeness of drug absorption. The second samples also provide information regarding the elimination of drugs that have short half-lives, such as INH and rifampicin, provided that absorption was nearly completed 2-hours post-dose.
>
> The normal pattern for TB drug serum concentrations shows the 2-hour values substantially higher than the 6-hour values. Should the 2-hour and 6-hour values be similar, often somewhat below the expected 2-hour ranges, or should the 6-hour values be higher than the 2-hour values, delayed absorption likely is occurring. In these situations, it is possible that the peak concentrations occurred between the two blood draws. One may recommend that the patient take the drugs on an empty stomach, especially for INH and rifampicin. Finally, if both values are well below the expected ranges, malabsorption likely is occurring. With malabsorption, protein-free drug exposures may be lower than the MICs, and higher doses of the drugs may be used.

From these instructions, it is clear that much can be learned about the status of the patient from only two blood draws after an observed, timed dose. While this does not provide complete information, it does provide enough information to make dosing decisions. Relatively few TB drugs have clear concentration-dependent toxicity. Ethambutol (optic neuritis), probably cycloserine (central nervous system toxicity), and arguably pyrazinamide (hepatic toxicity) are examples where high drug exposures may not be tolerated (8, 10, 18). Likewise, ethionamide is famous for gastrointestinal intolerance. For ethionamide, the tablet dissolved in the gastric fluid appears to be the source of the problem, not elevated serum concentrations. The result is similar: certain patients cannot tolerate an ethionamide dose larger than 500 mg, even though there is reason to believe it would be more effective.

Finding the right dose very much becomes a personalized decision, tailored to the needs of the patient to achieve efficacy (associated higher concentrations) and to tolerate the regimen. Experience to date with high-dose rifampin (now up to 40 mg/kg and moving to 50), high-dose rifapentine (up to 20 mg/kg), and high-dose levofloxacin (up to 20 mg/kg) has been very encouraging (11, 12, 32, 36). Higher initial doses should mean that fewer patients start therapy with low drug exposures. However, the variability inherent to oral drug absorption is not eliminated by higher initial doses. Therefore, the reasons for using TDM remain, even when these higher doses become standard doses.

The management of infections with nontuberculous mycobacteria (NTM) is much less researched or standardized than TB treatment (37–41). Further, very little work regarding the pharmacokinetic/pharmacodynamic relationships for these infections has been done (39–43). The main drugs for several of these infections are the macrolide clarithromycin and the azalide azithromycin. In general, these drugs are used interchangeably. Typical doses are clarithromycin at 500 mg twice daily and azithromycin at 250 to 500 mg once daily. Typical peak concentrations are 2 to 7 μg/ml for clarithromycin and 0.2 to 0.7 μg/ml for azithromycin (41). These doses largely are derived from the treatment of other bacterial respiratory infections. Further, considerations regarding the tolerability of oral doses, the potential for drug-drug interactions (primarily clarithromycin), and the potential for QTc interval prolongation or other possible cardiac effects generally has tempered enthusiasm for higher doses. Unlike for bacterial infections caused by *Haemophilus influenzae*, the 14-hydroxy metabolite of clarithromycin does not appear to be active against NTM (40). When combined with rifamycins, the clarithromycin parent drug concentrations are decreased and the concentrations of the inactive metabolite are increased. Therefore, TDM for clarithromycin can be advocated to ensure that reasonable amounts of the parent drug are available to treat the NTM. In general, NTM MICs are higher than they seem to be with either TB or other bacterial pathogens. Therefore, a strong argument can be made to err on the high side. That said, many NTM patients are older, and not uncommonly, these patients are somewhat frail (37). For reasons that are not abundantly clear, NTM patients tend to have higher rates of drug intolerance than patients with other types of infections. This makes "pushing the doses" particularly challenging in this patient population.

Although not well studied, the rationale for high-dose rifamycins seen with TB should apply, and even more so with NTM infections. Again, MICs tend to be much higher, so achieving the necessary area under the concentration-time curve for the free, unbound fraction of a drug (*f*AUC)/MIC is much more difficult with these pathogens. Nevertheless, to my knowledge, no

TABLE 2 Pharmacokinetic parameters of the anti-TB drugs[a]

Drug	Normal adult dose	Normal C_{max} (μg/ml)	Normal T_{max} (h)	Normal $t_{1/2}$ (h)
Isoniazid	300 mg daily 900 mg BIW	3–6 9–15	0.75–2	Polymorphic: Fast, 1.5; slow, 4
Rifampin	600 mg daily	8–24	2	2–3
Rifabutin	300 mg daily	0.45–0.90[b]	3–4	25–36
Rifapentine	600 mg daily[c]	8–30	5	15
Pyrazinamide	25–35 mg/kg daily 50 mg/kg BIW	20–60 60–90	1–2	9
Ethambutol	25 mg/kg daily 50 mg/kg BIW	2–6 4–12	2–3	Biphasic: 2–4, then 12–14
Cycloserine	250–500 mg daily or BID	20–35	2	7
Ethionamide	250–500 mg daily or BID	2–5	2	2
Streptomycin/ kanamycin/amikacin	15 mg/kg daily 25 mg/kg BIW	35–45[d] 65–80[d]	0.5- to 1.5-h i.m. dose or calculated to the end of i.v. infusion	3
PAS granules	4,000 mg BID	20–60	4–8	1
Levofloxacin	500–1,000 mg daily	8–13	1–2	9
Moxifloxacin	400 mg daily	3–5	1–2	7
Linezolid	300–600 mg most often once daily	12–26	1.5	5–6
Clofazimine	100 mg daily	0.5–2.0	2–7	Biphasic: several days, then many weeks

