Advances in Pediatric Therapeutic Drug Monitoring

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Therapeutic drug monitoring (TDM) is indicated for drugs with narrow therapeutic indices, whereby clinicians can adjust drug dosing to promote efficacy while limiting toxicity risk. Such monitoring is particularly important in managing infectious diseases, as both patient- and organism-specific factors must be considered to achieve optimal clinical responses. Innovation in pediatric TDM lags behind adults, largely due to a paucity of data and feasibility issues with lab draws and pharmacy resources. Emerging techniques in pharmacokinetic (PK) modeling, PK study design, flexible sampling strategies, and reduced sample volume requirements are particularly promising for TDM advancement in neonates and children. In this article, we discuss recent advancements in vancomycin TDM as a model case. Vancomycin is commonly used to treat serious gram-positive infections in children, and monitoring was historically performed using trough concentration–based guidance. Emerging data suggest that vancomycin troughs are not reliable surrogates for efficacy or toxicity and that trough-based monitoring is associated with increased risk of nephrotoxicity without clinical benefits. The area under the concentration-time curve (AUC) is the optimal pharmacokinetic-pharmacodynamic metric to measure overall vancomycin exposures, and consensus infectious diseases and pharmacist society guidance has formally recommended a shift toward AUC-based monitoring and away from trough-based monitoring in all age groups—including in neonates and children. We compare approaches to TDM in infectious diseases and summarize the body of literature describing application of vancomycin AUC-guided monitoring in children and neonates. Finally, we highlight opportunities and potential barriers to implementation of AUC-guided TDM in pediatric populations.

GOALS OF THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring (TDM) is used to individualize drug dosing to achieve therapeutic effect and to reduce the risk of drug-associated toxicities. Since the 1960s, TDM (informed by pharmacokinetic [PK] and pharmacodynamic [PD] principles) has been used to optimize exposures to drugs with narrow therapeutic indices and to assess adherence to prescribed drug regimens. The ability to perform TDM is thus predicated on the ability to measure drug concentrations and to define drug concentration ranges that promote optimal clinical outcomes and limit risks of adverse drug effects.[1] Drugs commonly requiring TDM encompass multiple classes and indications (Table 1). Despite TDM's clear utility in supporting safe and efficacious drug administration, its development and adaptation in children and neonates has lagged. Contributing factors include PK variability in the setting of developmental maturation, absence of robust PK models and TDM efficacy targets validated in children, and limited blood sampling volumes.[2]

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Dr Coggins conceptualized and designed the study, performed the literature review, drafted the initial manuscript, and critically reviewed and revised the manuscript. Drs Wade and Downes conceptualized and designed the study and critically reviewed and revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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TABLE 1. Pharmaceutical Classes Commonly Using Therapeutic Drug Monitoring

Class	Examples of Drugs Benefiting From TDM
Antiarrhythmics	Digoxin
	Lidocaine
	Quinidine
	Procainamide
Anticoagulants	Heparin
	Warfarin
Antiepileptics	Carbamazepine
	Phenobarbital
	Phenytoin
	Valproic acid
Anti-infectives	Vancomycin
	Gentamicin
	Isoniazid
	Voriconazole
Antineoplastics	Carboplatin
	5-fluorouracil
	Methotrexate
Immunosuppressants	Cyclosporine
	Mycophenolic acid
	Sirolimus
	Tacrolimus
Methylxanthines	Caffeine
	Theophylline
Psychoactives	Clozapine
	Haloperidol
	Lithium
	Tricyclic antidepressants

Abbreviation: TDM, therapeutic drug monitoring.

In this article, we review current TDM practices in pediatric care, including advantages and disadvantages of trough-based sampling for TDM. Next, we describe the TDM concept based on the area under the concentration-time curve (AUC), which is a more pharmacologically relevant parameter for many drugs. We use vancomycin TDM as an illustrative example, given that vancomycin is one of the most commonly prescribed antibiotics in hospitalized children[3] and neonates[4,5] and often undergoes TDM to guide treatment and limit potential toxicity. We compare the rationales, approaches, and clinical implications of trough- and AUC-guided TDM in hospitalized children. We end with an overview of emerging innovations in TDM, which hold promise to improve medication dosing, efficacy, and safety in pediatric care.

RATIONALE FOR VANCOMYCIN TDM

Vancomycin is a glycopeptide antibiotic with bactericidal activity solely against gram-positive pathogens, such as staphylococci, enterococci, and streptococcal species. The drug is minimally metabolized; within 24 hours of administration, up to 80% to 90% of a single dose may be recovered unchanged in urine.[6] Vancomycin is primarily renally eliminated. Young children (aged <2 years) and neonates have slower vancomycin clearance due to factors influencing renal maturation and function.[7–11] Additionally, critical illness may further alter vancomycin PK due to increases in volume of distribution (eg, increased third spacing, capillary leak, extracorporeal supports) or reduced clearance in the setting of kidney disease.[12] Nephrogenesis is not complete until at least 36 weeks' gestation,[13] and renal maturation further develops over the first several years of age,[14] contributing to increasing drug clearance per body weight over early childhood.

The primary drivers for vancomycin TDM are (1) achievement of drug exposures that facilitate bacterial killing and (2) avoidance of toxicity. In particular, nephrotoxicity results from concentrated drug in the proximal tubule causing oxidative stress and acute tubular necrosis.[15] The prevalence of vancomycin-associated nephrotoxicity in children is estimated as 12%.[16] Neonates and young children (with higher unbound drug fractions, slower clearance, and ongoing maturational renal changes) may be at particular risk for vancomycin-associated nephrotoxicity, but TDM guidelines historically focused solely on adults. Trough-based approaches were the mainstay of vancomycin TDM for decades, until mounting evidence demonstrated that trough monitoring did not effectively optimize vancomycin exposures for treatment benefit or safety.[17] The newest guidelines specifically include pediatric recommendations and promote TDM using a more pharmacologically relevant vancomycin PD parameter: the 24-hour area under the concentration-time curve (AUC_{24}).[18]

In vitro, animal, and human studies demonstrate that the AUC to minimum inhibitory concentration ratio (MIC; AUC/MIC) best correlates with vancomycin efficacy (goal range 400–600), while AUC_{24} greater than 600 best predicts nephrotoxicity regardless of MIC. Studies of AUC-guided vancomycin TDM demonstrate that attainment of target vancomycin AUC exposures correlates poorly with troughs[19–21] and that AUC monitoring is superior to trough monitoring in mitigating nephrotoxicity.[22,23] Taking this into account, 2020 consensus guidelines by major US adult and pediatric infectious diseases and pharmacist societies formally recommended AUC-based TDM in all age groups.[24,25] Adoption of this guidance in pediatric care can be limited by lacking awareness, implementation challenges, and need for clinician and pharmacy expertise to support AUC monitoring.

TROUGH-BASED TDM

Trough-based TDM relies on measuring drug concentrations at the end of a dosing interval, obtained within

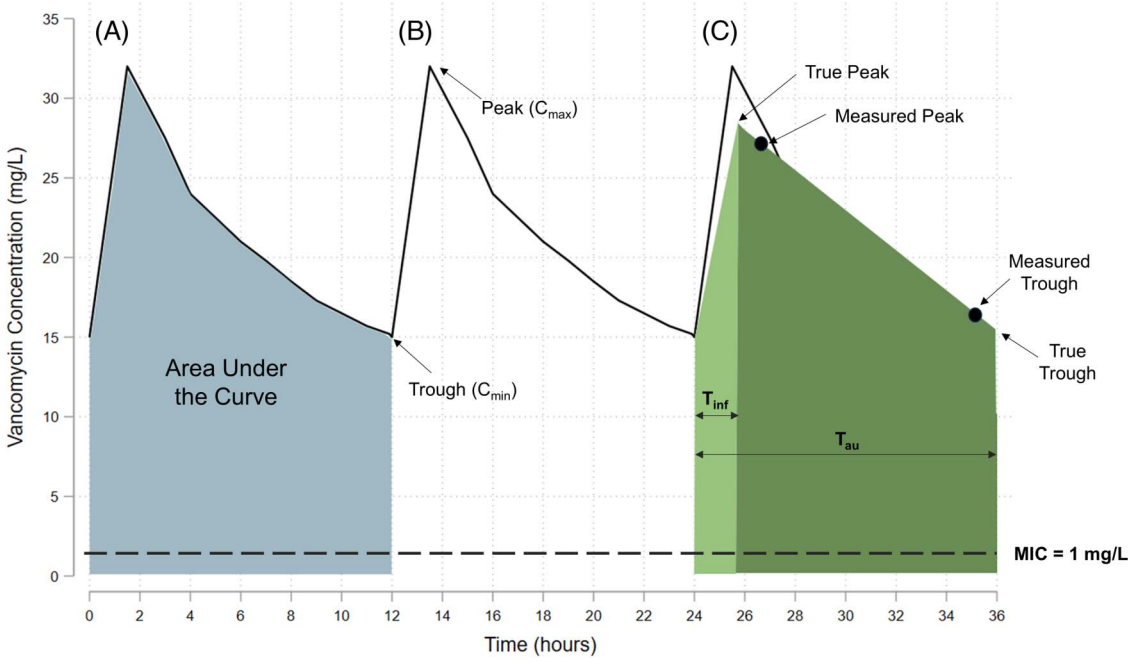

FIGURE 1.
A hypothetical concentration-time curve reflecting vancomycin concentrations in an every-12-hour dosing schedule. (A) The shaded area reflects the area under the concentration-time curve (AUC). The dotted horizontal line represents MIC for *Staphylococcus aureus* (1 mg/L). (B) Arrows demonstrate where trough and peak concentrations occur on the concentration-time curve surrounding a vancomycin dose. (C) A visual representation of how trapezoidal methods (2-point kinetics) are used to calculate AUC. Additional specifics available in Table 2.
Abbreviations: MIC, minimum inhibitory concentration; T_{au}, duration of the dosing interval; T_{inf}, infusion time.

30 minutes prior to administration of the next scheduled dose (Figure 1). Trough concentrations are less affected by variations in drug distribution than earlier time points in the dosing interval. The biggest advantage of trough-based TDM is its simplicity: only 1 serum drug measurement is needed, sample timing is easily understood, and interpretation is straightforward based on the relationship of the trough concentration to an established therapeutic window. For some drugs, like gentamicin, trough-based TDM is defined largely by safety thresholds: ideal trough concentrations are less than 2 mg/L, reflecting adequate drug elimination prior to a subsequent dose.[26,27] In this setting, troughs are used to ensure drug elimination and reduce toxicity risk rather than to guide efficacy. In contrast, vancomycin trough targets were proposed to guide both efficacy and toxicity bounds as a range (eg, 10–15 mg/L) and dose adjustments are made based on whether concentrations fall above or below this window.

There are several disadvantages of trough-based TDM, particularly for medications whose total drug exposure is related to efficacy and toxicity (Table 2). First, troughs must be collected at steady state (typically, after 5 half-lives or ~3–4 doses). Trough assessment thus may not be possible for days, and clinicians miss earlier opportunities to optimize drug dosing to achieve a clinical response. A substantial proportion (40%) of trough samples are mistimed, most often too early prior to the true trough interval or prior to achievement of steady state.[28–30] Early trough assessment prior to the true trough interval risks overestimation of the true trough level, whereas measurement prior to achieving steady state risks underestimation of the true trough value. Both scenarios can subsequently impede appropriate dose adjustment. Most importantly, for drugs like vancomycin where trough target ranges encompass both efficacy and toxicity bounds, troughs are surrogates for overall drug exposure (ie, AUC). Mounting data demonstrate trough concentrations often correlate poorly with AUC in children, raising concerns that troughs cannot adequately guide medication dosing when AUC is the target.

Past 2009 and 2011 Infectious Disease Society of America guidelines for adult and pediatric patients recommended goal vancomycin trough concentrations of 10 to 15 mg/L, with higher trough goals of 15 to 20 mg/L for management of serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections (eg, bacteremia, meningitis).[24,25] Adult data suggested that most patients had AUC_{24} of greater than or equal to 400 mg $*$ h/L when these trough concentrations were achieved, based on a low level of evidence.[24,25] However, trough concentrations poorly and inconsistently predict AUC_{24},[21] as explained by large variations in PK across pediatric age groups. In a small cohort of children administered vancomycin at 15 mg/kg

TABLE 2. Comparison of Vancomycin TDM Approaches

	Trough	2-Point AUC Calculation	Bayesian Modeling
Method	Measure serum vancomycin concentration before the next dose is due and interpret in relation to goal range.	Measure 2 serum vancomycin concentrations to calculate AUC_{24} using first-order PK equations.	Combine population PK models, patient-specific data, and serum vancomycin levels to estimate patient-specific PK.
Sampling and timing	Requires 1 vancomycin level obtained immediately (<30 min) prior to a dose. Must reach steady state; otherwise, value will be underestimated and not interpretable.	Requires 2 levels: vancomycin trough and peak concentrations surrounding a steady-state dose, or following a dose during the same dosing interval. Steady state must be achieved; if obtained too early, "peak" and "trough" values will underestimate the AUC.	Can be measured at any time, although number of samples and sample timing can influence accuracy of estimations, depending on the PK model used as the Bayesian prior. Steady state not required; harnesses mathematical modeling to predict concentration-time curves based on drug levels obtained before steady state.
Therapeutic target	10–20 mg/L (with 15–20 mg/L goal recommended for "serious infections")	AUC_{24} of 400–600 mg*h/L	AUC_{24} of 400–600 mg*h/L
Advantages	Single sample. Results easily interpretable.	Can be performed manually or with calculators. Minimal expertise needed to perform AUC estimation/calculations.	Most accurate approach for AUC estimation. Flexible sample timing; can use a single sample. Incorporates patient-specific information (eg, weight, renal function). Can optimize dosing early in course, before steady state is achieved. In specific populations, can predict starting doses.
Disadvantages	Poorly reflects overall drug exposure (ie, correlates poorly with AUC targets). Window for sample collection is small and samples are often not informative. Results are not easily translated into targeted dose adjustments. Associated with higher nephrotoxicity risk, compared with AUC-based monitoring.	Oversimplifies true vancomycin distribution (ie, assumes 1-compartment disposition). Must be performed at steady state. Requires 2 precisely timed samples.	Computationally complex. Requires specialized software and training. Most useful when the PK model population is similar to the individual patient of interest.

Abbreviations: AUC, area under the concentration-time curve; AUC_{24}, 24-hour area under the concentration-time curve; PK, pharmacokinetic; TDM, therapeutic drug monitoring.

every 6 hours, the probability of attaining AUC/MIC greater than 400 ranged from 16% to 90% when the median trough was 11.4 mg/L.[31] Among 40 children with *S aureus* infections, mean trough concentrations were 11 mg/L and mean AUC/MIC was 534, but troughs and AUCs were very poorly correlated ($r^2 = 0.082$).[32] Other pediatric studies report variable but much higher correlations between trough and AUC ($r^2 = 0.68$ and $r^2 = 0.80$).[33,34] Meanwhile, among 249 neonates treated with vancomycin, 89% had an AUC_{24} greater than 400 mg $*$ h/L when the trough value was 10 mg/L.[11] These data suggested that lower troughs (10–15 mg/L, rather than 15–20 mg/L) should be used for children with serious invasive infections, and most centers adopted this practice. Further, higher troughs reflect higher concentrations achieved across the dosing interval that may result in excessive exposure (as reflected in the AUC) and toxicity risk.

For at least 2 decades, the AUC/MIC ratio has been recognized as the optimal PK/PD parameter describing vancomycin efficacy. Difficulty in AUC computation hindered adoption of this preferred metric. We now know that vancomycin troughs are unreliable proxies for AUC targets,[35–38] and trough-based TDM produced vancomycin exposures exceeding requirements for clinical or microbiologic response.[19,37,39–41] Furthermore, trough-based dosing is associated with high nephrotoxicity rates[42–44]; a large meta-analysis identified that trough values greater than or equal to 15 mg/L were associated with 2.7-fold higher odds of nephrotoxicity compared with troughs less than 15 mg/L.[43] With growing availability of AUC calculation tools, major US infectious diseases and pharmacist societies published consensus guidance in 2020 that shifted to formally endorse AUC-guided vancomycin TDM for treatment of MRSA[18,45] (Table 3). In this guidance, the goal AUC/MIC ratio is 400 to 600 (assuming that MIC equals 1 mg/L). Trough-only monitoring is no longer advised, including in pediatric populations. Because obese individuals have a larger volume of distribution, a loading dose of 20 mg/kg is recommended for children with obesity who are younger than 12 years. Notably, these recommendations

TABLE 3. Comparison of 2011 and 2020 Vancomycin TDM Guidance for Children With Suspected MRSA Infections

Category	2011 Recommendation	2020 Recommendation
Optimal monitoring parameter	Trough concentration	AUC/MIC via Bayesian approach
Optimal TDM parameter range for serious infections[a]	15–20 mg/L[b]	400–600 mg*h/L
Optimal TDM parameter range to avoid nephrotoxicity	No recommendation	AUC < 600 mg*h/L
Timing of monitoring	Obtain trough at steady state, prior to the fourth or fifth dose	Initiate monitoring within the first 24–48 h of treatment; can start prior to achievement of steady state
Recommended empiric dosing for serious infections		
Children	60 mg/kg/day divided every 6 h intravenously	60–80 mg/kg/day divided every 6–8 h intravenously
Neonates	No recommendation	10–20 mg/kg/dose every 8–48 h intravenously
Loading dosing	No recommendation	Loading dose of 20 mg/kg recommended in the setting of obesity
Continuous vs intermittent dosing	No recommendation[c]	Continuous infusion may be considered if AUC is not attainable with intermittent dosing

Abbreviations: AUC, area under the concentration-time curve; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; TDM, therapeutic drug monitoring.

[a] Refers to invasive infections including bacteremia, meningitis, endocarditis, bone and joint infections, etc.

[b] Based on limited efficacy and safety data.

[c] Continuous infusions were not recommended in adults at this time.

are specific to treatment of MRSA infections and not for other gram-positive organisms that may be treated with vancomycin (eg, coagulase-negative *Staphylococcus* [CoNS], enterococci).

AUC-BASED TDM

As opposed to the snapshot provided by a single trough concentration measurement, the AUC more accurately reflects total drug exposure over a dosing interval. The AUC is essentially an integral that expresses drug concentrations over time (mg ∗ h/L) and is influenced by drug dosage, distribution, and clearance (Figure 1). Whereas troughs offer limited information about an individual's overall drug profile, an AUC gives a more complete picture of drug exposure to inform dose adjustments. AUC is typically a more reliable predictor of drug efficacy and toxicity risk for many medications. Understandably, AUC determination is more difficult and may require more than 1 blood sample.

There are multiple approaches to estimating AUC, each with advantages, disadvantages, and assumptions (Table 2; Figure 2). The 2-point kinetics approach uses linear (first order) PK equations to estimate AUC based on 2 drug concentrations—a peak obtained 1 to 2 hours after infusion (after the distribution phase) and a trough (Table 4). These levels are ideally collected during the same dosing interval but can be obtained as a trough prior to and peak following a single dose. Online AUC calculators based on 2-point kinetics are available, although some centers use local spreadsheet-based calculators.[46] However, the equation-based approach has limitations. It is agnostic to age and the child's clinical condition. In the case of vancomycin, this approach oversimplifies its true disposition by ignoring the alpha distribution phase and assuming vancomycin behaves as a 1-compartment drug. As with troughs, patients must be at steady state when samples are collected to avoid underestimation of AUC. Steady state typically occurs beyond the first 24 hours of therapy and can be difficult to gauge in critically ill patients or in others whose physiology (ie, PK) may be changing. If a child's drug clearance is delayed due to clinical illness, then steady state may occur later than expected.

A second approach uses Bayesian AUC estimation methods. This approach combines existing population PK models (Bayesian prior), patient-specific covariate data (eg, renal function estimates), and measured drug levels to generate individual PK estimates that most likely describe a patient's concentration-time curve (Figure 2).[47] Required patient-specific information depends on the model used but may include age, weight, serum creatinine, and concurrent medication exposures.[39,48,49] Bayesian modeling can reliably estimate AUC using as few as 1 sample (depending on the robustness of the base population PK model). This remains true among complex, critically ill neonates or children, as long as the base PK model is informed by similar patients.[36,48] Importantly, this approach does not require steady state attainment; by harnessing the mathematical concept of superposition, the concentration-time curve calculated after the first dose can predict future aggregate concentration-time curves.[50,51] When based on robust models, Bayesian estimation often provides accurate AUC estimation regardless of sample timing.[48] Bayesian approaches constitute an important tool in emerging model-informed

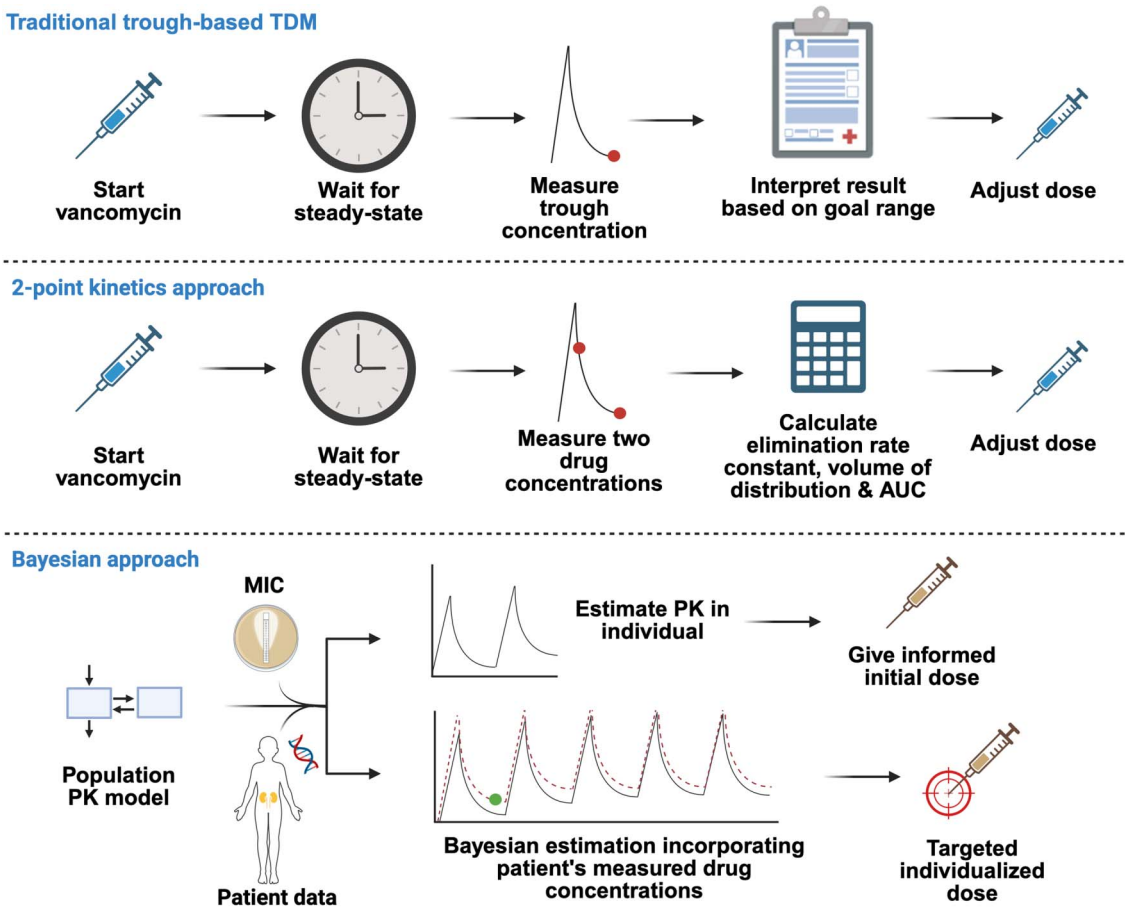

FIGURE 2.
Graphical representation of approaches to vancomycin TDM. Traditional trough-based TDM involves collection of a vancomycin trough at steady state and interpretation of the result based on a goal range (ie, 10–15 mg/L). If the trough is out of range, doses are typically adjusted by a percentage of the daily dose (ie, 10%, 20%) or the interval is changed, depending on how far out of range the level is. The 2-point kinetics approach uses 2 concentrations collected at steady state to calculate key PK parameters—elimination rate constant and volume of distribution—using log-linear regression equations. From these, an AUC can be calculated and doses adjusted in a commensurate manner targeting an AUC of 400 to 600 mg ∗ h/L. The Bayesian approaches use a software program to estimate individual-level PK and AUC. A robust population PK model informed by similar patients serves as prior information (Bayesian prior; describing how the drug behaves in a population) and is combined with patient-specific information (eg, renal function, weight, genotype) to generate individual PK parameter estimates (Bayesian posterior). Estimation can be done before administration of the drug to derive a reasonable starting dose or can incorporate measured drug concentrations to more precisely generate patient-specific PK and AUC estimates and inform targeted dosing.
Abbreviations: AUC, area under the concentration-time curve; MIC, minimum inhibitory concentration; PK, pharmacokinetic; TDM, therapeutic drug monitoring.

precision dosing efforts, in which software programs use individual PK estimates to develop personalized dosing recommendations that optimize AUC target attainment. When integrated into the electronic health record, patient-specific information can automatically be incorporated into the modeling to minimize clinician burden and potential data entry errors.

Bayesian approaches are complex and have only recently been incorporated into clinical care. They require specialized software and rely on richly sampled population PK models, which may not be available for all pediatric subpopulations. Bayesian estimation most accurately estimates PK (and AUC) when the individual patient is similar to the population informing the derivation PK model. For example, a population PK model derived in a general pediatric population may not accurately describe the PK of a critically ill child on renal replacement therapy. Clinicians need to be attuned to the model being used to inform AUC estimations.

AUC-GUIDED VANCOMYCIN TDM IN CLINICAL CARE

Much research has focused on improving outcomes and limiting toxicity with AUC-guided vancomycin TDM. In a meta-analysis among hospitalized adults with *S aureus* infections, achieving vancomycin AUC/MIC above study-specific targets (ranging 211–451) was associated with significant reductions in all-cause mortality and treatment failure,

TABLE 4. Calculation of the AUC_{24} Using 2-Concentration (Trapezoidal) Approach

Step	Equation	Worked Example[a]
1. Calculate the elimination rate constant (ke)	$ke = \frac{\ln\left(\frac{\text{Measured Peak}}{\text{Measured Trough}}\right)}{T_2 - T_1}$	$ke = \frac{\ln\left(\frac{30.0\ mg/L}{12.7\ mg/L}\right)}{11.33\ h - 2.8\ h}$ **ke = 0.10**
2. Calculate true peak	$\text{True Peak} = \frac{\text{Measured Peak}}{e^{(-ke)(T_1 - T_{inf})}}$	$\text{True Peak} = \frac{30.0\ mg/L}{e^{(-0.10)(2.8\ -\ 1.0)}}$ **True Peak = 29.5 mg/L**
3. Calculate true trough	$\text{True Trough} = (\text{Measured Trough})\left(e^{(-ke)(\text{tau} - T_2)}\right)$	$\text{True Trough} = (12.7\ mg/L)\left(e^{(-0.10)(12\ -\ 11.33)}\right)$ **True Trough = 11.9 mg/L**
4. Calculate AUC under the infusion curve (AUC_{inf})	$AUC_{inf} = \frac{(\text{True Trough} + \text{True Peak})}{2}(T_{inf})$	$AUC_{inf} = \frac{(29.5\ mg/L + 11.9\ mg/L)}{2}(1)$ **AUC_{inf} = 20.7 mg∗h/L**
5. Calculate AUC under the elimination curve (AUC_{elim})	$AUC_{elim} = \frac{\text{True Peak} - \text{True Trough}}{ke}$	$AUC_{elim} = \frac{29.5\ mg/L - 11.9\ mg/L}{0.10}$ **AUC_{elim} = 176 mg∗h/L**
6. Calculate AUC_{24}	$AUC_{24} = [(AUC_{inf}) + (AUC_{elim})] * \frac{24}{tau}$	$AUC_{24} = [(20.7) + (176)] * \frac{24}{12}$ **AUC_{24} = 393.4 mg∗h/L**

Abbreviations: AUC, area under the concentration-time curve; AUC_{24}, 24-hour area under the concentration-time curve.

[a] The worked example utilizes a hypothetical preterm infant being treated for methicillin-resistant *Staphylococcus aureus* bacteremia with vancomycin at 15 mg/kg every 12 hours. Calculations performed using the following parameters: measured peak = 30 mg/L, measured trough = 12.7 mg/L, T_1 = 2 hours, 48 minutes, T_2 = 11 hours, 20 minutes, T_{inf} = 1 hour, tau = 12 hours. T_1: Time (in hours) from start of vancomycin infusion to measurement of peak concentration; T_2: Time (in hours) from start of vancomycin infusion to measurement of trough concentration; T_{inf}: Duration (in hours) of vancomycin infusion; tau (τ): Dosing interval (in hours).

compared with patients with low AUC/MIC.[52] Another systematic review and meta-analysis demonstrated that AUC-guided TDM was associated with significantly lower nephrotoxicity risk compared with trough-guided TDM (odds ratio [OR] 0.53, 95% CI 0.32–0.89).[22] Single-sample Bayesian AUC estimation was similarly associated with reduced nephrotoxicity compared with trough-based dosing (2.8% vs 17.4%, respectively) without additional required sampling.[23]

Children

Multiple studies report that labeled 40 mg/kg/d pediatric vancomycin dosing is insufficient to achieve target AUC/MIC greater than 400 for treatment of MRSA[53] and that higher total daily dosing is needed for children with normal renal function.[39,54] More recent studies endorse dosing of at least 60 mg/kg/d to achieve goal AUC/MIC,[34,55–57] with daily dosing requirements appearing to decrease as age increases among older infants and children.[56,57] Personalized vancomycin dose adjustment using AUC-guided TDM is feasible in children. Among patients with cystic fibrosis, AUC-guided compared with trough-guided TDM promoted significantly higher achievement of goal AUC 400 to 600 (71% vs 39%, respectively)[58] and reductions in severe acute kidney injury (AKI).[59] Additional reports have identified the feasibility of AUC monitoring following pediatric liver transplantation[60,61] and bone marrow transplantation.[62]

There are limited data to validate vancomycin TDM target attainment with favorable clinical or microbiologic outcomes in pediatric MRSA infections, regardless of the strategy. Among 67 MRSA bacteremia episodes in children treated with vancomycin, 9 (13%) had treatment failure (persistent bacteremia, or recurrent bacteremia or mortality within 30 days),[63] which was not associated with the trough nor was AUC/MIC achieved. Another analysis among 110 critically ill children identified no association of trough or AUC/MIC with author-defined clinical efficacy.[64] In a third study of 73 children with MRSA bacteremia (median vancomycin dose 40 mg/kg/d),[65] initial AUC/MIC less than 300 was associated with persistent bacteremia at 48 to 72 hours of therapy, but not with 30-day mortality. The multifactorial nature of clinical illness and treatment response makes it challenging to establish just one therapeutic target for vancomycin efficacy among all children.

Stronger retrospective data support the association of vancomycin AUC and nephrotoxicity in children. Among 112 children receiving AUC-guided vancomycin TDM, the AUC threshold for AKI development was greater than 583 mg ∗ h/L, and rising AUC was associated with increasing risk.[66] The study in 110 critically ill children mentioned above identified a similar AUC threshold predictive of nephrotoxicity (>537 mg ∗ h/L).[64] Few prospective studies have evaluated AKI among children with AUC-guided TDM.

Neonates

Empirical vancomycin administration is common among preterm and critically ill neonates.[5] This is particularly true when late-onset infection is suspected beyond 3 days of age, as approximately 30% of cases are due to CoNS, another 23% to *S aureus*, and 5% to *Enterococcus*.[67] Trough-guided vancomycin TDM remains commonplace, though with limited data to inform efficacy or safety in neonates. Simulations across a wide gestational age range show that common vancomycin dosing regimens do not reliably achieve trough concentrations greater than or equal to 10 mg/L.[11] Neonatal studies report variable correlations

between vancomycin trough concentrations and AUC,[41,68] often with lower troughs required to attain target AUC/MIC compared with adults. In multiple studies of preterm and term neonates, troughs of 7 to 11 mg/L achieve AUC greater than 400 mg ∗ h/L.[11,41,69]

Emerging research describes neonatal outcomes after AUC-guided TDM. Among 30 infants with bacteremia (28 CoNS, 2 MRSA), AUC attainment greater than 300 mg*h/L was associated with a 7.8-fold increase in the likelihood of bacteriologic cure.[70] Another study of 40 infants with gram-positive bacteremia (predominantly CoNS, and the rest MRSA or *Enterococcus*) suggested an AUC/MIC target greater than 425 to predict clinical efficacy in gram-positive bacteremia (although predictive ability weakened substantially when MIC was >2 mg/L).[71] A third study among 153 neonates with CoNS bacteremia identified an optimal AUC/MIC target greater than 281 for clinical efficacy, while AUC greater than 602 mg*h/L increased nephrotoxicity risk.[72] Finally, among 123 infants with gram-positive bacteremia, attainment of AUC/MIC 420 to 650 was associated with significantly lower odds of persistent infection or 30-day mortality (OR 0.29, 95% CI 0.08–0.86).[73] Multiple population PK models are available to describe vancomycin disposition in term and preterm neonates. Importantly, AUC-guided monitoring has been successfully implemented in the neonatal intensive care unit setting, indicating feasibility even among the most complex neonates.[74]

ADDITIONAL CONSIDERATIONS FOR TDM IN INFECTIOUS DISEASES

Antimicrobial TDM requires special consideration of other aspects of drug monitoring that impact antimicrobial effect and clinical response. First, most clinical assays measure total drug concentrations, but drug protein binding (typically to albumin) can have substantial impacts on drug activity. Highly protein-bound drugs have a low concentration of free, unbound drug available to exert antimicrobial effects. Although not typically done for vancomycin, clinicians will often adjust total concentrations based on typical protein binding to calculate the free fraction of drug (eg, for β-lactam agents). Protein binding is an important concept in neonatal care, as these patients' low protein stores translate into higher free drug concentrations.

Second, the site of infection and antimicrobial tissue penetration can also impact the efficacy relationship with TDM based on serum drug concentrations, particularly when treating infections in compartments not available for TDM (eg, bone, brain, or lungs).[75,76] The blood-brain barrier has varied permeability to specific antimicrobial agents based on molecular and protein-binding properties; however, central nervous system penetration increases in the setting of meningeal inflammation by up to 3-fold.[6] Given this variability, clinicians cannot easily estimate how much drug gets to extravascular sites of infection.

The MIC, which reflects the concentration needed to inhibit bacterial growth, is a key component of any antibiotic efficacy target. However, the reported MIC for a given bacterial isolate can differ based on the method used (eg, broth microdilution, Etest, automated systems) and inherent test variability. According to the Clinical Laboratory Standard Institute, acceptable variability is within +/−1 $\log_2$ dilution (ie, doubling), meaning that an MIC reported as 1 mg/L could be 0.5 or 2 mg/L if testing was performed using another method or if the same test method was repeated. Thus, clinicians should recognize that even the MIC is not an absolute therapeutic target. Furthermore, the AUC/MIC goal of 400 to 600 assumes an MIC of less than or equal to 1 mg/L as defined by the broth microdilution technique[18]; for isolates with MIC greater than or equal to 2, alternative antimicrobial agents may be required if clinical response is insufficient based on AUC calculations that assume MIC = 1.

All of these issues are relevant to vancomycin TDM. Intravenous vancomycin widely distributes into various tissues, although penetration into lung and the central nervous system varies.[6] Among children, volume of distribution (Vd) varies substantially because total body water content (as a fraction of body weight) decreases with age.[12] Vancomycin Vd (per kilogram body weight) is higher among infants compared with older children, producing lower peak concentrations for the same weight-based dose.[12,77] Children administered vancomycin also have a significantly higher unbound/free active drug fraction (~90% in neonates, 80% in older children)[78,79] compared with adults (50% unbound),[6] which has implications for varying "free, unbound" drug activity at equivalent administered doses across the pediatric age spectrum. Finally, when treating MRSA, adjusting vancomycin TDM based on the actual MIC reported is not recommended.[18] Instead, MIC of 1 mg/L is assumed (as the most common MIC from national surveillance data) and the AUC is targeted directly. Because toxicity is MIC-independent, targeting a vancomycin AUC/MIC of 400 to 600 when the MIC is greater than or equal to 2 mg/L carries an untoward nephrotoxicity risk. CoNS is the most common organism causing late-onset neonatal infections,[67] yet limited data are available to derive an ideal AUC/MIC efficacy target for this and other non-MRSA organisms (eg, enterococci).

AUC-GUIDED TDM IMPLEMENTATION

Transitioning from trough- to AUC-guided TDM is a significant practice change, and multiple barriers have slowed its adoption in pediatric and neonatal care. Literature describing AUC monitoring in pediatrics is still emerging, and data-driven guidance for optimal AUC target selection remains to be confirmed. As mentioned previously, AUC/MIC targets may vary by organism, and measurement is expected to require different PK models in different age groups.

