ORIGINAL RESEARCH

Achieving Therapeutic Vancomycin Levels in Pediatric Patients

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ABSTRACT

Background: Vancomycin is widely used to treat infections caused by methicillin-resistant *Staphylococcus aureus*. Data for dosing and monitoring of this drug in pediatric patients are lacking, and clinicians who are treating children often follow guidelines established for adults.

Objectives: To examine the total daily doses of vancomycin required to reach therapeutic trough levels (i.e., 10–20 mg/L) in infants, children, and adolescents, and to assess the number of pediatric patients in whom therapeutic trough levels are achieved with current empiric doses (40–60 mg/kg daily).

Methods: This chart review evaluated patients 1 month to 18 years of age for whom vancomycin was prescribed at a single institution between November 2011 and October 2012. Patients' demographic characteristics, vancomycin dosing parameters, and subsequent steady-state trough concentrations were analyzed.

Results: Overall, the proportion of patients who reached therapeutic trough levels with current empiric doses was 39% (74 of 188). The mean total daily dose (± standard deviation) required to achieve therapeutic trough levels was 57.8 ± 11.5 mg/kg for patients 1 to 5 months of age, 68.9 ± 15.4 mg/kg for those 6 to 23 months of age, 65.8 ± 13.0 mg/kg for those 2 to 12 years of age, and 55.7 ± 11.8 mg/kg for those 13 to 18 years of age.

Conclusions: Common empiric vancomycin dosing regimens (40–60 mg/kg daily) are not high enough to achieve trough levels of 10–20 mg/L in the majority of pediatric patients. Given these data, the authors suggest a starting dose of 60 mg/kg daily for patients 1 to 5 months of age and those 13 to 18 years of age and a starting dose of 70 mg/kg daily for patients 6 months to 12 years of age.

Keywords: vancomycin, pediatrics, dose, trough levels, pharmacokinetics

RÉSUMÉ

Contexte : La vancomycine est couramment utilisée pour traiter les infections à *Staphylococcus aureus* résistant à la méthicilline. Or, il n'y a pas assez de données sur l'adaptation posologique pour ce médicament et sur son suivi pharmacologique chez l'enfant. Les cliniciens qui traitent des enfants suivent donc souvent des lignes directrices conçues pour les adultes.

Objectifs : Analyser la posologie quotidienne de vancomycine nécessaire à l'atteinte de concentrations minimales thérapeutiques (c.-à-d. 10–20 mg/L) chez le nourrisson, l'enfant et l'adolescent, et évaluer le nombre d'enfants chez qui les concentrations minimales thérapeutiques ont été atteintes à l'aide des posologies empiriques utilisées présentement (40–60 mg/kg par jour).

Méthodes : L'étude consistait en l'analyse des dossiers médicaux de patients âgés entre 1 mois et 18 ans qui se sont vu prescrire la vancomycine, et ce, dans un seul établissement entre novembre 2011 et octobre 2012. Les données démographiques des patients, les paramètres posologiques de la vancomycine et les subséquentes concentrations minimales à l'état d'équilibre ont été analysés.

Résultats : Dans l'ensemble, la proportion de patients chez qui les concentrations minimales thérapeutiques ont été atteintes à l'aide des posologies empiriques présentement utilisées était de 39 % (74 sur 188). La posologie quotidienne moyenne (± l'écart-type) nécessaire pour atteindre les concentrations minimales thérapeutiques était de 57,8 ± 11,5 mg/kg pour les patients âgés de 1 à 5 mois, de 68,9 ± 15,4 mg/kg pour ceux âgés de 6 à 23 mois, de 65,8 ± 13,0 mg/kg pour ceux âgés de 2 à 12 ans et de 55,7 ± 11,8 mg/kg pour ceux âgés de 13 à 18 ans.

Conclusions : Les posologies empiriques courantes de 40–60 mg/kg par jour de vancomycine ne sont pas assez élevées et ne permettent pas d'atteindre des concentrations minimales de 10–20 mg/L chez la majorité des patients en pédiatrie. Compte tenu de ces données, les auteurs suggèrent une dose de départ quotidienne de 60 mg/kg pour les patients âgés de 1 à 5 mois et ceux âgés de 13 à 18 ans, et une dose de départ quotidienne de 70 mg/kg pour les patients âgés de 6 mois à 12 ans.

