abstract

OBJECTIVE: To determine the incidence with which a vancomycin dosing regimen of 15 mg/kg per dose every 6 hours achieves steady-state trough concentrations of 15 to 20 mg/L in pediatric patients with complicated infections.

METHODS: We performed a retrospective chart review for patients admitted to our children’s hospital between July 1, 2009, and June 30, 2011. Patients were included if they were between 1 month and 18 years of age, had at least 1 steady-state vancomycin trough obtained, received an initial vancomycin dose of 15 mg/kg per dose every 6 hours, and were being treated for a diagnosis of meningitis, pneumonia, osteomyelitis, bacteremia/sepsis, or endocarditis.

RESULTS: Seventy-four patients were enrolled, mean age of 4.2 ± 3.9 years and weight of 17.0 ± 11.2 kg. Five (6.8%) patients obtained an initial trough of 15 to 20 mg/L. Patients between 1.0 and 5.9 years of age were significantly less likely to achieve an initial trough of 15 to 20 mg/L compared with other age groups evaluated (P = .041). Thirty-four patients with initial subtherapeutic troughs received a dose adjustment and a follow-up vancomycin trough. Of these patients, 15 (44.1%) achieved a trough between 15 and 20 mg/L. The median dose for patients achieving a therapeutic trough at any point during the study was 80 mg/kg per day.

CONCLUSIONS: A vancomycin dosing regimen of 15 mg/kg per dose every 6 hours is not likely to achieve a trough concentration of 15 to 20 mg/L in pediatric patients with complicated infections. An initial regimen of 80 mg/kg per day for these patients may be more likely to result in therapeutic steady-state concentrations of vancomycin.

Vancomycin is a glycopeptide antibiotic first introduced into clinical practice during the 1950s with excellent antimicrobial activity against gram-positive microorganisms, particularly methicillin-resistant Staphylococcus aureus (MRSA).1 The pharmacokinetics of vancomycin can vary greatly among age groups, and pediatric patients generally show an increased clearance of the drug compared with adults.2 Traditionally, serum drug concentrations have been measured to assess for drug efficacy and toxicity,1,4 although this has recently been a topic of great controversy in the medical literature. In response to this controversy, new recommendations for the monitoring of vancomycin were released in 2009.5 Although specific to adult patients, the theories and rationales behind these new recommendations can be applied to pediatric patients (Table 1). In 2011, the Infectious Diseases Society of America reaffirmed these guidelines but noted that additional studies are needed for pediatric patients.6 Pediatric clinicians currently face difficulties with appropriate vancomycin dosing to achieve appropriate trough concentrations.
concentrations, particularly for the treatment of complicated infections in which a trough of 15 to 20 mg/L is recommended. Over the past 60 years, recommendations for vancomycin dosing in pediatrics have varied from 40 mg/kg per day up to 60 mg/kg per day divided every 6 to 8 hours; however, there is limited evidence to suggest that this dose results in the recommended steady-state trough concentrations of 15 to 20 mg/L. Based on the existing literature, our institution reached a consensus to use a vancomycin dosing regimen of 15 mg/kg per dose every 6 hours for our pediatric patient population.

We performed a retrospective chart review to determine the incidence with which this vancomycin dosing regimen achieves steady-state trough concentrations of 15 to 20 mg/L.

### MATERIALS AND METHODS

Our institution is a 105-bed children’s hospital connected to a 361-bed non-profit, adult teaching hospital. This study was a retrospective chart review of patients admitted to the children’s hospital between July 1, 2009, and June 30, 2011, and was approved by the institutional review board. Inclusion criteria included the following: age 1 month to 18 years; at least 1 steady-state vancomycin trough obtained; received an initial vancomycin dose of 15 mg/kg per dose intravenously every 6 hours; and diagnosed with a complicated infection (meningitis, pneumonia, osteomyelitis, bacteremia/sepsis, or endocarditis). Our institution defines all pneumonias as complicated because of the difficulty of vancomycin penetration into the lungs, as well as the increasing incidence of community-associated pneumonia caused by MRSA. Exclusion criteria included the following: age <1 month or >18 years; weight >50 kg; admission to the newborn nursery or NICU; receiving vancomycin therapy as an outpatient before admission; evidence of acute kidney injury or renal failure; diagnosis of cystic fibrosis; and diagnosis of an underlying oncology disorder or other disorder that would have affected normal pharmacokinetic parameters. To ensure that vancomycin steady-state concentrations were reached, the policy of our institution is to obtain initial troughs no earlier than just before the fifth vancomycin dose. Peak concentrations were not monitored. Our primary outcome was the incidence with which vancomycin doses of 15 mg/kg given every 6 hours achieves a steady-state vancomycin trough of 15 to