Finally, many hospitals do not have access to Bayesian software capable of AUC calculation in children and neonates, nor are staff trained in their use. Models may also be limited in their application to unique physiology in critically ill children that affects drug PK (eg, extracorporeal membrane oxygenation, dialysis).[80]

Implementation concerns are commonly cited barriers to use of pediatric clinical AUC monitoring.[46,81] Vancomycin AUC enactment timelines are reported to require 7 to 14 months.[74,82] Implementation requires a literature review to choose a specific PK model reflecting the target population, dissemination to key stakeholders (pharmacists, infectious diseases physicians, antimicrobial stewardship teams), and establishing the AUC determination approach (ie, 2-point kinetics, Bayesian estimation). Selection of commercially available Bayesian dosing software includes consideration of cost, functionality, analytic support, electronic health record integration, and availability of modules tailored to pediatric and neonatal populations.[74] Finally, workflows must be developed, including assignment of AUC monitoring responsibilities (eg, ordering, interpretation, timing of blood draws), documentation processes, and nursing and pharmacy guidance.[74,83,84] Staff education is necessary to implement and sustain AUC monitoring processes. Pharmacy, physician, and nursing leadership must support workflow changes affected by AUC implementation. Ongoing audits can track adherence to AUC monitoring protocols and clinical outcomes of interest (eg, vancomycin-associated nephrotoxicity, total vancomycin exposures), as feasible. It is also important to continuously evaluate updated software modeling capabilities and the availability of new modules (ie, population PK models to inform Bayesian AUC estimation).[74,82] Resource toolkits are available to support centers implementing vancomycin AUC monitoring (https://sidp.org/Vancomycin-AUC-Implementation-Toolkit-Guide).

Multiple studies cite benefits of implementing vancomycin AUC monitoring. One study in adults found that AUC monitoring was associated with a 13% reduction in total daily vancomycin doses and longer dosing intervals (compared with trough monitoring).[85] Two single-center studies showed that the frequency of dose adjustment did not differ between trough- and Bayesian AUC–guided TDM approaches[86,87]; however, when dosing adjustments were needed, the AUC-based approach was associated with reduced likelihood of dose increases.[86] Cost-effectiveness of AUC- compared with trough-based monitoring is specifically cited due to reductions in AKI.[88,89] Fewer vancomycin serum measurements and smaller vancomycin doses may net additional savings.[83,90] In an interrupted time-series analysis, pediatric AUC-guided monitoring was associated with a 57% reduction in the number of TDM samples obtained, significantly fewer dosage adjustments, and no increase in AKI, compared with a preceding trough monitoring epoch.[91]

INNOVATIONS IN TDM

Computational advances in model-informed precision dosing hold promise to further optimize TDM by incorporating sources of variability specific to children and neonates. One approach, model-informed precision dosing (MIPD), incorporates population-level data and individual characteristics (eg, renal function) to better "personalize" dosing based on individual pediatric patient characteristics.[92] MIPD is increasingly feasible, given improved availability of commercial software that can be integrated into the electronic health record.[58,74] Incorporation of pharmacogenetic testing into MIPD efforts may provide valuable adjuncts to TDM. For example, identification of gene variants associated with reduced activity of proteins involved in drug transport and metabolism can inform empirical dosing decisions, prior to the performance of TDM.

Emerging microsampling technologies are particularly relevant to TDM in pediatric care. Microsampling uses blood sample volumes less than 50 μL, which can be measured via small volume assays and specialized analytic methods (eg, high-performance liquid chromatography, tandem mass spectrometry).[93] For comparison, conventional vancomycin or gentamicin trough TDM using clinical laboratory immunoassays requires at least 10 times that blood volume (~0.5 mL). Chromatographic methods require dedicated instrumentation and expertise and are more expensive than immunoassay methods. However, high-volume clinical laboratories may recoup this return on investment. Microsampling is possible via dried blood spots obtained from fingerpricks[94] or with volumetric absorptive microsampling devices via capillary action.[95] Alternative specimen sources for TDM (eg, saliva, urine) is an emerging area of research.[96]

CONCLUSIONS

Evolving TDM capabilities offer opportunities to individualize pediatric drug dosing to maximize efficacy while limiting toxicity risk. Vancomycin trough monitoring, although no longer recommended, may still be in use in hospitals that have not yet implemented AUC monitoring. For treatment of MRSA infections, AUC is superior to trough monitoring with respect to safety, and AUC monitoring is both feasible and beneficial in pediatric populations. Furthermore, AUC-based TDM supports the goals of precision dosing, particularly among pediatric populations at highest risk of adverse drug events and high variability in PK (eg, critically ill or immunocompromised populations, neonates). Ongoing research is required to fill knowledge gaps regarding the impact of AUC-guided monitoring on clinical outcomes in

children and neonates and optimal approaches to implementing AUC-guided TDM into clinical care.

ABBREVIATIONS

AKI: acute kidney injury
AUC: area under the concentration-time curve
CoNS: coagulase-negative *Staphylococcus*
MIC: minimum inhibitory concentration
MIPD: model-informed precision dosing
MRSA: methicillin-resistant *Staphylococcus aureus*
OR: odds ratio
PD: pharmacodynamic
PK: pharmacokinetic
TDM: therapeutic drug monitoring
Vd: volume of distribution

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