Journal of Clinical Tuberculosis and Other Mycobacterial Diseases 36 (2024) 100444

Contents lists available at ScienceDirect

Journal of Clinical Tuberculosis and Other Mycobacterial Diseases

journal homepage: www.elsevier.com/locate/jctube

Role of therapeutic drug monitoring in the treatment of multi-drug resistant tuberculosis

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ARTICLE INFO

Keywords:
Tuberculosis
Multi-drug resistant tuberculosis
Therapeutic drug monitoring
Pharmacokinetics

ABSTRACT

Tuberculosis (TB) is a leading cause of mortality worldwide, and resistance to anti-tuberculosis drugs is a challenge to effective treatment. Multi-drug resistant TB (MDR-TB) can be difficult to treat, requiring long durations of therapy and the use of second line drugs, increasing a patient's risk for toxicities and treatment failure. Given the challenges treating MDR-TB, clinicians can improve the likelihood of successful outcomes by utilizing therapeutic drug monitoring (TDM). TDM is a clinical technique that utilizes measured drug concentrations from the patient to adjust therapy, increasing likelihood of therapeutic drug concentrations while minimizing the risk of toxic drug concentrations. This review paper provides an overview of the TDM process, pharmacokinetic parameters for MDR-TB drugs, and recommendations for dose adjustments following TDM.

1. Background

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (Mtb) that remains a major cause of global mortality. Multidrug-resistant TB (MDR-TB) is due to Mtb with resistance to at least isoniazid and rifampin, two potent TB drugs. In 2022, 10.6 million people were infected with TB and an estimated 410,000 new cases of rifampicin-resistant and MDR-TB were identified [1]. Approximately 3.3 % of all new TB cases are MDR, and 17 % of previously treated TB cases are due to MDR-TB or rifampin monoresistant strains [1]. Following the COVID-19 pandemic, and further exacerbated by conflicts in various countries which interrupt effective and timely treatment, the number of MDR-TB cases has been increasing [2].

The treatment regimens for drug-resistant TB have historically been toxic, expensive, and long in duration, upwards of 18–24 months [3]. This results in significant medical and economical burdens and impacts a patient's quality of life [4]. The development of shorter, all-oral regimens for rifampin-resistant TB and MDR-TB, such as BPaL (bedaquiline, pretomanid, linezolid) and BPaLM (bedaquiline, pretomanid, linezolid, moxifloxacin), have the potential to improve treatment duration, patient quality of life, and drug adherence. The BPaL and BPaLM regimens are 6 months in duration and have an estimated 90 % treatment success against drug-resistant tuberculosis [5,6].

Previous reviews discussing therapeutic drug monitoring (TDM) in TB treatment have been published [7,8]. However, with the advent of new regimens such as BPaL and BPaLM, an updated review on TDM specifically for MDR-TB is warranted. TDM is a tool that can be used to minimize interpatient variability to TB drug exposure, maximizing the benefit of the drug to a patient and reducing the risk of treatment failure. It provides objective information to the clinician that can help make informed decisions and manage complex disease states and drug interactions. Dose adjustments following TDM have been shown to decrease time to sputum sterilization, reducing the period where patients are infectious to others [7]. TDM for optimizing the management of TB that has been endorsed by guidelines such as the ATS/CDC/ERS/IDSA clinical practice guideline for the treatment of drug-resistant tuberculosis [9].

Given the recent advances in treatment as well importance of appropriate drug exposure during treatment of MDR-TB, this review paper provides an overview of the TDM process, pharmacokinetic parameters for MDR-TB drugs, and recommendations for dose adjustments following TDM.

2. Therapeutic drug monitoring overview and considerations

TDM most commonly uses serum or plasma to assess drug concentrations in order to individualize drug therapy and maximize the time drugs stay within therapeutic range. Therapeutic range is a "range of

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https://doi.org/10.1016/j.jctube.2024.100444

Available online 24 April 2024

drug concentrations within which the probability of the desired clinical response is relatively high and the probability of unacceptable toxicity is relatively low."[10]. These ranges are derived from population-based averages where the majority of patients would be expected to respond to drug therapy with minimal to acceptable side effects. However, interpatient variability exists as a result of pharmacokinetic differences including bioavailability, completeness of gastrointestinal absorption, body size and composition, distribution through fluid compartments, binding to inactive sites, and how quickly the drug is metabolized and excreted [11]. For example, patients may have therapeutic responses below the expected range whereas others may experience toxicities at concentrations typically therapeutic. Therefore, therapeutic ranges are not a guarantee of clinical success and should serve as a guide to be used in conjunction with other measures of clinical response and toxicity [12]. In addition, ranges related to the emergence of antimicrobial resistance may differ from those associated with clinical success and toxicity [13]. However, by maintaining a patient within typical drug ranges, we can hopefully remove drug underexposure as a reason for treatment failure.

Performing TDM requires an understanding of the pharmacokinetic/pharmacodynamic (PK/PD) target that will be optimized. Pharmacokinetics describes the behavior of a drug in a patient's body, including absorption, distribution, metabolism, and excretion [14], whereas pharmacodynamics describes the drug's molecular, biochemical, or physiologic effects or actions in the body [15]. There are three main antimicrobial PK/PD targets; the peak drug concentrations relative to minimum inhibitory concentration (C_{max}/MIC), the percentage of time within a dosing interval that concentrations exceed MIC (%T > MIC), and the area under the concentration time curve to MIC ($AUC_{0-\tau}$/MIC), most commonly over 24 h (AUC_{0-24}) [16]. For most TB drugs, AUC/MIC ratio has been predicted as the index for efficacy. Some exceptions include C_{max}/MIC as the primary efficacy target for aminoglycosides and %T > MIC for carbapenems and cycloserine [16,17]. Only free (f), or unbound, drug molecules can diffuse through biological membranes and exert a pharmacological effect. This is especially important to consider for drugs with protein binding higher than 70–80 %, as any change in the binding can significantly impact free fraction of drug [18]. In clinical practice, total drug concentrations are typically measured and reported due to the time and costs associated with measuring free concentrations. Free concentrations can be approximated using protein binding estimates from the literature.

While AUC/MIC targets are common for anti-TB drugs, measuring AUC for every patient is not practical, as it typically requires a minimum of six to seven samples following dose administration. However, a limited sampling strategy can be used to estimate the AUC using one to three post-dose samples with linear regression equations or a population PK model. While this approach may not be as precise as a rich sampling strategy, it reduces the sampling burden for the patient while still providing useful information to the clinician, including drug clearance or accumulation. Linear regression equations are less time intensive and are useful in resource-limited settings, where more expensive approaches, such as Bayesian models, may not be practical. A Bayesian approach can provide patient-specific dosing recommendations utilizing prior information from a population model, patient-specific variables such as serum creatinine or weight, and TDM results. While powerful and flexible regarding the sampling time, a Bayesian approach requires software that can be expensive to purchase and time intensive to learn and use [7].

3. Indications for therapeutic drug monitoring

In general, indications for TDM may include compliance monitoring, individualizing therapy, establishing if a patient is underdosed, avoidance of drug concentration related toxicities, and managing drug interactions [19]. Performing TDM in all patients with MDR-TB may be reasonable, rather than waiting to perform it in patients with poor response [9]. However, given limited resources, priority may be given to patients at risk for treatment failure from drug underexposure or patients at risk for drug toxicities. Patients at risk include those living with human immunodeficiency virus (HIV), type 2 diabetes, gastrointestinal complications, organ dysfunction such as renal and hepatic impairment, and those who are severely ill. Patients with comorbidities such as diabetes and HIV are at risk for malabsorption from the gastrointestinal tract, increasing the risk of treatment failure [20]. Patients showing adverse effects or are slow to respond to drug treatment are excellent candidates as well [7]. The more critically ill a patient is, the less room there is for a dosing error. It is better to correct the dose early, rather than allow a sequence of bad events to play out.

3.1. Renal dysfunction

The connection between contracting TB and chronic renal failure has been described since the 1970s, with multiple proposed mechanisms such as oxidative stress, malnutrition, vitamin D metabolism dysfunction, and a compromised immune system [21]. Patients receiving chronic hemodialysis have increased susceptibility to tuberculosis, most likely due to impaired cellular immunity [22]. In addition, patients with compromised renal function are at risk of drug accumulation and overexposure, leading to adverse effects. Package insert dosing provides dosing adjustments for patients with decreased renal function. However, even with individually estimated creatinine clearance, these dosing recommendations may not be adequate to control drug exposures [23,24]. Special consideration should be given to MDR-TB therapies with renal clearance including aminoglycosides, carbapenems, cycloserine, ethambutol, and levofloxacin. Two post-dose samples will not only provide information regarding drug absorption, but accumulation and clearance as well. When evaluating drug concentrations, those higher than typical range without evidence of adequate clearance may indicate the patient has renal dysfunction. If a patient is receiving hemodialysis, drawing pre and post dialysis samples can be used to assess the impact of dialysis on drug concentrations [7].

3.2. Hepatic dysfunction

Patients with hepatic dysfunction can present challenges to clinicians managing MDR-TB. Hepatic function and its impact on drug clearance cannot be estimated based on tests such as aspartate transaminase, alanine aminotransferase, alkaline phosphatase, or bilirubin, unlike renal function's relationship with serum creatinine. Liver test abnormalities have occurred in up to 30 % of patients treated with multiple drug regimens [25]. Examples of MDR-TB drugs undergoing hepatic metabolism or that may contribute to hepatotoxicity include bedaquiline, pyrazinamide, pretomanid, and moxifloxacin. In addition, it may be difficult to discern whether nausea patients experience is due to hepatic impairment or from the drugs themselves. Therefore, liver tests should be measured throughout therapy and TDM is recommended [25]. Available guidelines strongly support baseline liver function tests (LFTs), but are vague on when and how often to repeat testing [26,27]. In our experience, clinicians vary widely on when they repeat LFTs.

3.3. Patients with diabetes mellitus (DM)

The global burden of patients living with DM and infected with TB continues to increase. DM increases the risk of developing TB approximately two to four fold, and high fasting plasma glucose is a risk factor for drug-resistant TB [28–30]. DM weakens a patient's immune response to TB, allowing more rapid progression and a higher bacterial burden [31]. Pooled data from 2013 to 2022 in China demonstrated that while TB cases had trended down, the number of type 2 diabetes patients with pulmonary TB hospitalizations significantly increased, reinforcing the detrimental impact DM has on TB control [32].

The benefits of TDM in DM patients have been documented, as

patients with DM are more likely to be slow responders and have subtherapeutic drug concentrations [29,33]. In a retrospective, observational cohort study in the United States, patients with active pulmonary TB and DM who received TDM had shorter time to negative sputum cultures and shorter treatment durations than patients who did not receive TDM [33]. In addition to weakening the immune response against TB, DM impacts the pharmacokinetics of anti-TB drugs, particularly during the absorption phase [34]. Delayed absorption or malabsorption in patients with DM can occur due to gastropathy or polypharmacy interactions [4]. In these cases, the second post-dose sample, such as a 6-hour sample, can rule out whether a patient with diabetes is experiencing delayed absorption or malabsorption.

In addition to altered drug pharmacokinetics, adverse effects from anti-TB drugs can overlap with diabetes progression. Neuropathies and renal damage from diabetes progression can present similarly to side effects from anti-TB drugs [4]. By utilizing TDM, clinicians can assess if adverse effects are likely due to drug overexposure and make dose adjustments as necessary.

3.4. Patients living with HIV

Patients living with HIV and co-infected with TB present unique challenges to clinicians. TB and HIV are synergistic to each other, with both pathogens hastening the deterioration of the immune system [35]. MDR-TB patients co-infected with HIV, particularly advanced HIV with low CD4 count, are at risk for subtherapeutic drug exposures [36]. This can be due to gastrointestinal disease, diarrhea, and numerous drug interactions [37]. Not only is there concern about low anti-TB drug concentrations, but HIV drug concentrations may be subtherapeutic as well, increasing risk of therapy failure and resistance in both diseases. Management therefore requires monitoring for drug interactions and adverse effects, which TDM can be used for [37].