<table>
<thead>
<tr>
<th>Variable</th>
<th>Recommendation</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Monitoring of peaks</td>
<td>Peak concentrations should no longer be routinely monitored.</td>
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<tr>
<td>Monitoring of troughs</td>
<td>Trough concentrations are considered to be the best predictor of clinical efficacy, and are most practical for monitoring.</td>
<td>An AUC:MIC ratio ≥400 has been shown by various studies to be the best marker for vancomycin efficacy, but because of the difficulty of calculating the AUC in a clinical setting, trough concentrations should be used as a surrogate marker.</td>
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<tr>
<td>Target trough concentrations</td>
<td>Troughs should be maintained at or above 10 mg/L. For pathogens with an MIC of &gt;1 mg/L, trough concentrations should be targeted at 15–20 mg/L.</td>
<td>Trough concentrations should not fall below 10 mg/L to avoid developing pathogen resistance. Concentrations above 10 mg/L will help attain a higher AUC:MIC ratio and address the growing problem of higher MIC values to vancomycin in susceptible organisms. For pathogens with an MIC ≥1 mg/L, the trough must be kept between 15 and 20 mg/L to achieve the target AUC:MIC ratio of 400.</td>
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<tr>
<td>Target trough concentrations for complicated infections</td>
<td>Trough concentrations should be maintained between 15 and 20 mg/L for the following infections: - Bacteremia - Endocarditis - Osteomyelitis - Meningitis - Hospital-acquired pneumonia caused by Staphylococcus aureus</td>
<td>Troughs of 15–20 mg/L should be targeted in these serious infections to increase antibiotic penetration and increase the likelihood of obtaining an AUC:MIC ratio of 400.</td>
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<tr>
<td>Pathogens with high MIC values to vancomycin</td>
<td>For pathogens that have an MIC value of ≥2 mg/L, an alternative therapy to vancomycin should be considered.</td>
<td>Because an AUC:MIC ratio of 400 is unlikely to be obtained for pathogens with an MIC ≥2 mg/L, an alternative drug therapy to vancomycin should be considered in these patients.</td>
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20 mg/L in pediatric patients. Secondary outcomes included initial and final vancomycin trough concentrations for pediatric patients stratified by age and final vancomycin doses for patients who achieved a vancomycin trough of 15 to 20 mg/L at any point in the study versus those who did not.

**Statistical Analyses**
The primary outcome was evaluated using descriptive statistics. A 1-way analysis of variance was used to compare mean trough concentrations among patients based on age. A Mann-Whitney rank sum test was used to compare final vancomycin doses between patients who achieved goal troughs at any time during the study and those who did not.

**RESULTS**
A total of 125 patients were identified as having a complicated infection. Seven patients were excluded from the study: 2 due to preexisting renal dysfunction, 1 for receipt of hemodialysis, and 4 due to initially receiving a dosing regimen different than 15 mg/kg per dose every 6 hours. Steady-state trough concentrations were obtained for a total of 74 patients (Table 2). Only 5 (6.8%) initially obtained a therapeutic trough, defined as a trough concentration of 15 to 20 mg/L. No initial steady-state troughs were supratherapeutic, defined as a trough concentration of >20 mg/L.

