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The Effect of Age and Weight on Vancomycin Serum Trough Concentrations in Pediatric Patients

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Abstract

Background—Vancomycin treatment failure has been associated with low serum vancomycin trough concentrations, prompting recommendations to increase the daily doses in adults and children. Despite more aggressive vancomycin dosing, there continues to be significant variability in vancomycin trough concentrations in pediatric patients.

Methods—To determine if vancomycin trough concentrations in pediatric patients differ by age and weight, we reviewed records of hospitalized patients who received vancomycin between 2008 and 2012. Patients were divided into groups that received vancomycin 40 mg/kg/day (2008 to 2009) or 60 mg/kg/day (2010 to 2012). Vancomycin trough concentrations were compared between groups and within the 60-mg/kg/day group, stratified by patient age and weight.

Results—After increasing the vancomycin dose from 40 mg/kg/day to 60 mg/kg/day, initial trough concentrations increased significantly in patients younger than 2 and greater than 6 years of age, but not in patients between the ages of 2 and 5 years. In the 60-mg/kg/day group, only 16.7% of patients between 2 and 5 years of age had initial trough concentrations in the therapeutic range (10 mcg/mL to 20 mcg/mL). Initial trough concentrations were therapeutic in a greater proportion of patients ages 6 years to 12 years (38.7%) and 13 years to 18 years (63.0%). Patients between the ages of 13 and 18 had the highest proportion of supratherapeutic initial vancomycin trough concentrations (14.8%). Patients weighing > 50 kg had significantly higher trough concentrations than patients < 50 kg (17.1 mcg/mL vs. 9.3 mcg/mL; $p < 0.001$).

Conclusion—Although increasing the vancomycin dose from 40 mg/kg/day to 60 mg/kg/day led to a significant increase in vancomycin trough concentrations, a large proportion of patients receiving 60 mg/kg/day of vancomycin had trough concentrations outside of the therapeutic range. Specifically, patients younger than 6 years tend to have low trough concentrations, while adolescents and children > 50 kg are more likely to have elevated trough concentrations. Vancomycin dosing strategies in pediatric patients should consider age and weight as well as renal function and indication.

Keywords

vancomycin; pediatric; weight; age

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Introduction

Vancomycin is the gold standard therapy for invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections.¹ However, vancomycin treatment failures have been reported for MRSA isolates with higher vancomycin minimum inhibitory concentrations (MIC)^{2–6} and in patients with lower serum vancomycin trough concentrations.⁴ These observations, combined with the poor penetration of vancomycin into bone, lung, and the central nervous system (CNS) prompted an increase in the recommended vancomycin dosing for adults⁷ and children.^{1,8}

Vancomycin trough concentrations guide dosing¹ and correlate with the area under the curve (AUC) to MIC ratio (AUC/MIC), which is the pharmacodynamic parameter that best predicts vancomycin efficacy. For an MRSA isolate with a vancomycin MIC = 1 mcg/mL in an adult patient, vancomycin trough concentrations of 15 mcg/mL to 20 mcg/mL predict an AUC/MIC > 400, which is the value associated with optimal outcomes in invasive MRSA infections.^{9,10} A recent study reported that lower trough concentrations might be sufficient in pediatric patients to achieve the AUC/MIC threshold of > 400.¹¹ Data from several studies suggest that a vancomycin daily dose of 60 mg/kg^{12,13} or higher^{11,14} is needed to achieve an AUC/MIC > 400 in pediatric patients. However, there are no data correlating vancomycin efficacy with trough concentrations or AUC/MIC in pediatric patients.

Current clinical practice extrapolates pediatric vancomycin dosing and target trough concentrations from adult data. Further, weight-, obesity- and age-associated differences in vancomycin pharmacodynamics in the pediatric population are not well characterized. No pediatric studies have evaluated associations between vancomycin dosing, trough concentrations, and actual body weight. Two studies have evaluated vancomycin trough concentrations in overweight pediatric patients (defined by BMI percentiles), but were limited by a small sample size¹⁵ and the use of every 8 hour dosing in the majority of patients.^{15,16} Of the few studies that have evaluated age-associated differences in vancomycin concentrations, one found no association with age¹⁷ and another reported that patients younger than 6 years of age had consistently lower vancomycin trough concentrations than older children receiving the same daily dose and dosing interval of vancomycin.¹⁸

Vancomycin dosing was increased from 40 mg/kg/day (10 mg/kg/dose every 6 hours) to 60 mg/kg/day (15 mg/kg/dose every 6 hours) at our children's hospital in January, 2010, in keeping with current guidelines from the Infectious Disease Society of America.¹ In our clinical experience, vancomycin trough concentrations vary widely in the pediatric population despite this new dosing regimen. To better understand pediatric age- and weight-associated differences in vancomycin pharmacokinetics, we reviewed records for all hospitalized patients receiving vancomycin at our institution before and after implementation of the dosing change.