4. Therapeutic drug monitoring process

TDM is primarily performed using blood samples such as serum, plasma, or dried blood spots. Serum and plasma are the most common matrices used for TDM. For dried blood spot testing, patients use a lancet to prick their finger and collect capillary blood on a designated card, which is then dried and shipped to the laboratory for analysis. This method is less invasive, allows at home sampling, and is easier to ship than liquid samples. However, samples need to be relatively heat stable, and because of the small volume size, very sensitive techniques are required [38]. Alternative matrices to blood, such as oral fluid/saliva, urine, or hair have been studied as less invasive ways of measuring drug concentrations. For oral fluid and saliva, the window of detection starts approximately 1–2 days after therapy initiation and contamination of saliva by food or drink is a barrier to accurate quantification [38,39]. However, this sample type seems promising for some drugs. For example, linezolid collected from oral fluid samples after two weeks of therapy were found to be similar to serum concentrations, with no correction factor needed [40]. Regarding urine samples, drug concentrations do not appear to correlate with drug efficacy and toxicity. For example, Zentner et al. tried to determine whether a urine test can identify TB patients with adequate serum pyrazinamide exposures. The test was 97 % sensitive, but had only 50 % specificity [41]. Similar results were found with rifampin, so additional research is needed to develop urine tests [42]. More invasive sample types, such as cerebrospinal fluid (CSF), are collected to gain a better understanding of drug concentrations at difficult to penetrate sites [38]. This review paper will discuss TDM using serum or plasma.

Accurate, useful timing of samples depends on multiple factors, including the dosing route, drug formulation, drug PD characteristics, PK target parameters (AUC, peak, trough), and other factors, such as organ replacement therapy [43]. The exact times of the drawn samples as well as the dose amount and time prior to sample collection should be recorded for the best interpretation of results. When ordering TDM, clinicians may consider collecting samples once the drug is at steady state, or after approximately 5 half-lives [19]. If the patient is critically ill or has a severe infection, samples can be ordered sooner. In practice, for non-rifamycin drugs with relatively short half-lives such as pyrazinamide, ethambutol or fluoroquinolones, TDM can be drawn within days after initiation. Drugs with longer half-lives such as bedaquiline or clofazimine can take weeks to achieve steady state concentrations.

In the absence of AUCs, a 2-sample post-dose approach is reasonable to assess absorption, distribution, and clearance for most drugs. Time points for collection are based upon anticipated time to peak drug concentration (T_{max}) to capture C_{max} and to assess for delayed absorption. Troughs are collected for select drugs to assess for clearance and adverse effect risk, such as with linezolid. For drugs with short half-lives, there usually is a strong correlation between C_{max} and $AUC_{0\text{-}\tau}$, so these PK/PD indexes can be considered similar [44]. This is because AUC is a composite of both concentration and time. If a drug has a short half-life and is quickly eliminated from the body, the AUC will be driven mainly by C_{max}. Thus, for drugs like rifampin, isoniazid, and ethionamide, having a good estimate of C_{max} provides most of the information regarding AUC. A single sample, whether it is after an oral, intramuscular (IM), or intravenous (IV) dose, is not as useful as two or more samples. After an oral dose, a single sample cannot differentiate between delayed absorption or malabsorption. While malabsorption may not be a concern following an IV dose, information about half-life and clearance is vital to extrapolate desired PK parameters such as C_{max} (an aminoglycoside target), and this is difficult to accurately determine with one sample.

If a patient has normal absorption, many drugs for MDR-TB will have peak serum concentrations 2 h post oral dose. However, some patients will not have peak concentrations at the anticipated T_{max}. Therefore, when performing TDM following an oral dose, at least two post-dose samples are recommended. For many MDR-TB drugs, this can be 2- and 6-hour samples. If the 2-hour sample is within normal peak range and higher than the 6-hour sample, the patient most likely has normal absorption. In this case, the 6-hour sample can be used to assess clearance of the drug. If the 6-hour sample is substantially higher than the 2-hour sample, the patient most likely has delayed absorption. If both concentrations are below the normal range, the patient most likely has malabsorption, and dose increases should be considered. If the patient has malabsorption, the protein-free, or unbound, drug concentrations may be lower than TB MICs, risking treatment failure or development of resistance [7,45]. Table 1 provides recommended sampling times for each drug.

It may be asked whether dose increases following TDM may increase a patient's risk for drug-related toxicities. With documented malabsorption, higher doses of the medication can be used. It is unlikely to lead to increased risk of adverse effects because patient-specific objective data show that a large proportion of the dose administered has not reached systemic circulation [7]. However, repeat serum concentrations should be checked following dose increases to verify target concentrations have been attained. In addition, as the patient's condition improves, absorption may improve, which can increase drug concentrations. In our clinical experience, this is commonly seen with isoniazid. Early malabsorbers of isoniazid may clinically improve while receiving larger doses. Once normal gut function returns to such patients, it may be possible to revert to the lower, standard dose.

Clinicians should confirm with the performing lab which collection tubes are preferred, but in general, blood samples for TDM can be collected in plain red or plain green top tubes. Red top tubes contain no additives or anticoagulants and the coagulation cascade is activated as the blood contacts tube surfaces. Therefore, red top tubes must clot completely (30–60 min) prior to centrifuging and harvesting serum. Green tubes contain heparin which prevents coagulation and can be centrifuged immediately to collect plasma [46]. Serum separator tubes, such as gold tops, should be avoided as the gel can bind drugs, resulting

Table 1
Pharmacokinetic parameters of drugs used for MDR-TB.