All patients with subtherapeutic troughs received a dose increase to their regimen. However, not all patients had repeat troughs obtained because therapy with vancomycin may have been discontinued before obtaining a repeat trough. After the dose adjustment, repeat troughs were obtained in 34 (46%) patients. Of these 34 patients, 15 (20%) had therapeutic troughs on repeat, and 3 patients had supratherapeutic troughs of 21.5, 21.7, and 21 mg/L. Only a total of 20 patients (27%) achieved therapeutic troughs at any point during the study. These patients received a median dose of 80 mg/kg per day. Sixteen patients with follow-up troughs never achieved therapeutic concentrations, despite a median dosage increase to 90 mg/kg per day. Although the goal of this study was to specifically examine the dosing required to achieve a trough of 15 to 20 mg/L, we noted that, of the initial 74 patients who had a trough obtained, only 32 (43.2%) obtained an initial trough between 10 and 15 mg/L. The remaining 37 patients (50%) patients had an initial trough <10 mg/L (Fig 1).

Mean initial vancomycin troughs were significantly different among age groups ($P = .041$) (Table 3). Of all age groups evaluated, patients who were ≥1 and <6 years of age had the lowest mean initial vancomycin trough. Table 4 compares vancomycin doses between patients who achieved target vancomycin troughs at any time during the study with those who never achieved a therapeutic trough. Patients with initial vancomycin troughs below goal who did not have a follow-up concentration obtained were excluded from this analysis.

**DISCUSSION**
Because of the currently limited amount of data, vancomycin dosing and monitoring is an important topic to address for pediatric patients. Based on the results from our study, a dosing regimen of 60 mg/kg per day is not likely to achieve a trough concentration of 15 to 20 mg/L. In fact, exactly half of...
the patients receiving this dosage regimen did not even achieve troughs ≥10 mg/L. A number of pediatric studies have been published that question the utility of the traditional pediatric dosing of 40 mg/kg per day.17-12 These studies generally found that 60 mg/kg per day was necessary to achieve trough concentrations of 5 to 15 mg/L, which is not consistent with current recommendations of maintaining trough concentrations at least >10 mg/L. None of these studies focused specifically on the dosing needed to obtain troughs of 15 to 20 mg/L.

In 2011, findings from Eiland et al17 revealed that an average dosing regimen of 59 mg/kg per day resulted in trough concentrations of 10 to 15 mg/L in only 27% of the study population, and 15 to 20 mg/L in 22%. These authors also derived a predictive dosing equation to determine trough concentrations in which a dosing regimen of 70 mg/kg per day would correlate to a trough of 10 mg/L, and 85 mg/kg per day would correlate to a trough of 15 mg/L. Although this equation has not yet been validated, these findings are consistent with our results, which showed a median dosage adjustment up to 80 mg/kg per day for patients who obtained a target trough of 15 to 20 mg/L during the study period.

Madigan et al18 published a study in 2013 on the effects of age and weight on vancomycin trough concentrations in pediatric patients. The mean vancomycin trough concentration in all patients who received 60 mg/kg per day (15 mg/kg per dose every 6 hours) was 10.7 mg/L. When stratified according to age, only 16.7% of patients between the ages of 2 and 5 years achieved a therapeutic trough, defined as a concentration of 10 to 20 mg/L; this incidence was significantly less than other age groups in the study. A previous study by Gordon et al19 reported that children younger than 6 years had lower trough concentrations than older patients receiving the same vancomycin dose and interval. Both of these studies support our finding that patients between 1 and ∼6 years of age were less likely to achieve an initial therapeutic trough than patients in other age categories.

Cies and Shankar20 performed a study in PICU patients to examine the incidence of nephrotoxicity in patients with trough concentrations of 15 to 20 mg/L compared with patients with trough concentrations <15 mg/L. Nephrotoxicity was defined as an absolute increase in serum creatinine of 0.3 mg/dL or a 50% increase in serum creatinine from the baseline value. There was no significant difference in the incidence of nephrotoxicity between the 2 groups, suggesting that higher vancomycin trough concentrations are not associated with an increase in nephrotoxicity. In our study, no patients experienced vancomycin-induced nephrotoxicity by using this definition, consistent with the Cies and Shankar20 results. Although this study was not specifically designed to assess dosing, the authors reported that the mean dosage for patients in the high-trough cohort was 63.5 ± 17.3 mg/kg per day. However, one-third of these patients received a vancomycin dosing frequency of every 4 hours, which would significantly affect vancomycin trough concentrations and potentially explain why this dose resulted in therapeutic drug concentrations.