Methods

We conducted a retrospective review of vancomycin use at the Mayo Clinic Children's Hospital, a tertiary care referral center in Rochester, MN, between January 1, 2008 and February 1, 2012. Patients were divided into groups that received vancomycin 40 mg/kg/day every 6 hours (10 mg/kg/dose every 6 hours) between January 1, 2008 and December 31, 2009 and 60 mg/kg/day every 6 hours (15 mg/kg/dose every 6 hours) between February 1, 2010 and February 1, 2012. The institutional vancomycin dosing change was implemented in January, 2010 by modifying the standard vancomycin order for children in the electronic ordering system from 10 mg/kg/dose to 15 mg/kg/dose every 6 hours. Because the dosing

change was implemented in January, 2010, data from that month were not included. This study was approved by the Mayo Clinic's Institutional Review Board.

Pharmacy records were used to identify hospitalized patients who received vancomycin during the study periods. Patients were included if they were between the ages of 1 month and 18 years, received vancomycin as an inpatient at our institution during the study period, and had at least one vancomycin trough concentration drawn no more than 60 minutes before the fourth dose or any subsequent dose. The daily dose, interval, and trough vancomycin concentrations (drawn at the beginning and throughout a vancomycin treatment course), concurrent nephrotoxic medications, comorbidities, age, and weight were obtained via chart review. If patients received more than one course of vancomycin therapy during either study period, only the first course was included. For patients who received vancomycin during both the 40 mg/kg/day and the 60 mg/kg/day periods, the first course in each period was included. All patients were followed until the end of vancomycin administration as inpatients. Patients were excluded if their initial trough concentrations were drawn at inappropriate times, if they received greater than 10% above or below the recommended dose, if they did not receive vancomycin every 6 hours, if they had preexisting renal disease, or if they were in the cardiac intensive care unit, because cardiac surgery or use of extracorporeal membrane oxygenation (ECMO) can affect renal perfusion. Vancomycin trough concentrations were ordered as part of routine care by treating physicians and were determined by the clinical laboratory. The lowest reportable vancomycin concentration at our laboratory is 5 mcg/mL. The vancomycin dose was adjusted by treating physicians based on trough concentrations. A goal or therapeutic vancomycin trough concentration was defined as 10 mcg/mL to 20 mcg/mL. Trough concentrations < 5 mcg/mL were considered undetectable, whereas trough concentrations > 20 mcg/mL were considered supratherapeutic.¹

We reviewed patient records to identify adverse events associated with vancomycin, including the development of red man syndrome and nephrotoxicity. Patients were considered to have red man syndrome if this was documented in their medical record or if vancomycin was co-administered with diphenhydramine and infused for 120 minutes. Nephrotoxicity was defined as a 2-fold rise in baseline serum creatinine concentrations that was attributed to vancomycin by treating physicians.

We have observed that young children clear vancomycin rapidly. Gordon and colleagues also reported that children younger than 6 years of age had different vancomycin trough concentrations than older children.¹⁸ Based on these observations, we divided patients into 4 age groups: 1 to 23 months, 2 to 5 years, 6 to 12 years, and 13 to 18 years. The body mass index (BMI) percentile of children older than 2 years of age was calculated using the Center for Disease Control BMI calculator for children.¹⁹ Patients with a BMI > 85th percentile were considered overweight. Patients under the age of 2 were not included in the body weight analysis because BMI percentile categories are not established in infants and young children.¹⁹ Patients were additionally divided into weight categories of 25 kg, 25 kg to 50 kg, and > 50 kg, because we observed that patients receiving vancomycin 60 mg/kg/day who weighed > 50 kg had significantly different trough concentrations than all other pediatric patients.

Differences in categorical variables were analyzed using chi-square or Fisher's exact tests as appropriate, and differences in continuous variables were analyzed with student's t-test. A p-value < 0.05 was considered statistically significant.

Results

Patient Population

A total of 501 courses of vancomycin were prescribed to 397 patients during the study period. After exclusion of repeat courses and patients who did not meet the study criteria, 78 patients were included in the 40 mg/kg/day group, and 144 patients were included in the 60 mg/kg/day group (Figure 1). Demographic and clinical characteristics of the study patients are shown in Table 1. The groups were well matched for age, weight, gender, baseline creatinine concentrations, indications, or underlying disorders (Table 1). There were fewer patients with central nervous system (CNS) and shunt infections in the 40 mg/kg group because higher doses of vancomycin were generally used for these indications.

Effect of Increased Vancomycin Dose

Patients who received 60 mg/kg/day of vancomycin had higher mean initial vancomycin trough concentrations than patients treated with vancomycin 40 mg/kg/day (10.7 mc/mL vs. 7.4 mcg/mL, $p<0.001$) (Table 2). These differences were statistically significant regardless of weight category or BMI, except in children 2 to 5 years of age (Table 2). Fewer patients in the 40 mg/kg/day group than in the 60 mg/kg/day group had undetectable initial vancomycin trough concentrations (13.2% vs. 29.5% vs; $p<0.001$) (Figure 2). At any point during a vancomycin course, more patients in the 60 mg/kg/day group than in the 40 mg/kg/day group had therapeutic trough concentrations (47.2% vs. 23.1%; $p<0.001$) and supratherapeutic trough concentrations (8.3% vs. 0%; $p=0.001$).

The 40 mg/kg/day and 60 mg/kg/day groups had similar rates of red man syndrome (17/78 [21.8%] vs. 40/144 [27.8%]; $p=0.33$) and nephrotoxicity (2/78 [2.6%] vs. 2/144 [1.4%]; $p=0.54$). Two patients with renal complications had concomitant administration of nephrotoxic agents, amphotericin B ($n=1$) and cyclosporine ($n=1$). There were no significant differences in mean initial vancomycin trough concentrations or in the proportion of patients with therapeutic trough concentrations (measured initially or at any point during therapy) for patients with malignancies compared with other comorbidities for either dose group.

Effect of Body Weight on Vancomycin Trough Concentrations

We divided patients receiving vancomycin 60 mg/kg/day into groups divided by 10-kg weight increments and observed that patients weighing more than 50 kg had significantly different trough concentrations than all other patients. Those patients with body weight > 50 kg had higher mean initial trough concentrations than patients in the < 25-kg group (17.1 mcg/mL vs. 8.7 mcg/mL, $p<0.001$) and 25 kg to 50 kg group (17.1 mcg/mL vs. 10.6 mcg/mL, $p<0.001$). Although trough concentrations increased with age, the relationship between trough concentration and weight was not linear. The odds ratio (OR) for achieving goal initial trough vancomycin concentrations for patients weighing > 50 kg was 11-fold greater than for patients weighing < 25 kg (OR 11.22, CI 3.91 – 37.73, $p<0.001$). Similarly, patients in the 25-kg to 50-kg group were twice as likely to achieve goal initial trough concentrations than patients in the < 25 kg group (OR 2.36, CI 1.02 – 5.43, $p=0.04$).

The distribution of initial vancomycin trough concentrations differed significantly between the weight categories (Figure 3A). The proportion of patients with initially undetectable trough concentrations was lowest in the > 50-kg group (0%), higher in the 25-kg to 50-kg group (3/36, 8.3%), and highest in the < 25-kg group (16/70, 18.6%). The proportion of patients with therapeutic trough concentrations at any time during the vancomycin course was highest in children > 50 kg and decreased with weight category (77.2% in > 50 kg, 55.6% in 25 kg to 50 kg, and 36.1% in < 25 kg; $p=0.001$). Similarly, the proportion of patients with supratherapeutic trough concentrations at any time during the vancomycin

course was highest in children > 50 kg (22.7%) and decreased with weight category (11.1% in 25 kg to 50 kg, 3.5% in < 25 kg; $p=0.02$).

There were no differences in the rates of red man syndrome ($p=0.15$) or nephrotoxicity ($p=0.06$) between weight categories. When stratified into weight categories of < 50 kg or > 50 kg, no differences were observed between overweight and normal weight children in terms of initial trough concentrations, toxicity, or the proportion of patients attaining goal trough concentrations initially or during the course of therapy.

Effect of Age on Vancomycin Trough Concentrations

There were significant age-related differences in vancomycin trough concentrations for patients in the 60 mg/kg/day group. The proportion of patients with undetectable initial trough concentrations was greatest for the 2 to 5 years age group (22.2%) and lowest for patients ages 1 to 23 months (16.2%) and 6 to 12 years (11.4%). No patients in the 13 to 18 year age group had undetectable initial vancomycin trough concentrations (Figure 3B). Goal initial trough concentrations were achieved by 32.4% of patients in the 1 to 23 month group, 16.7% in the 2 to 5 year group, 38.6% in the 6 to 12 year group, and 63.0% in the 13 to 18 year group (Figure 3B). The highest mean initial trough concentrations occurred in patients in the 13 to 18 year group (15.3 mcg/mL) ($p<0.001$) (Table 2). Compared to patients in the 1 to 23 month group, the odds of achieving goal initial trough concentrations were higher for patients in the 13 to 18 year group (OR 3.54, CI 1.28 – 10.37, $p=0.01$) and 6 to 12 year group (OR 1.31, CI 0.53 – 3.33, $p=0.56$) and lower in the 2 to 5 year group (OR 0.42, CI 0.13 – 1.23, $p=0.11$). Supratherapeutic trough concentrations occurred more often in patients 6 years than in younger patients (10/71 [14.1%] vs. 2/73 [2.7%]; $p=0.01$). Patients in the 13 to 18 year group had the highest proportion of supratherapeutic concentrations (18.5%) followed by patients between the ages of 6 and 12 years (11.4%).

Discussion

We report one of the first studies to evaluate associations between vancomycin trough concentrations, age, and weight in a pediatric population. There is wide variability in vancomycin trough concentrations among patients receiving the same mg/kg dose and dose interval of vancomycin. Increasing the vancomycin dose from 40 mg/kg/day to 60 mg/kg/day increased the frequency of therapeutic vancomycin trough concentrations in patients older than 6 years of age. In contrast, increasing the vancomycin daily dose did not significantly alter vancomycin trough concentrations in patients between the ages of 2 and 5 years, and a substantial proportion of patients in this age group continue to have subtherapeutic vancomycin concentrations. Patients weighing more than 50 kg have higher (and sometimes supratherapeutic) vancomycin trough concentrations compared to children weighing < 50 kg.

Increasing the vancomycin dose from 40 mg/kg/day to 60 mg/kg/day resulted in a greater number of goal (10 – 20 mcg/mL) vancomycin trough concentrations in patients younger than 2 and older than 6 years, but not in patients between the ages of 2 years and 5 years. To our knowledge, these findings have not been previously reported. Several studies have evaluated the effects of increasing the daily dose of vancomycin in pediatric patients, but few have stratified the data by patient age^{12,20–22}. Only one other study has reported that children younger than 6 have lower trough concentrations than older children receiving the same dose and interval of vancomycin.¹⁸ Frymoyer and colleagues observed that a daily vancomycin dose of 60 mg/kg substantially increased the likelihood of achieving therapeutic drug concentrations compared to 40 mg/kg/day.¹³ Others found that despite receipt of higher daily doses of vancomycin, only 37% to 49% of pediatric patients achieved the recommended goal trough concentrations of 10 mcg/mL to 20 mcg/mL.^{20–22} The

mechanism for the increased vancomycin clearance in patients between the ages of 2 and 5 years is not clear and deserves further study. Importantly, like others,²¹ we did not see a difference in the rate of nephrotoxicity or red man syndrome in patients receiving vancomycin 40 mg/kg/day vs. 60 mg/kg/day. However, we did observe an increase in the number of patients with supratherapeutic trough concentrations in the 60-mg/kg/day group, which has not been previously reported.²² Others have described increased vancomycin clearance in pediatric patients with malignancies.^{23,24} In our study, vancomycin trough concentrations did not differ between patients with and without malignancies in either the 40-mg/kg/day or 60-mg/kg/day groups. Reasons for this discrepancy also are not clear and warrant additional study.