Drug	Typical Adult Dose	Average C_{max} and C_{min} (mg/L)	T_{max} (h)	Recommended Sampling Strategy
Bedaquiline [54,56–58]	400 mg daily or 200 mg TIW	C_{max}: - Week 2: 2.8–3.3 - Week 8: 1.7 - Week 24: 1.3 C_{min}: - Week 2 (24 h): 0.73–0.96 - Week 8 (48 h): 0.62 - Week 24 (48 h): 0.36	4–6	Trough, 2 and 5–6 h
Carbapenems [178–181]	Varies, ~1000 mg every 6–8 h	C_{max}: 30–70	End of infusion	1-hour post infusion and trough
Clofazimine [59,71,72]	100 mg	C_{max}: 0.5–2.0	2–7	2 and 6-hour
Cycloserine [7,81,83,84]	250–750 mg daily, can be divided into 2 doses	C_{max}: 20–35	2	2–3 and 6–7 h
Ethambutol [97,98]	15–25 mg/kg daily 50 mg/kg BIW	C_{max}: 2–6 C_{max}: 4–12	2–3	2–3 and 6–7 h
Levofloxacin [109,110]	750–1000 mg	C_{max}: 8–12	1-2	2 and 6-hour
Linezolid [127,129]	600 mg	C_{max}: 12–26 C_{min}: - BID: 3–9 - Once daily: <2	2	Trough, 2 and 5–6 h
Moxifloxacin [109,117,185]	400 mg	C_{max}: 3–5	1-2	2 and 6-hour
Pretomanid [145,146]	200 mg	C_{max}: 2.3–4.3 C_{min}: 1.0–2.4	5	Trough, 2 and 5–6 h
Pyrazinamide [151,152]	25 mg/kg daily 50 mg/kg BIW	C_{max}: 20–60* C_{max}: 60–80	2	2 and 6-hour
Amikacin [174]	15 mg/kg daily 25 mg/kg BIW	C_{max}: 35–45 C_{max}: 65–80	0.5–1.5 (IM) or end of infusion (IV)	2 and 6-hour
Streptomycin [171]	15 mg/kg daily 25 mg/kg BIW	C_{max}: 35–45 C_{max}: 65–80	0.5–1.5 (IM) or end of infusion (IV)	2 and 6-hour

C_{max}, peak serum drug concentration; C_{min}, minimum serum drug concentration during dosing interval; T_{max}, time to C_{max}; TIW, three times weekly; BIW, twice weekly; BID, twice daily; IM, intramuscular; IV, intravenous.
*Evidence suggests better outcomes when C_{max} values exceed 35 mg/L [152].

in falsely low concentrations. This may be especially relevant for lipid soluble drugs, such as those with a logP value ≥ 3 [47,48].

Following collection, blood samples should be processed and tested as soon as possible. Many drugs, such as carbapenems, are not very stable at room temperature and subject to significant degradation if not processed quickly. Various instabilities contribute to analyte degradation prior to quantification. Analytes may aggregate, precipitate, bind to the surfaces of the tube, have inherent chemical instability, or be metabolized by components in the sample, such as blood cells. The longer the analyte is exposed to suboptimal conditions, the larger the extent of the loss [49]. Even if stored properly, long-term storage of clinical samples prior to testing is not recommended, as this may not accurately reflect the current clinical condition of the patient. To ensure stability and minimize degradation of the drugs, if the samples need to be stored prior to testing, they should be frozen, ideally at −70 to −80 °C. Clinicians may want to reach out the performing lab for additional details regarding drug stability, but in our experience, cycloserine, carbapenems, and clofazimine are MDR-TB drugs with the most instability at room temperature (>20 % loss over one week).

Drug concentrations can be quantified with techniques such as high performance liquid chromatography (HPLC) with triple quadrupole mass spectrometry (LC-MS/MS). LC-MS/MS methods have high specificity for the analyte as well as high sensitivity, enabling quantification of very low drug concentrations, even with low sample volume [43]. In addition, LC-MS/MS has a favorable turnaround time and multiple drugs run on the same assay (Ex: BPaL regimen drugs can be validated on the same assay). However, LC-MS/MS startup and maintenance costs and need for staff members with higher technical expertise may prohibit use [50]. More affordable options such as HPLC with dual wavelength ultraviolet detection can be an alternative for most TB drugs [51]. While these options are more affordable, they are considered less sensitive than LC-MS/MS.

5. Drugs and drug classes

5.1. Bedaquiline

Bedaquiline is a bactericidal diarylquinolone first approved for use against TB in 2012 as part of combination therapy in adults for those with pulmonary MDR-TB. AUC/MIC has been proposed as the PK/PD driver of bactericidal activity based upon murine models, but an optimal AUC/MIC exposure is still being established [52].

Dosing is via oral administration as 400 mg daily for two weeks, then 200 mg three times weekly for 22 weeks. Alternative dosing of 200 mg daily for 8 weeks followed by 100 mg daily for 18 weeks has been evaluated in the ZeNix trial, which would allow for all drugs in the regimen to be given daily [5,53]. Bedaquiline should be administered with food to increase the drug's bioavailability [54]. C_{max} concentrations occur approximately 4 to 6 h post dose, irrespective of dose amount, and exposure to bedaquiline and its metabolite increases linearly with dose administered [55]. At week 2 (loading phase) of bedaquiline therapy, C_{max} concentrations range from 2.8 to 3.3 mg/L. At week 8 in the maintenance phase, C_{max} concentrations are approximately 1.7 mg/L and at week 24, approximately 1.3 mg/L. C_{min} concentrations also vary depending on the timepoint in therapy. A 24-hour C_{min} sample taken during week 2 ranges from 0.73 to 0.96 mg/L. A 48-hour C_{min} at week 8 is approximately 0.62 mg/L and at week 24 of the maintenance phase, 0.36 mg/L [56–58]. Variations around both C_{max} and C_{min} values are to be expected. Weight has been shown to be inversely associated with C_{min} and males tend to have both higher C_{min} and AUC than females, which may partially be due to a lower fat mass [59]. There is a lack of evidence on how to adjust bedaquiline doses. Dose adjustments require caution, as the terminal half-life is approximately 5.5 months [54]. When performing TDM, some variation about typical peak and trough values should be expected, as previously mentioned. For values significantly out of range, retesting and dose

adjustments may be considered. For values that are very high, clinicians may consider testing LFTs as well.

Tissue distribution is extensive and protein binding is more than 99 % for both bedaquiline and its metabolite, M2 [57]. Bedaquiline and M2 appear to penetrate into the CSF of pulmonary TB patients with a presumably intact blood–brain barrier, although concentrations are low and somewhat challenging to measure [60]. Bedaquiline has been shown to have limited but measurable penetration into brain tissue in an animal model [61]. Despite evidence of some penetration, no clinical data on the efficacy of bedaquiline-containing regimens for TB meningitis is available, and bedaquiline and M2 concentrations may be significantly lower than in the lungs at relevant doses, resulting in inferior efficacy [62]. Further investigation is needed.

Bedaquiline is metabolized by the liver primarily through CYP3A4 to form M2, which is then metabolized to M3. M2 is roughly 5-fold less potent against TB than the parent drug. Elevations in liver enzymes and QT prolongation have been previously reported with bedaquiline use [63–65]. M2 is considered the driver for QT prolongation with a proposed $AUC_{0\text{-}24} > 3.2$ mg*hr/L as a threshold [66]. However, in clinical practice, bedaquiline-based regimens may only lead to modest increases in QTc interval with minimal clinical effect [67].

5.2. Clofazimine

Clofazimine is a fat-soluble riminophenazine dye primarily used to treat leprosy. It appears to have both sterilizing antimycobacterial and anti-inflammatory properties [9]. Limited PK/PD data is available for clofazimine with TB. However, higher exposure susceptibility ratios have been strongly associated with 2 and 6 month culture conversion, and data from patients with MDR-TB demonstrated an AUC/MIC ratio > 50 was associated with faster time to sputum conversion [68–70].

Typical dosing is 100 mg daily administered orally. C_{max} concentrations are normally in the range of 0.5 to 2 mg/L roughly 2–7 h post dose, but this can vary considerably [59,71,72]. Administration of clofazimine with a high fat meal may provide the greatest bioavailability; however, this has inter and intra-subject variability [73]. Clofazimine is highly protein bound, and can accumulate in fat, tissue macrophages, and reticuloendothelial organs, resulting in a long terminal half-life. The half-life is biphasic, first occurring over several days, then over weeks [7]. Median terminal half-life is estimated at approximately 34 days, and can be significantly longer in women. Due to its ability to accumulate in tissues and a strong tendency to distribute into fat, a higher body weight is generally associated with lower AUC and C_{min} values [59,74]. Model-based simulations have estimated a loading dose of 200 mg daily for 2 weeks could achieve average daily concentrations above target concentrations 37 days earlier than a typical TB participant [74].

The correlation between clofazimine serum concentrations and effect are not well established. TDM may primarily assist in confirming absorption is taking place. This has been shown to be the case in children with nontuberculous infections [75]. Providers may consider changes in skin appearance as one possible indication of adequate tissue penetration. Skin changes with clofazimine include a brown skin pigmentation (75–100 % of patients) and ichtyosis (8–20 %) [9]. In addition to skin changes, other side effects from clofazimine include gastrointestinal side effects, including deposits, which may also be seen in the eyes [76].

An additional consideration when performing clofazimine TDM is that in countries with limited TB burden, an obstacle when considering dose increases is that clofazimine can be difficult to obtain [77].

5.3. Cycloserine

Cycloserine is a second line MDR-TB drug that works by inhibiting cell wall synthesis [78]. It is second line mostly due to frequency of adverse central nervous system (CNS) effects, such as lethargy, difficulty concentrating, depression, psychosis, and neuropathy [7,79]. %T > MIC above 30 % has been proposed as the PK/PD target [17].

Typical doses of cycloserine are 250 mg to 500 mg once or twice daily, administered via dose escalation [80]. Modeling studies have proposed doses up to 1500 mg daily to optimize TB killing. Regimens such as 750 mg twice daily may be needed to achieve target exposure in 92 % of lung cavities and 500 mg twice daily to achieve target concentrations in 85 % of TB meningitis patients [17,81,82]. However, despite improved target attainment, utilizing doses larger than 750 mg daily would most likely be difficult for patients to tolerate.

Antacids and orange juice have minimal impact on cycloserine whereas food decreases the absorption of cycloserine, so administration on an empty stomach is recommended [83]. Expected C_{max} values 2 h after a 250 or 500 mg dose in adults are in the range of 20–35 mg/L [7,81,84]. Concentrations in the CSF and pleural fluid appear to approach those in serum, and detectable concentrations of cycloserine have been found in ascitic fluid, bile, sputum, lymph, and lung tissues [85,86]. Lung cavitary penetration, however, is considered to be poor [17,87].

Cycloserine is primarily cleared by renal elimination, with 70 % excreted unchanged [88]. The half-life in patients with normal renal function is approximately 12 h, so it may be best to wait at least 3 days prior to sampling to allow achievement of steady state concentrations [85]. Patients with renal dysfunction may have elevated cycloserine concentrations and increased risk for adverse effects. Once daily dosing instead of twice daily dosing can be considered to allow adequate time for drug clearance.

Cycloserine is an excellent candidate for TDM, as CNS side effects (dizziness, excitation, headache, insomnia, anxiety, etc) have been reported to occur in 20 to 30 % of patients [89]. Concentrations > 35 mg/L may increase toxicity risk so dose reductions may be considered when peak concentrations begin exceeding this threshold [79,90,91] However, lethargy and difficulty concentration have been reported even within the normal range [7]. An 8 % increased risk of peripheral neuropathy has been identified for every 100 mg*hr/L increase in $AUC_{0\text{-}24}$. [79]. In addition, an $AUC_{0\text{-}24}$ of 718.7 mg*hr/L has been identified as a threshold for psychiatric AEs [66]. Possibly due to its reported impact on pyridoxine metabolism [92], cycloserine is commonly given with pyridoxine (Vitamin B6) to reduce the risk of CNS adverse effects [93]. However, evidence regarding the efficacy of this common practice is lacking.

5.4. Ethambutol

Ethambutol is an inhibitor of mycobacterial arabinosyl transferases which impacts Mtb cell wall synthesis [94]. The role of ethambutol in MDR-TB is limited to when more effective drugs cannot be used to achieve the five-drug regimen [9]. $AUC_{0\text{-}24h}/MIC > 119$ has been linked to microbial kill [95,96].

Ethambutol should be administered as a single daily dose and normal C_{max} concentrations 2 to 3 h following an oral dose of 15–25 mg/kg range between 2 to 6 mg/L [97,98]. With biweekly doses of 50 mg/kg, the typical C_{max} range is 4–12 mg/L. Ethambutol has a biphasic half-life, initially 2 to 4 h the first 12 h post dose, followed by a 12–14 h half-life [7]. Samples drawn as early as day 2 of therapy are expected to produce concentrations approaching steady-state values [97]. Ethambutol has a large volume of distribution partly due to binding erythrocytes and uptake by macrophages [97]. Concentrations in epithelial lining fluid and alveolar cells have been reported to be high, which may contribute to treatment success [99]. CSF concentrations of ethambutol are generally considered to be low, even in the presence of inflamed meninges, so alternative drugs for TB meningitis may be preferred [93].

Ethambutol clearance is reliant upon renal elimination. Reduced renal function may result in elevated concentrations, increasing risk for adverse drug effects, especially ocular neuritis, which is concentration dependent and can be irreversible [100]. Three times weekly dosing can be considered when creatinine clearance is less than 30 mL/min, followed by TDM. Hemodialysis has been shown to remove ethambutol,

but anecdotal data suggests that peritoneal dialysis does not efficiently remove it from the blood [101]. Utilizing ethambutol in patients with known or suspected renal function is best accompanied by TDM and close monitoring for adverse effects. In addition, both visual acuity and red-green color discrimination may be impacted with ocular toxicity. Monitoring for ocular toxicity should occur monthly, and if detected, ethambutol should be discontinued [9].

5.5. Fluoroquinolones

Fluoroquinolones, such as levofloxacin and moxifloxacin, directly inhibit bacterial DNA synthesis with efficacy correlated to $fAUC_{0\text{-}24}$/MIC [102–104]. When treating MDR-TB, fluoroquinolone containing regimens have demonstrated higher rates of treatment success and fewer deaths than regimens without fluoroquinolones due to greater *in vitro* activity, with moxifloxacin demonstrating the highest activity [105,106]. Fluoroquinolones have excellent bioavailability, approaching 90 % or above. Tissue penetration is high, with concentrations often higher than concurrent serum concentrations [107,108].

5.5.1. Levofloxacin

In hollow fiber models, levofloxacin $AUC_{0\text{-}24}/MIC > 146$ has been associated with TB killing [103]. C_{max} concentrations following a 750 to 1000 mg oral dose of levofloxacin are 8–12 mg/L, peaking at approximately 2 h [109]. The pharmacokinetics of levofloxacin after a single dose versus at steady state are not significantly different. Levofloxacin demonstrates dose proportionality, and increasing the dose by 100 mg tends to increase serum concentrations by approximately 1 mg/L [109,110]. In the Opti-Q study, 101 participants randomized to weight banded levofloxacin doses from 11 to 20 mg/kg/day (minimum dose 750 mg, maximum dose 1500 mg) showed dose proportionality, with increased doses leading to increased C_{max}s and $AUC_{0\text{-}24}$s [110]. Published safety data from Opti-Q is pending [NCT01918397]. Following publication of safety results, higher starting doses of levofloxacin may be considered, especially considering 50 % of MDR-TB patients with higher MICs may not have enough levofloxacin exposure with current doses of 750 mg to 1000 mg [111]. Also, levofloxacin activity could be equivalent to moxifloxacin and able to achieve suppression of acquired drug resistance when 1500 mg/day is used [103].

Oral bioavailability is excellent, approaching 100 % [107,112]. Increasing the levofloxacin dose does not appear to alter the rate of absorption [110]. Food may increase the T_{max}, and levofloxacin should be administered separately from products containing aluminum, magnesium, and ferrous sulfate, as this may decrease absorption [112]. Levofloxacin has a large volume of distribution, and penetrates most body tissues, including CSF [112,113]. Normal half-life is around 6–8 h [112]. Levofloxacin undergoes renal elimination, so in patients with renal impairment, half-life and AUC are increased [114]. Moxifloxacin can be considered an alternative, as it has less renal clearance that levofloxacin.

5.5.2. Moxifloxacin

Moxifloxacin $fAUC/MIC > 42$ and $fAUC/MIC > 53$ has been associated with treatment efficacy and suppression of drug resistance, respectively [44,104]. Moxifloxacin C_{max} concentrations approximately 2 h after a 400 mg dose are generally in the range of 3–5 mg/L. Bioavailability of moxifloxacin is consistently high, with estimates > 90 % [108]. Moxifloxacin appears to demonstrate dose proportionality, with every 100 mg increasing serum concentrations by approximately 1 mg/L [115–117].

Moxifloxacin is metabolized via glucuronide and sulphate conjugation within the liver and appears to be a safer choice than levofloxacin for patients with renal dysfunction. In patients with impaired renal function, single doses of 400 mg were well tolerated and renal function had minimal impact on plasma pharmacokinetics of moxifloxacin [117]. Moxifloxacin concentrations are reduced by over 25 % when co-administered with rifampin and rifapentine, [118,119]. It should be noted that the degree of reduction of moxifloxacin concentrations by rifapentine depend on whether the latter is given once weekly or daily [120].

Moxifloxacin 800 mg has been proposed as the dose to optimize TB treatment and minimize acquired drug resistance [104]. However, moxifloxacin prolongs the QT_c interval in a concentration dependent manner, by a reversible and dose-dependent blockage of hERG potassium channels [104,121–123]. $AUC_{0\text{-}24} > 49.3$ mg*hr/L has been identified as a potential threshold for QT prolongation and regular ECG monitoring [66]. Therefore, dose increases for moxifloxacin should be carried out cautiously. Patients with C_{max} concentrations below the typical range should ideally have both 2 and 6-hour samples drawn to rule out delayed absorption prior to increasing the dose, especially to an 800 mg dose. An alternative dosing strategy of 400 mg twice daily has been proposed in modeling studies to achieve $fAUC/MIC > 42$ while also minimizing risk of QT prolongation [122]. However, further research is needed.

5.6. Linezolid

Linezolid is a synthetic oxazolidinone that inhibits mycobacterial protein synthesis and demonstrates AUC/MIC bacterial killing [124,125]. Hollow fiber models for TB suggest a $fAUC_{0\text{-}24}/MIC$ ratio of 119 [126]. Although highly impactful in the treatment of MDR-TB, adverse effects, including myelosuppression and neuropathies may limit long-term use. Linezolid was originally dosed as 1200 mg daily in the BPaL regimen. However, following increased safety and demonstrated efficacy in the ZeNix trial, the starting dose has been reduced to 600 mg daily [5]. Oral bioavailability of linezolid is excellent, nearing 100 % [127]. C_{max} concentrations following a 600 mg dose of both oral or intravenous doses range from approximately 12–26 mg/L, with a T_{max} approximately 2 h post oral dose [7,127–129]. Dose-exposure proportionality may not be reliable with linezolid, even in patients with normal renal function [130]. In addition, linezolid is considered to have a narrow therapeutic index, making it an excellent candidate for TDM [131].

Trough concentrations that exceed 2 mg/L have been correlated with mitochondrial toxicity-related adverse effects in participants being treated for drug-resistant TB [132]. In Wasserman et al., a trough concentration ≥ 2.5 mg/L was proposed to better describe changes in hemoglobin and treatment-emergent anemia than 2 mg/L [133]. However, until further evidence becomes available, utilizing a more conservative trough threshold of 2 mg/L is reasonable. If 24-hour trough values are > 2 mg/L with once daily dosing, three times weekly dosing can be considered. If the patient is on three times weekly dosing, a 48-hour trough < 2 mg/L is a reasonable target to minimize risk of adverse effects. Evidence suggests long-term use of 600 mg daily results in significant elevation in troughs. In Jeyakumar et al., trough concentrations increased significantly (1.98 vs 3.16 mg/L, $p = 0.001$) between the 8th and 16th weeks of patients receiving 600 mg daily [134]. TDM may need to be repeated in patients receiving long-term linezolid, even if previously therapeutic.

Linezolid has demonstrated tissue penetration into the CSF as well as lung cavity caseous lesions [135,136]. Clearance of linezolid may occur both renally and nonrenally, the latter estimated to account for approximately 65 % [137]. Median linezolid concentrations in patients with renal insufficiency were 1.46 times higher than in patients with normal renal function, and overexposure of linezolid has been associated with a creatinine clearance ≤ 40 mL/min [138]. Liver cirrhosis has also been associated with higher trough concentrations and treatment discontinuation [139].

5.7. Pretomanid

Pretomanid is an oral nitroimiazooxaine that works by inhibiting

mycolic acid biosynthesis and kills actively replicating cells by blocking cell wall production [140]. It is a prodrug that gained FDA approval in 2019 for the treatment of highly-resistant TB, in conjunction with bedaquiline and linezolid as part of the BPaL regimen [141]. Both %$fT > MIC$ and $fAUC/MIC$ have been associated with efficacy [142,143].

Following a single dose of 200 mg, C_{max} concentrations range from 1.4-2.6 mg/L with a T_{max} 5 h post dose [54]. C_{max} concentrations at steady state range from 2.3 to 4.3 mg/L and C_{min} concentrations are approximately 1.0 – 2.4 mg/L. Administration with food is recommended and has been shown to increase both C_{max} and AUC in adults by 76 % and 88 %, respectively [144]. Pretomanid displays dose proportionality over a range of 50–200 mg and less than dose proportionality from 200 mg to 1000 mg [145,146]. Pretomanid has a long half-life of approximately 16–20 h and is therefore dosed once daily. Steady state is achieved after approximately 4 to 6 days of daily dosing [147]. Dose adjustments following TDM for pretomanid are not well established. Examination of doses ranging from 200 to 1200 mg in a 14-day study in patients with pulmonary TB found efficacy at all doses was similar, and that the smallest dose of 200 mg daily was enough to optimize %100 T > MIC. However, the majority of patients in the study had a TB MIC < 0.1 μg/ml [145]. For values significantly out of range, retesting and dose adjustments may be considered. For values that are very high, clinicians may consider testing LFTs as well.

Pretomanid is metabolized extensively through multiple pathways and 53 % of the total dose is excreted in urine as metabolites [140,148]. Adverse effects include peripheral neuropathy, anemia, GI upset, and elevated liver enzymes [8]. A study in healthy volunteers receiving pretomanid doses from 50 mg to 1000 mg found no clear relationship between pretomanid dose and adverse effects [146].

5.8. Pyrazinamide

Pyrazinamide is a prodrug activated to pyrazinoic acid *in vivo* by pyrazinamidase, which is believed to interfere with mycobacterial fatty acid synthase [9]. It can be included in treatment regimens for MDR-TB as a second-line option, but drug-susceptibility testing should be documented beforehand as pyrazinamide resistance has been correlated with rifampin resistance [9]. Sterilizing activity of pyrazinamide has been related with $AUC_{0\text{-}24h}$/MIC ratios, and AUC values less than 363 mg*h/L have been associated with treatment relapse, failure, and death [149,150].

Pyrazinamide has substantial oral absorption, which is minimally impacted by food. C_{max} concentrations following a 25–35 mg/kg oral daily dose are usually in range of 20–60 mg/L [7,151]. Concentrations are generally proportional to the dose, and twice weekly dosing will produce higher pyrazinamide concentrations, in the range of 60–80 mg/L. C_{max} concentrations above 35 mg/L may be associated with improved outcomes. In a study of Botswanan patients, concentrations below 35 mg/L had a 3.4-fold increased risk of poor treatment outcomes after adjusting for HIV infection and CD4 cell count [152]. Simulations suggest 30 to 40 mg/kg doses are needed to achieve C_{max} concentrations > 35 mg/L in > 90 % of patients [153]. However, while higher doses may result in more efficacious regimens, adverse effects may limit their use. Early pyrazinamide studies at doses of 40–50 mg/kg given for 24 weeks or longer caused liver toxicity at rates of 5–10 %. Rates were substantially lower if the duration or dose was reduced, suggesting a relationship between the dose of pyrazinamide with hepatotoxicity [154]. Concentration related hepatotoxicity is a concern [155], so peak concentrations in excess of 60 mg/L may warrant dose reductions. Despite this, the mechanism behind hepatotoxicity is unclear, and the debate remains regarding the relationship between pyrazinamide dosing and toxicity [156].

Pyrazinamide undergoes metabolism in the liver to metabolites including pyrazinoic acid and 5-hydroxypyrazinoic acid. While the impact of these metabolites is not fully understood, they are cleared by the kidneys and may accumulate in renal dysfunction, increasing risk for toxicity [157]. Approximately 70 % of pyrazinamide is excreted as metabolites in the urine, and three times weekly dosing may be considered in patients with renal dysfunction [7]. Pyrazinamide has first-order elimination with a half-life of 9–10 h, which can be increased to 15 or more hours in patients with hepatic disease [158]. Samples drawn as early as day 2 of therapy will produce serum concentrations approaching steady state [151]. Clearance gradually increases over the course of treatment, most likely due to improved patient hepatic and renal function [159]. Pyrazinamide and its metabolites also inhibit the secretion of uric acid by the kidneys, resulting in elevated serum uric acid concentrations [160]. If uric acid is normal in the patient's serum and pyrazinamide is not present, the patient may be non-adherent with their regimen [7].

Intrapulmonary pyrazinamide concentrations have been reported to be high, with accumulation occurring at the site of disease [99,161]. In fact, pyrazinamide concentrations in the epithelial lining fluid (ELF) have been found to be higher than in the plasma [99]. Pyrazinamide generally does penetrate the CSF well, although results have varied across studies [93,162–164].

5.9. Aminoglycosides (Amikacin, streptomycin)

The role of aminoglycosides in MDR-TB regimens is limited to when susceptibility is confirmed and more effective/less toxic therapies are not an option [9]. Aminoglycosides are concentration- dependent, injectable antibiotics that inhibit bacterial protein synthesis via irreversible binding of ribosomes [165]. An amikacin $C_{max}/MIC > 75$ and $AUC_{0\text{-}24}/MIC$ of 103 have associated with bacterial killing [166]. Aminoglycosides have a post antibiotic effect and synergism with other antibacterial drugs [167], and cross resistance between streptomycin and other aminoglycosides is rare due to an alternative core structure in streptomycin [9].

Aminoglycoside bioavailability is poor, necessitating IV or IM administration. Tissue penetration (Ex: CNS) is limited due to their high polarity and water solubility [18]. To optimize concentration-dependent killing, prolong the post-antibiotic effect, and theoretically reduce risk of adverse effects, a once daily dosing scheme is utilized [168–170]. For amikacin and streptomycin, daily doses of 12 to 15 mg/kg result in C_{max} concentrations of 35–45 mg/L at the end of the infusion or 1-hour post IM dose [171]. To further optimize C_{max} /MIC ratios, some clinicians may use 25 mg/kg dosing 2 to 3 times weekly. In this case, C_{max} concentrations of 65–80 mg/L can be targeted [7].

Larger, once daily doses take longer to distribute than conventional doses, so using a conventional sampling approach of 30 min post dose can lead to falsely elevated C_{max} values if assuming a one compartment model [172]. Instead, 2- and 6-hour post dose samples is appropriate to avoid sampling during the distribution phase. The C_{max} can then be back calculated using first order pharmacokinetic equations.

Close monitoring of renal and auditory function should occur at baseline and monthly [173,174]. Hearing loss and nephrotoxicity have been observed in approximately 8 to 37 % of patients receiving aminoglycosides, worsening with prolonged treatment and higher doses [173,175,176]. Aminoglycosides are renally eliminated, so reduced renal function increases accumulation and adverse effects. To reduce accumulation, an extended dosing interval with 2 to 3 weekly doses can be used. All that being said, a clear relationship between aminoglycoside serum concentrations and overt toxicity has been very difficult to establish.

5.10. Carbapenems

Carbapenems, such as meropenem and imipenem, are beta-lactams whose efficacy depends on the amount of time drug concentrations remain above the bacterial MIC (%T > MIC). For TB, carbapenems are administered in conjunction with clavulanate, a beta-lactamase inhibitor that has synergy with and may potentiate the activity of

carbapenems, as demonstrated *in vitro* [177]. Clavulanate is not available in formulation by itself, so it is administered in combination with amoxicillin, as 125 mg of clavulanate with each dose of carbapenem [9].

Recommended draw times are approximately 1-hour post infusion and a trough sample prior to the next dose. Normal C_{max} concentrations can vary based upon the dose. However, C_{max} concentrations following a 1 g dose of imipenem or meropenem are generally in the range of 30–70 mg/L [178–181]. The C_{min} sample can be compared to the bacteria MIC to assess the percent of time of the dosing interval that concentrations exceed MIC. A potential challenge associated with carbapenem TDM is sample instability, as beta-lactam instability is well-recognized. For example, preanalytical instability for meropenem can be observed in as little as 4 h when kept at room temperature [182]. Samples subjected to less than ideal conditions, such as becoming thawed during transit, require caution during interpretation.

Carbapenems undergo renal clearance and can accumulate with decreased renal function. CNS toxicity is a concern, especially with imipenem. Meropenem has a slightly lower risk of CNS toxicity than imipenem [183]. Due to the risk of accumulation with renal insufficiency and toxicity concerns, carbapenems are excellent candidates for TDM.

Carbapenems used for TB are only available as intravenous formulations Intravenous formulations are less convenient for outpatient treatment and require IV access, increasing a patient's risk for infection. Ertapenem may be a good option pending further investigation against Mtb if the patient will be treated in the outpatient setting, as it only requires once daily dosing versus meropenem and imipenem, which are typically administered multiple times daily. Tebipenem, an oral carbapenem, has shown activity *in vitro* against TB, but further investigation into the clinical utility is warranted [184].

6. Conclusions

TDM is an evolving tool that allows the clinician to make informed decisions about drug dosing in patients with a serious and contagious disease – tuberculosis. Most TB drugs show concentration-dependent killing, meaning that low concentrations are associated with minimal killing. The available concentration ranges can be seen as setting the floor for drug exposure, with concentrations above the low end of the range being desirable. While techniques such as high performance liquid chromatography (HPLC) with triple quadrupole mass spectrometry (LC-MS/MS) are desirable for measuring concentrations, HPLC with dual wavelength ultraviolet (UV) detection is an affordable alternative for most TB drugs [51]. Thus, even resource-limited settings can consider using this tool to optimize treatment in their TB patients. Given the serious risk posed by the combined infections of TB and HIV, we advocate for using TDM early in the course of treatment to assure adequate drug exposures over the lengthy courses of treatment.

Ethical statement

Ethical approval was not applicable for this article. This article does not contain any studies with human or animal subjects. Informed consent is not applicable.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Nicole F. Maranchick: Conceptualization, Data curation, Investigation, Writing – original draft, Writing – review & editing. **Charles A. Peloquin:** Conceptualization, Data curation, Investigation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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