Mots clés : vancomycine, pédiatrie, dose, concentrations minimales, pharmacocinétique

[Traduction par l'éditeur]

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INTRODUCTION

Vancomycin is a glycopeptide antibiotic that is widely used in pediatrics to treat infections caused by methicillin-resistant *Staphylococcus aureus*. It exhibits age-related pharmacokinetics, and to reduce nephrotoxicity and optimize efficacy, serum trough concentrations are monitored. Given the lack of data for vancomycin dosing and monitoring in pediatric patients, clinicians treating patients in this age group often adopt guidelines developed for adults. Previously, serum trough concentrations were targeted to 5–10 mg/L in most situations or 10–15 mg/L for treatment of central nervous system infections.[1] In 2009, however, a consensus review of therapeutic monitoring of vancomycin in adults was developed and released in response to increasing resistance of *S. aureus* isolates and resultant treatment failures.[2] These guidelines suggested that serum trough concentrations of vancomycin should be maintained above 10 mg/L to avoid development of resistant *S. aureus* strains.[2] In addition, the guidelines recommended serum trough concentrations of 15–20 mg/L for complicated infections, including bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia caused by *S. aureus*.[2] Data to support these higher trough targets are limited, and recommendations in additional guidelines released in 2011 were based on moderate evidence (opinions of respected authorities, clinical experience, descriptive studies, or reports of expert committees).[3] As well, these higher trough targets have not consistently been associated with increased therapeutic efficacy.[2,3] However, to minimize the development of resistant strains, improve tissue penetration, and optimize vancomycin pharmacodynamics, the 2011 guidelines suggested targeting these higher trough concentrations.[3] In 2011, the authors' centre adopted the guidelines of the Infectious Diseases Society of America (IDSA)[2,3] for all vancomycin use, despite lower levels of *S. aureus* resistance in Canada than in the United States.

Following adoption of the new target trough levels for vancomycin, typical pediatric starting doses of 40–60 mg/kg daily (usually divided for administration q68h) have remained the same at many institutions, including that of the authors. Clinical experience and several recent studies have shown that such doses are frequently insufficient to achieve the new target trough levels.[4-8] As a result, repeated dose increases are required to address below-target trough levels. The delay in achieving the target trough level not only impedes early treatment of the infection but also promotes the development of resistant strains,[2] the issue that prompted the original recommendation for higher trough levels.

Because 80%–90% of vancomycin is cleared through the kidneys, the half-life of the drug in a patient's body depends heavily on renal function.[9-13] Given age-related differences in renal function and hence vancomycin clearance, it would seem that vancomycin dosing strategies should be adjusted according to age.

Recent studies have shown that significantly higher doses than those in current use are required to achieve these higher trough levels[4,6-8]; however, more data are needed to support starting doses above 60 mg/kg daily in pediatrics.[6] Several studies have shown low rates of achieving therapeutic vancomycin trough levels in pediatric patients with current starting doses,[4-8,14] and a few have suggested alternative starting doses, as summarized in Table 1.[4,7,8,14] No studies to date have examined the total daily dose required to reach therapeutic trough levels in pediatric patients. In addition, minimal data have been published regarding whether and how doses differ among infants, children, and adolescents. The primary objective of this study was therefore to examine the total daily doses required to reach therapeutic trough levels in infants, children, and adolescents. The study also aimed to assess the number of pediatric patients in whom therapeutic trough levels were achieved with current empiric doses.

METHODS

The Alberta Children's Hospital is a tertiary pediatric referral hospital with about 150 acute care beds. For this chart review, data were evaluated for patients aged 1 month to 18 years for whom IV vancomycin had been prescribed between November 2011 and October 2012. Patients were included only if samples for determination of trough levels had been appropriately drawn (i.e., at steady state, within 30 min before the fourth or a subsequent dose, according to institutional practice). The hospital's

Table 1. Studies Reporting Dosing of Vancomycin in Pediatric Patients

Study	No. and Age of Patients	Efficacy Parameter	Dosing Recommendations
McCabe et al. (2009)[8]	*n* = 63 (aged 1 mo to 18 yr)	Trough > 10 mg/L	Age 1 mo to 2 yr: 95 mg/kg daily Age 2–12 yr: 88 mg/kg daily Age 12–18 yr: 75 mg/kg daily
Frymoyer et al. (2009)[7]	Hypothetical children (aged 2 to 12 yr)	AUC_{24}/MIC > 400	Age 2–12 yr: 60 mg/kg daily
Eiland et al. (2011)[4]	*n* = 295 (aged 1 mo to 18 yr)	Trough 10–20 mg/L	Target trough 10 mg/L: 70 mg/kg daily Target trough 15 mg/L: 85 mg/kg daily
Le et al. (2013)[14]	*n* = 702 (aged 3 mo to 21 yr)	AUC_{24}/MIC ≥ 400	Age 3 mo up to 2 yr: 70 mg/kg daily Age > 2 yr: 60 mg/kg daily

AUC_{24}/MIC = ratio of area under the curve (24 hours) to minimum inhibitory concentration.

practice is not to draw samples for determination of peak levels of vancomycin. Patients with samples drawn inappropriately, neonates, and patients with renal dysfunction were excluded. Renal dysfunction, calculated with the Schwartz equation, was defined as glomerular filtration rate (GFR) less than 60 mL min^{-1} 1.73 m^{-2} for patients under 1 year of age and GFR less than 80 mL min^{-1} 1.73 m^{-2} for patients 1 year of age or older. For patients whose height was not stated in the medical record, height was calculated from the appropriate Centers for Disease Control and Prevention clinical growth chart (available from www.cdc.gov/growthcharts/), according to the patient's age and weight along the 50th percentile curve. For patients who received multiple courses of vancomycin during the study period, only the first course was included in the analysis. Patients who received only 24–48 h of empiric vancomycin therapy, despite not reaching therapeutic trough levels, were included, as long as samples for determination of trough levels were drawn appropriately at steady state.

Data were collected from a computerized charting database and were recorded electronically. A total of 1 year's worth of patients was predetermined as the sample size. Collected data included demographic characteristics, vancomycin doses and administration intervals, the respective serum trough concentrations, and serum creatinine levels. The study centre does not routinely use loading doses. The primary outcome was mean total daily dose (mg/kg) required to achieve therapeutic trough levels (10–20 mg/L) in infants, children, and adolescents. Infants were defined as patients 1 to 23 months of age; however, this group was further subdivided as 1 to 5 months and 6 to 23 months. Children were defined as patients 2 to 12 years of age, and adolescents were those 13 to 18 years of age. These age ranges were based on previous studies, expected renal function, and its ontogeny.[8] Results were analyzed using descriptive statistics. The study was approved by the University of Calgary Conjoint Health Research Ethics Board, and the need for informed consent was waived because of the retrospective nature of the study.

RESULTS

A total of 448 pediatric patients were screened. Of these, 78 (17%) were excluded because samples for determination of trough levels were drawn inappropriately, 10 (2%) because of renal dysfunction at the start of vancomycin therapy, and 36 (8%) because they were neonates. In addition, for 68 (15%) patients who were started on vancomycin, the therapy was stopped before determination of trough level. For another 19 (4%) patients, serum creatinine was not measured during the admission, so GFR could not be calculated. These 2 groups of patients were also excluded from analysis. Some patients met more than one exclusion criteria. Of the 448 patients, 257 were included in the analysis (Figure 1); their demographic characteristics are presented in Table 2.

Overall, only 74 (39%) of the 188 patients with empiric starting dosages (40–60 mg/kg daily) reached therapeutic (target) trough levels of 10–20 mg/L with the initial dose. Achievement of target levels with the initial dose was least frequent for patients 6 to 23 months of age (7/37 [19%]) and 2 to 12 years of age (35/94 [37%]). Achievement of target levels with the initial dose was greater for patients 1 to 5 months of age (15/27 [56%]) and

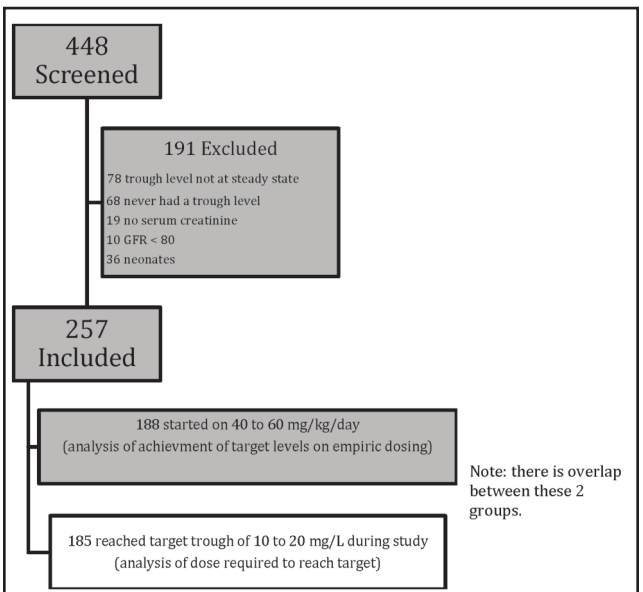

Figure 1. Flow of patients through the study. Among the 191 patients excluded from the analysis, some met more than one exclusion criterion. GFR = glomerular filtration rate (mL min^{-1} 1.73 m^{-2}).

Table 2. Demographic Characteristics

Characteristic	No. (%) of Patients or Median (IQR) (*n* = 257)
Sex, female	127 (49)
Age (yr)	3.47 (1.23–8.62)
Age group	
1–5 mo	34 (13)
6–23 mo	59 (23)
2–12 yr	120 (47)
13–18 yr	44 (17)
Weight (kg)	14.6 (10–27)
Baseline serum creatinine (mg/L)	
1–5 mo	19 (16.25–21)
6–23 mo	18 (15–21.5)
2–12 yr	27 (22–36)
13–18 yr	53.5 (43.75–64)
Vancomycin starting dose (mg/kg daily)	59.46 (47.17–60.19)
Unit of care	
General pediatrics	210 (82)
Pediatric intensive care unit	15 (6)
Oncology	32 (12)

13 to 18 years (17/30 [57%]). The mean total daily dose (± standard deviation [SD]) of vancomycin required to achieve therapeutic trough levels of 10–20 mg/L was 57.8 ± 11.5 mg/kg for patients 1 to 5 months of age, 68.9 ± 15.4 mg/kg for those 6 to 23 months of age, 65.8 ± 13.0 mg/kg for those 2 to 12 years of age, and 55.7 ± 11.8 for those 13 to 18 years of age (Figure 2).

The mean (± SD) magnitude of the increase in total daily dose of vancomycin required to reach the target trough level of 10–20 mg/L was 4.0% ± 19.8% for patients 1 to 5 months of age, 18.1% ± 27.3% for those 6 to 23 months, 19.1% ± 27.5% for those 2 to 12 years, and 8.9% ± 21.2% for those 13 to 18 years (Figure 3). For each age group, the dosing interval that resulted in the greatest proportion of therapeutic trough levels was q6h (Figure 4).

DISCUSSION

Since the IDSA released recommendations[2,3] to target higher therapeutic trough levels for vancomycin (10–20 mg/L), many studies[4-8,14] have tried to determine how many patients actually achieve the new targets with current empiric starting regimens of 40–60 mg/kg daily. Frymoyer and others[6] found that only 37% of patients receiving 60 mg/kg daily achieved the new target levels, whereas Eiland and others[4] found that only 49% of patients who received on average 59 mg/kg daily did so. In the study reported here, similar results were obtained: only 39% of patients with a starting dosage of 40–60 mg/kg daily achieved trough levels of 10–20 mg/L. The low proportion of pediatric patients reaching target trough levels with current empiric starting doses has prompted further studies[4,6-8,14,15] of vancomycin dosing to determine a new empiric starting dose.

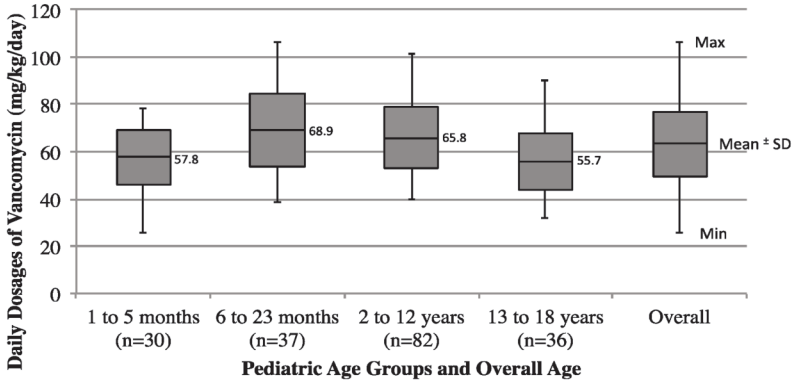

Figure 2. Daily dose of vancomycin required to reach therapeutic trough levels in pediatric age groups. Data are presented as mean ± standard deviation (boxes), with minimum and maximum values (vertical bars). Data represent the 185 patients who achieved a vancomycin trough level of 10–20 mg/mL during their course of therapy.

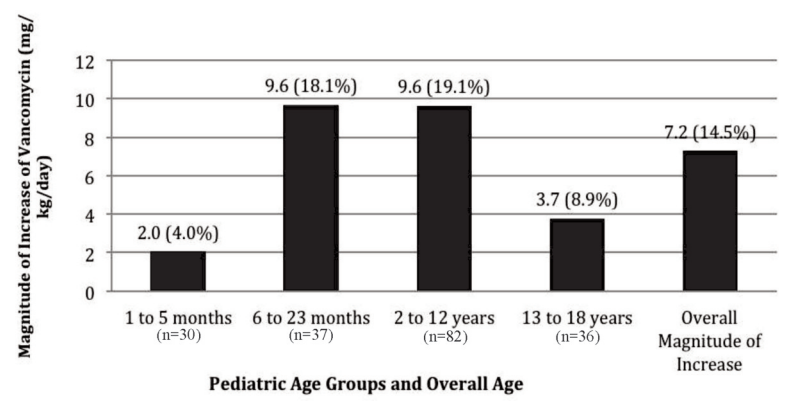

Figure 3. Increase in daily dose of vancomycin, relative to starting dose, required to reach therapeutic trough levels in pediatric age groups. Numeric data are presented as absolute values (mg/kg per day) with percentages (relative to starting dose) in parentheses. Data represent the 185 patients who achieved a vancomycin trough level of 10–20 mg/mL during their course of therapy.

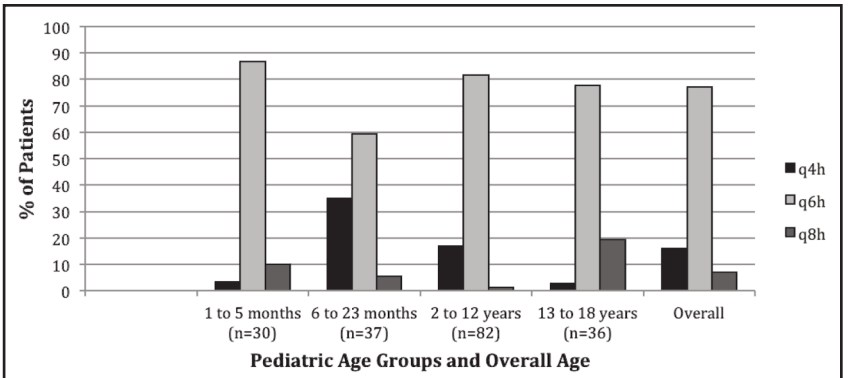

Figure 4. Dosing intervals for vancomycin that resulted in achivement of therapeutic trough levels. Data represent the 185 patients who achieved a vancomycin trough level of 10–20 mg/mL during their course of therapy.