Another important finding from our study is that pediatric patients weighing more than 50 kg had higher mean trough concentrations and were more likely to have supratherapeutic concentrations compared to patients with lower body weights. We are not aware of other studies comparing vancomycin trough concentrations in pediatric patients of different weight categories. Trough concentrations did not differ by BMI when patients were first stratified into groups of ≤ 50 kg and > 50 kg, suggesting that actual body weight, rather than BMI is related to vancomycin trough concentrations in the pediatric population. However, our study included relatively few overweight patients and was likely not powered to detect obesity-associated differences in vancomycin clearance. It is possible that in children, especially adolescents, obesity affects vancomycin volume of distribution, vancomycin protein binding,^{25–27} and renal clearance,^{28,29} as is observed in adults. With almost one-third of children in the United States being overweight,³⁰ studies evaluating obesity-associated differences in the pharmacokinetics and pharmacodynamics of vancomycin in children are needed.

Our analysis suggests that both age and weight could be important predictors of vancomycin clearance in children. However, these variables are related and their relative importance should be further investigated in pharmacokinetic and pharmacodynamic studies. We disagree with some authors who have recommended daily doses of 70 mg/kg/day or greater in all pediatric patients between the ages of 1 month and 18 years with normal renal function.²⁰ Rather, our data suggest that vancomycin dosing strategies in pediatric patients should consider age and/or weight, similar to dosing strategies for other antimicrobials, including ertapenem³¹ and voriconazole.³² A recent study by Le and associates, suggested a daily vancomycin dose of 60 mg/kg/day for patients 12 years of age and older and 70 mg/kg/day for children younger than 12.¹¹ According to our results, a daily vancomycin dose of 60 mg/kg/day appears appropriate for pediatric patients older than 6 years, but higher starting doses should be considered in patients between the ages of 2 and 5 years if they have normal renal function, invasive MRSA infections (when therapeutic concentrations are needed promptly), or an MRSA isolate with a vancomycin MIC ≥ 2 mg/L. Conversely, in adolescent patients or those weighing > 50 kg, lower vancomycin daily doses or longer dosing intervals, as in adult dosing regimens, might be warranted, because nearly 20% of such patients in our cohort had vancomycin trough concentrations > 20 mcg/mL. Current treatment guidelines that recommend a vancomycin dose of 15 mg/kg every 6 hours in all pediatric patients, regardless of age or weight¹ may need to be modified as we learn more about vancomycin pharmacokinetics in children. Goal trough concentrations of less than 15 mcg/mL to 20 mcg/mL might be adequate for pediatric patients with MRSA isolates that have low vancomycin MICs.¹¹

Our study has several limitations, including the single-center, retrospective design involving a heterogeneous population of pediatric patients and a limited number of obese and overweight patients. Also, the sample size was relatively small when we stratified the groups into different weight and age categories. We did not measure vancomycin peak

concentrations and did not calculate the AUC/MIC. We were unable to correlate vancomycin trough concentrations with clinical efficacy because we did not collect clinical outcome data and had few patients with invasive MRSA infections. Despite these limitations, our findings are among the first to evaluate vancomycin dosing and trough concentrations in pediatric patients of different weight and age groups and has important clinical implications.

In conclusion, increasing the vancomycin daily dose from 40 mg/kg to 60 mg/kg led to a significant increase in vancomycin trough concentrations overall without an increase in toxicity. However, when receiving higher daily doses of vancomycin, 75% of children younger than 6 years of age have subtherapeutic trough concentrations, while nearly 20% of adolescents and children > 50 kg have supratherapeutic trough concentrations. Additional studies of clinical outcomes and vancomycin pharmacokinetic and pharmacodynamic parameters in pediatric patients of different age and weight categories are needed to define therapeutic trough concentrations and modify current vancomycin dosing recommendations.

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References

1. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis. 2011; 52:e18–55. [PubMed: 21208910]
2. Lodise TP, Graves J, Evans A, et al. Relationship between vancomycin MIC and failure among patients with methicillin-resistant *Staphylococcus aureus* bacteremia treated with vancomycin. Antimicrob Agents Chemother. 2008; 52:3315–20. [PubMed: 18591266]
3. Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering RC Jr, Eliopoulos GM. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. J Clin Microbiol. 2004; 42:2398–402. [PubMed: 15184410]
4. Kullar R, Davis SL, Levine DP, Rybak MJ. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: support for consensus guidelines suggested targets. Clin Infect Dis. 2011; 52:975–81. [PubMed: 21460309]
5. Mahajan SN, Shah JN, Hachem R, et al. Characteristics and Outcomes of Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infections in Patients with Cancer Treated with Vancomycin: 9-Year Experience at a Comprehensive Cancer Center. Oncologist. 2012
6. van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in *Staphylococcus aureus* infections: a systematic review and meta-analysis. Clin Infect Dis. 2012; 54:755–71. [PubMed: 22302374]
7. Rybak MJ, Lomaestro BM, Rotschafer JC, et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis. 2009; 49:325–7. [PubMed: 19569969]
8. Jimenez-Truque N, Thomsen I, Saye E, Creech CB. Should higher vancomycin trough levels be targeted for invasive community-acquired methicillin-resistant *Staphylococcus aureus* infections in children? Pediatr Infect Dis J. 2010; 29:368–70. [PubMed: 19935448]
9. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious

- Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm.* 2009; 66:82–98. [PubMed: 19106348]
10. Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. Pharmacodynamics of vancomycin and other antimicrobials in patients with *Staphylococcus aureus* lower respiratory tract infections. *Clin Pharmacokinet.* 2004; 43:925–42. [PubMed: 15509186]
 11. Le J, Bradley JS, Murray W, et al. Improved Vancomycin Dosing in Children Using Area-Under-the-Curve Exposure. *Pediatr Infect Dis J.* 2013
 12. Frymoyer A, Hersh AL, Benet LZ, Guglielmo BJ. Current recommended dosing of vancomycin for children with invasive methicillin-resistant *Staphylococcus aureus* infections is inadequate. *Pediatr Infect Dis J.* 2009; 28:398–402. [PubMed: 19295465]
 13. Frymoyer A, Hersh AL, Coralic Z, Benet LZ, Joseph Guglielmo B. Prediction of vancomycin pharmacodynamics in children with invasive methicillin-resistant *Staphylococcus aureus* infections: a Monte Carlo simulation. *Clin Ther.* 2010; 32:534–42. [PubMed: 20399990]
 14. Cardoso Bourguignon da Silva D, Toribio Finoti Seixas G, Ribeiro de Araujo O, Arduini RG, de Moraes Costa Carlesse FA, Sergio Petrilli A. Vancomycin serum concentrations in pediatric oncologic/hematologic intensive care patients. *Braz J Infect Dis.* 2012; 16:361–5. [PubMed: 22846125]
 15. Moffett BS, Kim S, Edwards MS. Vancomycin dosing in obese pediatric patients. *Clin Pediatr (Phila).* 2011; 50:442–6. [PubMed: 21282257]
 16. Miller M, Miller JL, Hagemann TM, Harrison D, Chavez-Bueno S, Johnson PN. Vancomycin dosage in overweight and obese children. *Am J Health Syst Pharm.* 2011; 68:2062–8. [PubMed: 22011985]
 17. Broome L, So TY. An evaluation of initial vancomycin dosing in infants, children, and adolescents. *Int J Pediatr.* 2011; 2011:470364. [PubMed: 22046192]
 18. Gordon CL, Thompson C, Carapetis JR, Turnidge J, Kilburn C, Currie BJ. Trough Concentrations of Vancomycin: Adult Therapeutic Targets are not Appropriate for Children. *Pediatr Infect Dis J.* 2012
 19. [Accessed 08/08/2012, 2012] BMI Calculator for Child and Teen. 2012. at <http://apps.nccd.cdc.gov/dnpabmi/Calculator.aspx?CalculatorType=Metric>
 20. Eiland LS, English TM, Eiland EH 3rd. Assessment of vancomycin dosing and subsequent serum concentrations in pediatric patients. *Ann Pharmacother.* 2011; 45:582–9. [PubMed: 21521865]
 21. Kim DI, Im MS, Choi JH, Lee J, Choi EH, Lee HJ. Therapeutic monitoring of vancomycin according to initial dosing regimen in pediatric patients. *Korean J Pediatr.* 2010; 53:1000–5. [PubMed: 21253314]
 22. Frymoyer A, Guglielmo BJ, Wilson SD, Scarpace SB, Benet LZ, Hersh AL. Impact of a hospitalwide increase in empiric pediatric vancomycin dosing on initial trough concentrations. *Pharmacotherapy.* 2011; 31:871–6. [PubMed: 21923588]
 23. Chang D. Influence of malignancy on the pharmacokinetics of vancomycin in infants and children. *Pediatr Infect Dis J.* 1995; 14:667–73. [PubMed: 8532423]
 24. Chang D, Liem L, Malogolowkin M. A prospective study of vancomycin pharmacokinetics and dosage requirements in pediatric cancer patients. *Pediatr Infect Dis J.* 1994; 13:969–74. [PubMed: 7845750]
 25. Vance-Bryan K, Guay DR, Gilliland SS, Rodvold KA, Rotschafer JC. Effect of obesity on vancomycin pharmacokinetic parameters as determined by using a Bayesian forecasting technique. *Antimicrob Agents Chemother.* 1993; 37:436–40. [PubMed: 8460912]
 26. Grace E. Altered vancomycin pharmacokinetics in obese and morbidly obese patients: what we have learned over the past 30 years. *J Antimicrob Chemother.* 2012; 67:1305–10. [PubMed: 22382471]
 27. Ducharme MP, Slaughter RL, Edwards DJ. Vancomycin pharmacokinetics in a patient population: effect of age, gender, and body weight. *Ther Drug Monit.* 1994; 16:513–8. [PubMed: 7846752]
 28. Bauer LA, Black DJ, Lill JS. Vancomycin dosing in morbidly obese patients. *Eur J Clin Pharmacol.* 1998; 54:621–5. [PubMed: 9860149]

29. Blouin RA, Bauer LA, Miller DD, Record KE, Griffen WO Jr. Vancomycin pharmacokinetics in normal and morbidly obese subjects. *Antimicrob Agents Chemother.* 1982; 21:575–80. [PubMed: 7081978]
30. Ogden CL, Carroll MD, Curtin LR, Lamb MM, Flegal KM. Prevalence of high body mass index in US children and adolescents, 2007–2008. *JAMA.* 2010; 303:242–9. [PubMed: 20071470]
31. DailyMed. U.S. National Library of Medicine, National Institutes of Health, Health and Human Services; at <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=449c9a41-d61e-49fd-b5e3-d76f74b92acf#nlm34068m>.) [Accessed 11/19, 2012]
32. Friberg LE, Ravva P, Karlsson MO, Liu P. Integrated population pharmacokinetic analysis of voriconazole in children, adolescents, and adults. *Antimicrob Agents Chemother.* 2012; 56:3032–42. [PubMed: 22430956]

Figure 1.

Inclusion of children who received vancomycin and had vancomycin trough monitoring at the Mayo Clinic Children's Hospital. Vancomycin daily dose was 40 mg/kg (January 2008 to December 2009) or 60mg/kg (February 2011 to February 2012).

Figure 2.

Distribution of initial vancomycin serum trough concentrations for patients in the 40 mg/kg/day and 60 mg/kg/day groups. The numbers in brackets above the columns reflect the total number of patients.

*p-value for comparison of overall distribution of trough concentrations between the 40 mg/kg/day and 60 mg/kg/day groups.

Figure 3.

Figure 3A and 3B. Weight- (A) and age- (B) associated differences in initial vancomycin serum trough concentrations among children receiving vancomycin at 60 mg/kg/day. The number in brackets above the columns reflects the total number of patients. *p-values for comparison of overall distribution of trough concentrations between groups.

Table 1

Demographic and clinical characteristics of pediatric patients receiving vancomycin at the Mayo Clinic Children's Hospital from January 2008 to February 2012.

	40 mg/kg/d n=78	60 mg/kg/d n=144	p-value ^a
Male gender, no. (%)	48 (61.5)	77 (53.5)	0.25
Mean age, years (range 1 month – 18 years)	5.6	6.8	0.12
Age group, no. (%)			0.16
1 – 23 months	26 (33.3)	37 (25.7)	
2 – 5 years	17 (21.8)	36 (25.0)	
6 – 12 years	28 (35.9)	44 (30.6)	
13 – 18 years	7 (9.0)	27 (18.7)	
Mean weight, kg +/- SD	22.9 +/- 17.1	27.1 +/- 22.0	0.15
Weight category, no. (%)			0.32
25 kg	53 (67.9)	86 (59.7)	
25 – 50 kg	18 (23.1)	36 (25.0)	
> 50 kg	7 (9.0)	22 (15.3)	
no. (%) overweight ^b	13 (30.2)	24 (25.8)	0.59
Mean baseline Creatinine, mg/dl +/- SD	0.3 +/- 0.1	0.4 +/- 0.2	0.44
Indication for vancomycin, no. (%)			0.07
Fever and immunosuppression ^c	15 (19.2)	33 (22.9)	
Respiratory infection	12 (15.4)	23 (16.0)	
SSTI ^d	17 (21.8)	16 (11.1)	
Sepsis	9 (11.5)	11 (7.6)	
Orthopedic infection	7 (9.0)	10 (6.9)	
CNS ^e infection	1 (1.3)	10 (6.9)	
VP ^f shunt infection	1 (1.3)	13 (9.0)	
Surgical prophylaxis	3 (3.8)	7 (4.9)	
Empiric administration	5 (6.4)	8 (5.6)	
Surgical site infection	2 (2.6)	7 (4.9)	
Other	6 (7.7)	6 (4.2)	
Underlying condition, no. (%)			0.09
None	28 (35.9)	32 (22.2)	
Cancer	21 (26.9)	47 (32.6)	
Solid Organ Transplant	4 (5.1)	2 (1.4)	
Cystic fibrosis (CF)	2 (2.6)	4 (2.8)	
Neurologic	6 (7.7)	29 (20.1)	
Cardiac	3 (3.8)	3 (2.1)	
Immunodeficiency	0 (0)	2 (1.4)	
Respiratory (excluding CF)	4 (5.1)	4 (2.8)	

	40 mg/kg/d n=78	60 mg/kg/d n=144	<i>p</i>-value^a
Gastrointestinal	1 (1.3)	4 (2.8)	
Other	6 (7.7)	14 (9.7)	
Multiple (>1 of the above)	3 (3.8)	3 (2.1)	

^a for comparison of 40 mg/kg/day vs 60 mg/kg/day group

^b includes only patients 2 years and older for whom BMI percentiles could be calculated (n=43 in the 40 mg/kg/day and n=93 in the 60 mg/kg/day group).

^c immunosuppression was defined as neutropenia (absolute neutrophil count below 1000), exposure to chemotherapy, solid organ or stem cell transplant

^d SSTI = skin and soft tissue infection

^e CNS = central nervous system infection other than ventriculoperitoneal shunt infections, including meningitis (n=9) and meningoencephalitis (n=2)

^f VP = ventriculoperitoneal

Table 2

Mean initial vancomycin trough concentrations (mcg/mL) by age and weight in patients with detectable trough concentrations (≥ 5 mcg/mL) at the Mayo Clinic Children's Hospital from January 2008 to February 2012.

	40 mg/kg/day (mcg/mL) $\pm$ SD (no.)	60 mg/kg/day (mcg/mL) $\pm$ SD (no.)	p-value^a
All patients with trough concentrations ≥ 5 mcg/mL	7.4 $\pm$ 2.3 (n=55)	10.7 $\pm$ 5.2 (n=125)	<0.001
1 – 23 months	7.5 $\pm$ 2.3 (n=18)	9.5 $\pm$ 3.7 (n=31)	0.03
2 – 5 years	6.7 $\pm$ 2.0 (n=9)	7.5 $\pm$ 2.3 (n=28)	0.33
6 – 12 years	7.4 $\pm$ 2.5 (n=23)	10.7 $\pm$ 4.2 (n=39)	<0.001
13 – 18 years	7.8 $\pm$ 1.6 (n=5)	15.3 $\pm$ 6.8 (n=27)	<0.001
≤ 25 kg	7.3 $\pm$ 2.5 (n=34)	8.7 $\pm$ 3.7 (n=70)	0.02
25 – 50 kg	7.4 $\pm$ 1.9 (n=15)	10.6 $\pm$ 3.3 (n=33)	<0.001
> 50 kg	7.6 $\pm$ 1.5 (n=6)	17.1 $\pm$ 6.5 (n=22)	<0.001
Normal weight ^b	7.1 $\pm$ 2.4 (n=20)	10.4 $\pm$ 4.6 (n=59)	<0.001
Overweight ^b	7.7 $\pm$ 2.1 (n=11)	13.8 $\pm$ 7.1 (n=25)	<0.001

^a for comparison of 40 mg/kg versus 60 mg/kg group

^b includes only patients 2 years of age and older for whom BMI percentiles could be calculated. Normal weight was defined as BMI $< 85^{\text{th}}$ percentile and overweight as BMI $\geq 85^{\text{th}}$ percentile.