Our study does have a number of important limitations. First, it is a retrospective analysis with limitations inherent to its study design. In addition, our sample size was small, with only 74 patients meeting inclusion criteria. Although we were able to determine that 15 mg/kg per dose given every 6 hours is not adequate to achieve troughs of 15 to 20 mg/L, our small sample size, retrospective design, and low number of repeat troughs obtained due to drug discontinuation limited our ability to determine what dosing regimen would consistently achieve target trough concentrations. The low number of repeat troughs may call into question the utility of having obtained the initial troughs to begin with, as the drug was often discontinued early into therapy.

Based on the median dose for patients who did achieve a therapeutic trough at any point in the study, it appears that a better starting regimen for pediatric patients with complicated infections would likely be ∼80 mg/kg per day. This is supported by the predictive equation findings from Eiland et al,17 but further studies are needed to confirm these results. In addition, we noted

### TABLE 3 Mean Initial Trough Stratified by Age Group, P = .041

<table>
<thead>
<tr>
<th>Age range, y</th>
<th>&lt;1, n = 15</th>
<th>1.0–5.9, n = 39</th>
<th>6.0–11.9, n = 15</th>
<th>≥12, n = 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial trough, mg/L, mean ± SD</td>
<td>113 ± 2.9</td>
<td>8.7 ± 3.6</td>
<td>10.9 ± 3.9</td>
<td>10.6 ± 2.2</td>
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One patient excluded from this analysis because of a vancomycin trough concentration <3.5 mg/L.

<table>
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<tr>
<th>TABLE 4 Dose Comparison in Patients Achieving Versus Not Achieving Therapeutic Troughs, P = .054</th>
</tr>
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<tbody>
<tr>
<td>Achieved, n = 20</td>
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<tr>
<td>Final dose (mg/kg per day), median (IQR)</td>
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that a number of patients in our study never achieved therapeutic troughs despite a median dose increase to 90 mg/kg per day. We suggest that this might be because of individual pharmacokinetic differences among pediatric patients, but this should be evaluated in further studies. Last, our study was not designed to determine if higher trough concentrations translate to better outcomes in pediatric patients. Although it appears that achieving troughs of 15 to 20 mg/L in adult patients does improve outcomes and overcomes bacterial resistance, the literature is lacking for pediatric patients. One study that used predictive modeling demonstrated that a dose of 60 mg/kg per day achieved an area under the curve (AUC) to minimum inhibitory concentration (MIC) ratio >400. A second study showed that vancomycin troughs of 7 to 10 mg/L are likely predictive of AUC:MIC >400 when using a dosing regimen of 15 mg/kg per dose every 6 hours. Based on this modeling, it may not be necessary to achieve troughs of 15 to 20 mg/L to achieve an AUC:MIC >400 in pediatric patients. However, it is essential to note that both of these pharmacokinetic modeling studies used MRSA isolates with an MIC of 1 mg/L. For isolates with a higher MIC, higher trough concentrations would be required. Therefore, these studies do not negate the importance of achieving higher trough concentrations in some patients.

CONCLUSIONS
Pediatric patients with complicated infections are not likely to achieve trough concentrations of 15 to 20 mg/L with a dosing regimen of 15 mg/kg per dose every 6 hours (60 mg/kg per day). Furthermore, this dosing regimen often does not produce troughs >10 mg/L. Patients between the ages of 1.0 and 5.9 years are at particular risk for not achieving therapeutic troughs with this dosing regimen. We suggest that patients requiring trough concentrations of 15 to 20 mg/L be started at a higher initial dose than 60 mg/kg per day. Based on the results from our study, a starting regimen of approximately 80 mg/kg per day is suggested to better achieve higher troughs, but this must be further evaluated. Higher trough concentrations do not appear to be associated with increased rates of nephrotoxicity, but this again should be further evaluated in a prospective manner.

REFERENCES:


