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Pediatric Infectious Disease (M Mitchell and F Zhu, Section Editors)

Optimization of Pediatric Antibiotic Dosing Through Therapeutic Drug Monitoring

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Abstract

Purpose of review Review data and provide recommendations on the optimization of antibiotic dosing in pediatrics through therapeutic drug monitoring (TDM).
Recent findings Due to physiological alterations, there is growing evidence current weight-based antibiotic dosing regimens are inadequate in obese and critically ill children. Utilization of known PK/PD indices as TDM targets for certain antibiotics (aminoglycosides, vancomycin, β-lactams) in these patients has led to improved clinical results in adults, but pediatric literature remains significantly limited.
Summary There are significant potential clinical benefits to expansion of TDM from current use (vancomycin, aminoglycosides) to include β-lactams, particularly in the critically ill. The clinical benefits of linezolid and fluoroquinolone TDM remain unclear. There is significant potential for further optimization of TDM based dosing through use of population PK software with Bayesian modeling.

Introduction

Due to the concentration-dependent nature of bacterial responses to antibiotic exposure, optimizing antibiotic dosing to achieve targeted concentrations is essential in achieving the desired bactericidal effect of antibiotics. However, concentration alone does not determine the adequacy of antibiotic dosing. The maximum antimicrobial effect of an antibiotic varies by the pharmacokinetic (PK) and pharmacodynamic (PD) properties, resulting in distinct PK/PD indices for which their efficacy is related. Time-dependent antibiotics rely on time for which free (unbound) plasma drug concentrations are above the minimum inhibitory concentration (*MIC*) of the offending pathogens ($fT > MIC$). Concentration-dependent antibiotics rely on the ratio of peak concentration during a dosing interval (C_{Max}) and the *MIC* (C_{Max}/MIC). Concentration-dependent antimicrobials with time dependence rely on the ratio of the area under the concentration–time curve (*AUC*) of the unbound drug from 0 to 24 h and the *MIC* (AUC_{0-24}/MIC) [1••]. Classification of individual drug classes into these PK/PD indices are described Table 1. Optimization of pediatric dosing through utilization of these PK/PD indices faces significant challenges. There is a general paucity of pediatric PK data due to barriers in phlebotomy, informed consent, and risk–benefit of study participation resulting in small sample sizes [2]. Additionally, there is significant heterogeneity in pediatric patient populations due to age-related differences in absorption, distribution, metabolism, and elimination [3••]. Finally, there is significant variability in patient characteristics across pediatrics ranging from high inter-variability in hepatic metabolism in children [4] to neonates with diminished humoral immunity responses, reduced skin barrier, and low microbial variation in gut microflora [5].

Due to a relative paucity of pediatric PK/PD data [6], the extent of subtherapeutic serum concentrations with current antibiotic dosing regimens remains unclear. However, a retrospective review demonstrated subtherapeutic serum concentrations in 95% of children receiving conventional β-lactam antibiotic dosing in a pediatric intensive care unit [7]. The potential ramifications of suboptimal dosing are significant. Suboptimal dosing of antibiotics can select for and amplify the presence of resistant bacterial strains [8]. Junbe et al. demonstrated in a thigh infection model that suboptimal quinolone drug exposure rapidly selected for more resistant clones within 12 h of therapy initiation. By 28 h of therapy, a specific quinolone pump (the mechanism of resistance) had become the predominant pump expressed in resistant clones [9]. Conversely, supratherapeutic antibiotic dosing can also occur and has resulted in significant toxicity [10, 11].

Therapeutic drug monitoring (TDM), the process of measuring specific drug concentrations at designated intervals, has been used to optimize individual dosing regimens to maintain a constant concentration of drug within a targeted therapeutic range or window determined by each drug's PK/PD indices. Historically, it has been used primarily for monitoring drugs with narrow therapeutic ranges, marked PK variability, or with significant adverse effects outside of their therapeutic

Table 1 Pharmacodynamic index of common antibiotic classes

$fT_{>MIC}$	C_{Max}/MIC	AUC_{0-24}/MIC
β-lactams	Aminoglycoside	Fluoroquinolones
Carbapenems	Metronidazole	Aminoglycosides
Linezolid	Fluoroquinolones	Azithromycin
Erythromycin	Telithromycin	Tetracyclines
Clarithromycin	Daptomycin	Glycopeptides
Lincosamides		Tigecycline
		Linezolid

range [12]. As such, TDM has become standard clinical practice for use in antibiotics such as vancomycin and aminoglycosides (i.e., gentamicin, amikacin, tobramycin).

However, there has been increasing interest in the expansion of TDM into additional antibiotics to allow for individual optimization of antibiotic dosing. This is of particular interest in pediatric patients given the growing evidence that current weight-based dosing regimens do not accurately account for age related changes in drug absorption, distribution, metabolism, and excretion [13].

The target concentrations and their respective PK/PD indices for antibiotics in pediatrics will be reviewed to provide an update on TDM based dosing in both commonly used antibiotics (aminoglycosides, vancomycin) and potential additional antibiotics (fluoroquinolones, β-lactams, linezolid) in which application of TDM based dosing may improve clinical responses.

Patient considerations

A variety of characteristics can affect the predictability of a patient's PK, thereby increasing the likelihood that TDM should be utilized to ensure optimal dosing regimens.

Critically ill patients

Critically ill patients have been shown to have physiological changes that result in increased volumes of distribution (*Vd*), reduced renal clearance (Cl), and alterations in metabolism [14, 15]. Roberts et al. showed that 16% of adult ICU patients did not achieve the most conservative PK/PD target of 50% $fT > MIC$ for β-lactam antibiotics, and these patients were 32% less likely to have a positive clinical outcome [16•]. A post hoc analysis of the data showed patients which received prolonged infusion meropenem and piperacillin/tazobactam had significantly higher rates of attaining the target 50% $fT > MIC$. Additionally, prolonged infusion (and subsequently higher probability of achieving target 50% $fT > MIC$) was found to have statistically higher rates of clinical cure when compared to traditional intermittent infusion (73.3% vs 35%) in patients with a high sequential organ failure assessment (SOFA) score (≥9) [17]. Additionally, extracorporeal membrane oxygenation (ECMO) also increases the *Vd* of the patient and may also result in sequestration of the drug within the circuit, leading to prolonged pharmacological effects [18]. Therefore, the use of TDM should be considered in critically ill patients, particularly those on ECMO, to ensure optimal antibiotic dosing and increase the likelihood of positive clinical outcomes.

Obesity

The pediatric obese population is at particular risk for subtherapeutic serum concentrations of antibiotics. The body composition of obese children demonstrates higher total body water, body volume, lean mass, fat mass, and

bone mineral content when compared to non-obese children [19]. In obese adults, most antibiotics demonstrate increased *Vd*, unclear effects on hepatic metabolism/clearance, and baseline increase in renal clearance but higher rates of renal dysfunction [20]. However, it is unclear whether findings in obese adults are applicable to obese children given the paucity of pediatric PK/PD data available. However, clinically significant PK alterations in obese children were observed in 65% of the 21 studied drugs in a systemic literature review [21], which suggests that there is a high probability that some degree of correlation exists between adult and pediatric PK/PD data in obesity. As the prevalence of pediatric obesity increases (13.9% in 1999–2000 to 18.5% in 2015–2016) [22], there is an increased urgency to utilize TDM based dosing in this population to ensure adequate antibiotic exposure.

TDM target concentration dosing recommendations

Please refer to Table 2 for target PK/PD indices and preferred sampling method of the antibiotics reviewed.

Aminoglycosides

Aminoglycosides are hydrophilic molecules which distribute primarily to the extracellular fluid. Therefore, conditions, where significant changes in *Vd* are possible (sepsis, burn injuries, shock, pancreatitis, alteration in plasma protein binding [23]), can lower the C_{Max} of an aminoglycoside dosed with conventionally. Aminoglycoside clearance is proportional to glomerular

Table 2 Target pharmacokinetic/pharmacodynamic indices of common antibiotic classes

Antibiotic class	Target PK/PD index	Preferred sampling method
Aminoglycosides	C_{Max}/MIC 8–10	Peak Trough — clearance only
Vancomycin	$AUC_{0-24}/MIC > 400$*	Peak, trough
β-lactams	100% $fT_{>MIC}$	Peak, midpoint, trough
Fluoroquinolones		Peak, trough
PO levofloxacin	$AUC_{0-24}/MIC > 150$	
PO moxifloxacin	$AUC_{0-24}/MIC > 100$	
IV ciprofloxacin	$AUC_{0-24}/MIC > 100$	
Linezolid	$AUC_{0-24}/MIC > 100$	Peak, trough

*The efficacy of vancomycin AUC_{0-24}/MIC target of > 400 is published for MRSA. This target is often extrapolated to other organisms

filtration rate [24], and patients with impaired renal function may develop toxicity (most commonly acute kidney injury or ototoxicity).

TDM of aminoglycosides should be performed by obtaining a serum level 30 min after the end of the intravenous infusion [25] to measure C_{Max}. The *MIC* target should be guided by local antibiogram data if no antimicrobial sensitivities are available from bacterial culture. A C_{Max}/MIC ratio of 8–10 should be targeted [26]. Trough concentrations (target < 2 mCg/mL) are often measured to ensure reasonable clearance occurs in patients with renal compromise. Due to widespread use of once daily dosing and various nomograms (Sawchuk and Zaske, MacGowan and Reeves, Begg, Nicolau) to aid in dosing of adult patients, the use of TDM to monitor C_{Max} is often reserved to adult patients with significantly variable *Vd* [1••]. However, the use of active TDM (PK dosage optimization at the start of treatment by pharmacy, Bayesian adaptive control based on peak/trough level, and development of an individualized dosing regimen) has been shown to lower mortality for patients with an infection on admission, shorten hospitalization, and reduce nephrotoxicity for all patients when compared to traditional dosing with TDM use by attending request [27•]. Therefore, the expansion of TDM use in aminoglycosides into the general patient population has the potential for significant clinical benefits.

Given the significant variations in PK in children, similar use of TDM to optimize aminoglycoside dosing (C_{Max}/MIC 8–10) in children should be considered. Indeed, a retrospective cohort study of pediatric patients in Singapore found that utilization of first-dose TDM has been found to result in faster attainment of target serum concentrations when compared to steady state TDM [28]. As the rapid achievement of target serum concentrations (ideally by first dose) may minimize bacterial burden at infection site and reduce the risk of selecting for resistant strains [29], the more rapid achievement of target serum concentrations via first dose TDM may ultimately result in improved clinical outcomes in children.

Glycopeptides

The glycopeptide class of antibiotics are concentration-dependent antimicrobials with time dependence. The class includes both vancomycin and teicoplanin, but vancomycin is the predominant glycopeptide antibiotic in general use. A target AUC_{0-24}/MIC ratio > 400 has been associated with improved clinical outcomes and more rapid clearance of bacteria of MRSA pneumonia [30] and bacteremia [31]. A target AUC_{0-24}/MIC ratio of 400–600 has been adopted by the Infectious Diseases Society of America (IDSA), American Society of Health-System Pharmacists, and Society of Infectious Diseases Pharmacists for suspected or definitive infections in adults. However, a target of AUC_{0-24}/MIC ratio of 400 is thought to be more prudent in pediatrics to limit the development of exposure-related acute kidney injury [32••].

AUC-guided dosing and monitoring through either peak/trough monitoring or Bayesian software programs are now recommended for MRSA infections [32••]. Al-Sulaiti et al. performed a multicenter parallel group RCT

which showed that peak-trough-based TDM was associated with less vancomycin total daily doses, less dose adjustments, and higher rates of therapeutic cure when compared to tradition trough-based monitoring. However, similar rates of therapeutic troughs and *AUC*s were observed [33•]. An advantage of the peak-trough method is that the 2 vancomycin serum concentrations in 1 dosing period allows for direct calculation of the *AUC* via the trapezoidal method (formula below) [34] rather than extrapolating *AUC* from trough alone. Note that C_1 and C_2 denote the 2 separate concentrations drawn and $t_2 - t_1$ is the time between the 2 serum draws.

$$AUC = \frac{(C_1 + C_2)}{2} \times (t_2 - t_1)$$

There is insufficient evidence currently for the IDSA to recommend trough only or *AUC*-guided monitoring with noninvasive MRSA infections or other infections [32••].

However, there is significant evidence that trough-based dosing in pediatrics in undesirable due to wide variability in trough concentrations achieving AUC_{0-24}/MIC ratio of 400 in the pediatric population [32••]. Le et al. found the corresponding trough concentration for children ≥ 3 months old to be 8–9 mg/L after applying a population-based PK model to 702 patients who received vancomycin for ≥ 48 h. Indeed, the study found that vancomycin dosing by trough may lead to unnecessary increase in vancomycin exposure in 25–35% of subjects when targeting a trough of 15 mg/L and therefore recommended utilizing AUC_{0-24}/MIC in children over trough concentrations [35•]. Additionally, Frymoyer et al. found the $AUC_{0-24}/MIC > 400$ correlated with a trough of 7–10 mg/L when utilizing 3 published pediatric vancomycin models on a 25-kg child as base patient and a vancomycin dose of 15 mg/kg q6h [36] and a retrospective review by Kishk et al. found $AUC_{0-24}/MIC > 400$ correlated with a trough of 11 mg/L using the trapezoidal method in patients aged > 2 months to < 18 years old [34]. The Kishk study's slightly higher trough may be attributed to a large proportion of patients with $MIC > 1$.

Additional consideration should be given to 2 special populations with pediatrics: obese children and neonates.

Obese children are likely to have vancomycin exposures greater than normal weight children when dosed on a milligram per kilogram basis. Vancomycin is a hydrophilic molecule with decreased distribution into adipose tissue, leading to higher serum concentrations when dosed by milligram per kilogram. Therefore, therapeutic monitoring is likely to be particularly valuable in these children. Additionally, a loading dose of 20 mg/kg by total body weight is recommended in obese children to increase achievement of target *AUC*/*MIC* within the first 12 h of therapy [32••].

In neonates, vancomycin TDM is vitally important based on rapid maturation of renal function over the first weeks of life [37]. Zhao et al. determined that there is no expert consensus on an optimal dosing regimen when evaluating published neonatal PK models [38]. Therefore, the IDSA recommends *AUC*-guided TDM for neonates and infants up to 3 months with preferential use of Bayesian estimation for MRSA infections [32••].

In summary, *AUC*-guided dosing with a target AUC_{0-24}/MIC ratio of 400, through either peak/trough monitoring or Bayesian software programs, is

recommended by the IDSA for all pediatric MRSA infections. While there is insufficient evidence to recommend this for other infections, there is a preponderance of evidence toward variability of achieving targeted *AUC* with trough-based dosing in pediatrics alone and therefore *AUC*-guided dosing is also desirable for non-MRSA infections in pediatrics. Particular care should be given to obese children (loading dose recommended to aid in rapid achievement of target *AUC*) and neonates (where Bayesian software is preferred over peak/trough dosing).

β-lactams

β-lactam antibiotics are the most widely used antibiotics in clinical practice [39] with significant PK variability in patients who are critically ill, obese, burned, febrile neutropenic, and patients with AKI [1••]. β-lactams are time dependent antibiotics whose bactericidal effect is correlated with $fT > MIC$. The % $fT > MIC$ necessary to achieve 1–2 log reductions in bacterial colony forming units varies by β-lactam class (cephalosporins 50–70% $fT > MIC$, penicillins/monobactams 50% $fT > MIC$, carbapenems 40% $fT > MIC$) [40]. However, the optimal target for $fT > MIC$ clinically remains unclear.

Recent ICU studies in adults have used a target of 100% $fT > MIC$ for critically ill patients [41]. Mckinnon analyzed cefepime and ceftazidime PK/PD data from patients in 2 prospective, randomized clinical trials undergoing treatment of sepsis with bacteremia, lower respiratory tract infection, or complicated urinary tract infection. Patients who achieved 100% $fT > MIC$ had statistically greater rates of clinical cure (82% vs 33% $p = 0.002$) and bacteriological eradication (97% vs 44% $p < 0.001$) when compared to patients with < 100% $fT > MIC$ [42]. Additionally, some authors have used a higher target *MIC* (100% $fT > 4–10 \times MIC$) in critically ill patients [41, 43, 44]. Theoretically, these higher *MIC* targets would offset possible lower concentrations at the site of infection when compared to blood concentrations. However, Scharf et al. demonstrated a statistically faster reduction of CRP in patients with target attainment of 100% $fT > MIC$ but no benefit in patients with attainment of 100% $fT > 4 \times MIC$ [45].

There are no comparable studies in pediatrics currently. Cies et al. did demonstrate that 95% of pediatric ICU patients did not meet the target 40% $fT > 4–6 \times MIC$, and 100% of patients in the infected cohort demonstrated clinical cure following dosing adjustments within the first 48 h of β-lactam therapy [7]. However, this target of 40% $fT > 4–6 \times MIC$ differs significantly from the target 100% $fT > MIC$ in adult literature. Currently, there are no consensus targets for $fT > MIC$ for pediatric patients on β-lactam antibiotics [46]. Given the lack of comparative pediatric data to adult targets, it is recommended to continue to target 100% $fT > MIC$ for β-lactam antibiotics in pediatrics to reduce the risk of toxicity and given the preponderance of data on 100% $fT > MIC$ in adult literature.

The preferred method for obtaining β-lactam TDM would be obtaining multiple sampling time points throughout a single dosing interval followed by analysis with population PK software and Bayesian modeling. Fratoni et al.

recommend 3 sample points: 1 peak, 1 midpoint (or at least 30 min following infusion completion), and a trough level. If only 2 points can be drawn, a midpoint and trough is recommended to characterize clearance [47••]. A variety of software with Bayesian models for β-lactams are available including DoseMe, ID-ODS, MwPharm + +, and InsightRX [48].

However, if Bayesian modelling is not available, alternative methods can be used to estimate % *f*T > *MIC*. A 2-compartment model as defined by Turnidge [49] (formula below) can be used to calculate % *f*T > *MIC* with intermittent infusions but should be avoided with extended infusions (3–4 h). Note that *Vd* can be calculated by the formula $Vd = \text{Dose}/C_0$, where C_0 is the serum concentration at time 0 (immediately after a dose is given).

$$\%T > MIC = \ln\left(\frac{\text{Dose}}{Vd \times MIC}\right) \times \frac{\text{Drug half life}}{\ln(2)} \times \frac{100}{\text{Dosing Interval}}$$

Finally, rudimentary analysis of % *f*T > *MIC* can be estimated by simply evaluating sample concentrations at midway through the dosing interval and trough level. A β-lactam concentration above the *MIC* midway through the dosing interval correlates with 50% fT > *MIC* and a trough concentration above the *MIC* would correlate with 100% fT > *MIC*. However, this method would not allow individualized modifications based on patient PK.

Fluoroquinolones

Fluoroquinolones are both time-dependent and concentration-dependent antimicrobials, and antimicrobial activity is best correlated with AUC_{0-24}/MIC ratio [1••]. However, there is limited published data on fluoroquinolone TDM at this time. Van den Elsen et al. used a target $AUC_{0-24}/MIC > 150$ for oral levofloxacin and $AUC_{0-24}/MIC > 100$ for oral moxifloxacin (assuming 50% protein binding) in a prospective evaluation for TDM for multidrug-resistant tuberculosis patients (PERFECT study) [50]. Abdulla et al. used a target $AUC_{0-24}/MIC > 100$ for ciprofloxacin in a multicenter, randomized controlled trial designed to assess the efficacy and cost-effectiveness of model-based TDM of β-lactams and fluoroquinolones (DOLPHIN trial) [43]. Both studies used population PK software with Bayesian modeling (PERFECT: MWpharm + + and DOLPHIN: InsightRX) to calculate AUC_{0-24}. Two samples per dosing interval were used for both studies. The DOLPHIN trial obtained a trough concentration prior to infusion and peak concentration 30 min after completion of infusion. In contrast, the PERFECT study obtained 2 samples at time 0 and 5 h after drug intake once study state was achieved (7 days after initiation of therapy). However, these trials remain ongoing and clinical efficacy of these targets remains unclear.

Linezolid

Linezolid is an oxazolidinone antibiotic used in the treatment of gram-positive infections. Linezolid levels have been shown to fluctuate significantly in adult patients due to variability in renal function, drug-drug interactions, and pathophysiological conditions [51]. However, Galar et al. did not find any correlation with abnormal levels with adverse events, in-hospital mortality, or overall poor outcome [52•]. However, linezolid based TDM may be beneficial due to its narrow therapeutic window, particularly for long-term drug regimens such as those for multidrug-resistant tuberculosis [53]. Li et al. found that current linezolid dosing regimens lead to a high risk of underdosing children with bacterial $MIC \geq 2$ [54•]. Therefore, despite the well-known toxicities of linezolid (bone marrow suppression, peripheral neuropathy, lactic acidosis), the benefits of TDM in pediatrics remain unclear but should be considered in prolonged regimens [55].

There is limited data available on the PK/PD targets for linezolid, with published data to suggest correlation of antimicrobial activity with both AUC_{0-24}/MIC and $fT>MIC$. Rayner et al. performed a retrospective analysis of skin/soft tissue and lower respiratory tract infections and found that an AUC_{0-24}/MIC ratio of 80–120 and 80–100% $fT>MIC$ were both correlated with clinical cure and eradication of bacteria [56]. AUC_{0-24}/MIC and $fT>MIC$ were closely associated and were expected to perform similarly, although AUC_{0-24}/MIC may become more a relevant predictor of outcome once 100% $fT>MIC$ is reached. Therefore, it is recommended to utilize a target AUC_{0-24}/MIC ratio of at least 100 for linezolid (range 100–119 has been shown to be effective clinical studies) [55].

Alsultan et al. demonstrated correlation between $AUC_{0-24}/MIC > 100$ with trough levels of 2–5 μg/mL if $MIC < 2$, 5–8 μg/mL if $MIC = 2$, and difficult to achieve if $MIC > 2$ when utilizing a simulated model of 999 virtual patients [57]. However, it is unclear whether this model applies to pediatrics given the paucity of data available and known faster clearance in children < 12 years of age and neonates. Therefore, it is recommended to obtain both a peak and trough level to calculate AUC_{0-24}/MIC [55].

Target concentration intervention

Target concentration intervention (TCI) has been proposed as an alternative to TDM. The goal is to achieve a target concentration utilizing initial dosing to use individualized PK/PD parameters of a patient. Initial dosing is based on a patient's individual PK parameters (typically *Vd* and Cl). Subsequently, measured doses allow for revision of the initial PK indices to allow for adjustments to dosing in order to achieve and maintain the targeted concentration [58]. Proponents argue that the TCI allows for more optimal dose selection

as it focuses on individualized dosing and changing the dose to achieve a desired outcome. By comparison, TDM focuses on group dosing (utilizing weight, organ function) to maintain a concentration within a therapeutic range in which antimicrobial effect can vary, particularly at the borders.

Clinical use of TCI has been limited at this time given the significant infrastructure and expertise needed for individualized dosing [1••]. However, patient-tailored TDM through population modeling may provide an alternative to TCI due to its inherently lower resource utilization. Leroux et al. developed and implemented a model-based vancomycin dosing calculator, based on a population PK study, in 3 neonatal intensive care units. Patient tailored dose was calculated based upon patient characteristics including *Vd*, Cl, and weight. Neonates receiving continuous infusion of vancomycin were enrolled, and target attainment of 15–25 mg/L of first TDM trough was selected. Target attainment rate increased from 41 to 72% without any case of vancomycin-related nephrotoxicity [59]. With the increasing interest of model-informed dosing of antibiotics in pediatrics 3••, it is likely that utilization of this type of individualized pediatric antibiotic dosing will continue to increase.

Conclusion

There is growing evidence that the current weight-based antibiotic dosing regimens are inadequate, particularly in obese and critically ill children. While TDM is currently utilized commonly in a select group of antibiotics in pediatrics (vancomycin, aminoglycosides), there are significant potential clinical benefits to expansion of TDM to include β-lactams, particularly in the critically ill. However, pediatric data is still extremely limited and further research is necessary. The clinical benefit for TDM of linezolid and fluoroquinolones remains unclear. However, available evidence does suggest significant variability in linezolid levels which are concerning given the significant toxicities associated with linezolid (bone marrow suppression, peripheral neuropathy, lactic acidosis). Finally, there is significant potential for further optimization of TDM-based dosing through the use of population PK software with Bayesian modeling.

Declarations

Conflict of Interest
Dr. Frank Zhu declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any authors.

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