[a]BID, twice daily; BIW, twice weekly; C_{max}, peak serum drug concentration; i.m., intramuscular; i.v., intravenous; PAS, *p*-aminosalicylic acid; $t_{1/2}$, half-life; T_{max}, time to C_{max}. Adapted from reference 18, with permission.
[b]Increased from the prior range of 0.30 to 0.90 mcg/ml.
[c]Based on results of PHS studies 29 and 29X. The FDA-approved dose is BIW in the initial phase and once weekly in the continuation phase (for selected patients only).
[d]Calculated C_{max} using linear regression to 1 h post-i.m. dose or end of i.v. infusion. The streptomycin range also applies to amikacin, kanamycin, and capreomycin at similar doses.

high-dose rifampin or high-dose rifapentine studies have been performed with NTM patients. Rifabutin often has been used in NTM patients, although intolerance is fairly common. Unlike the other two rifamycins, rifabutin has clear concentration-related toxicities, making high-dose rifabutin an unlikely therapeutic option.

Aminoglycosides frequently are used for MDR-TB and for NTM. Traditional doses are 15 mg/kg daily, and some clinicians use higher (25-mg/kg) doses 2 or 3 times per week (8, 10, 18). Calculated maximum concentrations (C_{max}) associated with these doses are 35 to 45 and 65 to 80 μg/ml, respectively (18). Given the concentration-dependent nature of aminoglycoside activity, and given the fact that many NTM patients are older and have somewhat decreased renal function, the higher and less frequent 25-mg/kg dose could be seen as the preferred option. It provides a higher *f*AUC/MIC while allowing more time for the drug to be cleared. With either intramuscular doses or with short intravenous infusions (30 min), the 2- and 6-h sampling strategy described above works just fine. There seldom is a need for a predose trough, since that is not the pharmacodynamic-linked variable, and typically the concentrations are below the limit of detection for the assays. Further, using the 2- and 6-h samples, simple linear regression allows for back-calculation to C_{max} and forward calculation to the 24- or 48-h trough value. Therefore, measured trough concentrations generally are a waste of time and money. Similar strategies apply to capreomycin when used for MDR-TB.

There will always be drugs where the interpretation of serum concentrations will be challenging. Often these are lipophilic drugs or drugs that become trapped within cells, resulting in large volumes of distribution, including azithromycin, clofazimine, and bedaquiline. Because most of the drug is not in the plasma, most of the drug cannot be observed readily. TDM does allow for an assessment of not present, present in low concentration, or present in normal concentration. Bedaquiline has the additional challenge of having partially active metabolites that also can accumulate in the body like the parent drug does (44). Therefore, dose adjustment based on serum concentrations will remain challenging for these drugs.

At the other end of the spectrum from inadequate dosing is overdosing. As noted above, only a few TB and NTM drugs have clear concentration-related toxicity, including ethambutol and probably cycloserine (8, 10, 18). These drugs also rely heavily on renal clearance. Patients with kidney disease, and older patients with

age-related decreases in creatinine clearance, can accumulate these drugs, leading to overt toxicity. Injectable drugs, including aminoglycosides and capreomycin, have a less-well-defined relationship between serum concentrations and toxicity (8, 45). Nevertheless, overdosing can occur with injectable agents if doses are not adjusted for creatinine clearance. Clinicians are advised to determine renal function at the outset of treatment with these drugs and periodically during treatment.

It is not possible within the limited space of this chapter to provide a complete review of the pharmacokinetics of each drug used for TB, MDR-TB, and NTM infections. The references provided, and excellent on-line resources regarding clinical pharmacology, should be examined at the outset of treatment to avoid unpleasant clinical surprises. Table 2 lists the typical concentration ranges for some of the antimycobacterial drugs.

In conclusion, low drug exposure contributes to treatment failures, posttreatment relapses, and the selection of ARR. Clinicians should acquire actual MIC data when treating TB patients (rather than assessment as susceptible or resistant) in order to more fully understand the clinical challenge they face with each isolate. All TB isolates are not the same. MIC testing for NTM infections is more controversial. Clear correlations between NTM MICs and clinical outcomes are lacking for most drugs, except clarithromycin and possibly azithromycin. Patients with absorption problems, including diabetics and HIV-infected patients, may not absorb sufficient drug to cure their infections. Patients with extensive hepatic or renal disease may have difficulty clearing their drugs, potentially leading to toxicity. TDM can be used to identify patients with altered pharmacokinetics, and doses can be modified in order to avoid poor treatment outcomes. TDM also can be used to correctly dose patients with complicated drug-drug interactions. With these goals in mind, a strong argument can be made to perform TDM early in the course of treatment, before these adverse events occur.

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