Given the study centre's decision to follow the IDSA guidelines for empiric vancomycin treatment (i.e., not only for proven *S. aureus* infections), the primary purpose of this study was to determine the mean total daily dose of vancomycin required to achieve the higher therapeutic trough concentrations, as well as to determine whether these doses differed for different pediatric age groups. Given that the majority of vancomycin undergoes renal clearance and given rapid maturational changes in renal function during pediatric growth, it is reasonable to consider the age of a pediatric patient when selecting the appropriate dose of vancomycin. To the authors' knowledge, this study is one of the first to examine actual vancomycin dosing and subsequent trough concentrations in various pediatric age groups.

The results of this study suggest that total daily doses of vancomycin required to achieve therapeutic trough levels of 10–20 mg/L are higher than current empiric daily dosing for specific pediatric age groups; however, the required doses might not be as high as some of the current literature suggests. In this study, patients 6 to 23 months of age required the highest mean daily dose of vancomycin to reach target trough levels of 10–20 mg/L (68.9 mg/kg), and those 2 to 12 years required a slightly lower daily dose (65.8 mg/kg); for both age groups, the required total daily doses were greater than current empiric dosing (40–60 mg/kg daily). These 2 groups also required the greatest proportional increase from starting daily dose to the dose required to reach target (18.1% and 19.1%, respectively). Patients 1 to 5 months of age and 13 to 18 years of age required mean daily doses of vancomycin that were within (though at the upper end of) the current empiric dosing range: 57.8 and 55.7 mg/kg, respectively.

Despite similar median ages for the respective study samples, the observed daily doses required to reach therapeutic trough levels in the current study were appreciably lower than those identified by Eiland and others,[4] who suggested 70–85 mg/kg daily for target trough levels of 10–15 mg/L. One possible explanation for this substantial difference might be the timing of when samples were drawn for determination of trough levels. In the current study, the samples were drawn within 30 min before administration of the fourth or a subsequent dose; Eiland and others[4] did not report the timing of samples in relation to a particular dose. Determining vancomycin trough levels before steady state has been reached can result in trough levels that appear lower than the true (steady-state) value and may result in unnecessary dose escalation. Another explanation for the differences in suggested daily doses of vancomycin between studies could be differences in the patient populations. The majority of the 257 patients in the current study were from general pediatric floors, with only 15 (6%) from the pediatric intensive care unit (PICU) and 31 (12%) from the pediatric oncology unit. In contrast, 54% of the patients in the study by Eiland and others[4] were from the PICU, with the rest being from general pediatric floors. Additional variables affecting critically ill patients in the PICU may not be representative of pharmacokinetics in general pediatrics.[6,16]

The findings reported here support the hypothesis that different pediatric age groups require different weight-based daily doses of vancomycin. In this study, patients 6 to 23 months and 2 to 12 years of age required the highest daily doses of vancomycin. The half-life of vancomycin is shorter in these 2 age groups than in pediatric patients younger than 6 months or older than 12 years[5,11-13]; therefore, as a result of increased vancomycin clearance, it was expected that these patients would require a higher daily dose of vancomycin than the other pediatric age groups. With rapid maturational changes in pediatric renal function, it is difficult to suggest a single dosing range for all pediatric patients from 1 month to 18 years of age.

In addition to increasing the daily dose of a medication, increasing the frequency of administration is another way to increase trough levels. Traditionally in pediatrics, the daily dose of vancomycin has been divided for administration q6h. In this

study, we found that q6h dosing resulted in the greatest proportion of therapeutic troughs for all age groups. Among patients 6 to 23 months and 2 to 12 years of age, substantial proportions had q4h dosing, which reflects the shorter half-life of vancomycin in these age groups.

A variety of pharmacodynamic monitoring parameters have been proposed for vancomycin; however, a ratio of area under the curve to minimum inhibitory concentration (AUC/MIC) of 400 or greater has been advocated as the primary predictive efficacy parameter.[2] Many studies[7,14,17] have used AUC/MIC greater than or equal to 400 as a target for pediatric patients; however, in parallel with target serum trough levels, AUC/MIC has not been studied or verified in pediatric populations to correlate particular ratios with clinical outcomes. In their retrospective cohort study, Le and others[14] examined achievement of AUC/MIC in pediatric patients and highlighted that clinicians may be achieving target AUC/MIC of 400 or greater, despite apparently subtherapeutic trough levels. They recommended dosing regimens of 70 mg/kg daily for patients at least 3 months to under 2 years of age and 60 mg/kg daily for those 2 years and older to achieve an AUC/MIC value of about 400, which in their study was correlated with troughs of 8–9 mg/L.[14] The analysis reported here, with trough targets of 10–20 mg/L, suggested similar regimens. Although debate over AUC/MIC versus trough levels as the most appropriate therapeutic monitoring parameter is ongoing, choosing an appropriate starting dose is the immediate goal for improving patient care. Given the data presented here and the data of Le and others,[14] starting doses of 60–70 mg/kg daily are suggested for pediatric patients, with patients 1 to 5 months and 13 to 18 years of age starting at the lower end (60 mg/kg daily) and those 6 months to 12 years of age starting at the higher end (70 mg/kg daily) to better achieve target trough levels and/or AUC/MIC values similar to those reported by Le and others.[14] A prospective study to evaluate the safety and efficacy of these proposed starting doses is needed.

Questions remain as to whether the risk of nephrotoxicity is increased when higher trough concentrations are targeted, and we certainly cannot suggest broad changes in vancomycin dosing without examination of the toxicity of these doses. The currently available literature[18,19] does suggest that higher trough values are associated with an increased risk of nephrotoxicity. For example, McKamy and others[19] found that trough levels of 15 mg/L or higher in pediatric patients were associated with a 3-fold increase in the risk of nephrotoxicity; however, factors such as concomitant nephrotoxins and severity of illness also played a role. Non–vancomycin-precipitated renal dysfunction may lead to elevated vancomycin troughs and may be misinterpreted as vancomycin-induced nephrotoxicity. Twenty-five (10%) of the 257 patients in the current study database experienced nephrotoxicity, defined as an increase in serum creatinine greater than 30% from baseline. Of these 25 patients, 19 (76%) were also taking one or more concomitant nephrotoxic agents, such as aminoglycosides, amphotericin B, nonsteroidal anti-inflammatory drugs, or furosemide. Here, nephrotoxicity was considered as a post hoc outcome only, and the results should therefore be interpreted with caution. Nonetheless, they are similar to results reported elsewhere[19,20] in suggesting that nephrotoxicity may be less common than perceived and that other risk factors (such as concomitant nephrotoxins, elevated baseline renal dysfunction, severity of illness, and prolonged course of therapy) may all contribute to nephrotoxicity.

This study was limited by its sample size, especially given that the study attempted to examine dosing in small age-based subgroups. Larger studies are required before the dosing suggestions made here can be broadly applied; however, these data provide a starting point for future studies and may reassure practitioners that use of daily doses at the higher end of the empiric dosing range is unlikely to result in exceedingly high trough levels of vancomycin. In addition, the analysis was not stratified according to patients' units of admission, as it was thought that this approach would allow the results to be applied more generally. However, dosing in critically ill patients should be specifically examined, as it may differ from dosing in non–critically ill patients. Finally, the lack of clinical correlation of vancomycin levels with admission diagnosis and target levels is a major limitation common to studies in this area, including this one. However, such studies are necessary, as support for the efficacy and safety of higher vancomycin targets will provide the basis for all future vancomycin dosing studies.

CONCLUSIONS

Given poor achievement of target serum trough levels of 10–20 mg/L for vancomycin at current empiric starting doses, previous studies have suggested that empiric doses should be increased. The results presented here corroborate this conclusion, in that only 39% of patients achieved target levels with initial doses. In addition, a total daily dosing regimen of 60–70 mg/kg, administered at 6-h intervals, was required to reach target trough levels in the majority of pediatric patients. Specifically, for patients 1 to 5 months and 13 to 18 years of age, dosing at the lower end of this range (60 mg/kg daily) would be appropriate to better achieve target trough levels, and for patients 6 months to 12 years of age, dosing at the higher end of the range (70 mg/kg daily) would be appropriate. Further prospective studies are needed to confirm the efficacy and safety of these doses. Finally, targeting higher trough levels may increase the incidence of nephrotoxicity,[18,19] which highlights the importance of close monitoring of renal function in addition to assessment of patients' risk factors for nephrotoxicity throughout vancomycin therapy.

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