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Impact of Hospital-Wide Change in Empiric Pediatric Vancomycin Dosing and Associated Therapeutic Concentrations

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Abstract

Study Objective—To evaluate the impact of a hospital-wide increase in the recommended vancomycin starting dose in children from 45 to 60 mg/kg/day on vancomycin trough concentrations.

Design—Retrospective chart review.

Setting—Dedicated children's hospital located within a tertiary care, academic medical center.

Patients—Children aged 1 month–12 years with normal renal function who were treated with vancomycin during two one-year periods: July 2006–June 2007 (low dose [LD]; 45 mg/kg/day divided q8 hour; n=88) and July 2008–June 2009 (high dose [HD]; 60 mg/kg/day divided q6 hour; n=94).

Measurement and Main Results—Patient demographics along with vancomycin dose and initial vancomycin trough concentration were collected. No significant demographic differences existed in patients between the two periods. The mean initial vancomycin trough level increased from 7 ± 5 µg/ml to 9 ± 5 µg/ml (LD vs HD; $p < 0.001$). The percentage of patients with an initial trough < 5 µg/ml declined from 39% to 17% (LD vs HD; $p < 0.001$) while the percentage of patients with an initial trough concentration in the potentially adverse range (> 20 µg/ml) was unchanged between the two periods (2% vs 2%; $p = 0.9$). Less than 15% achieved a trough level between 15–20 µg/ml in the HD period of our study.

Conclusions—This is the first report of a hospital-wide increase in the recommended vancomycin starting dose to 60 mg/kg/day in children. The use of a vancomycin starting dose of 60 mg/kg/day decreased the likelihood of an initial low vancomycin trough < 5 µg/ml with no increase in the proportion of patients with trough levels in a potentially toxic range. The 60 mg/kg/

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day dose does not consistently achieve a vancomycin trough of 15-20 µg/ml, a goal suggested by some experts.

Keywords

vancomycin; children; pharmacokinetics; methicillin-resistant *staphylococcus aureus*

Introduction

The increase in the number of invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections in children¹⁻³ and reports of strains with reduced vancomycin susceptibility⁴ have reinforced the need for optimal vancomycin dosing in children.⁵ Conventional empiric dosing recommendations (40-45 mg/kg/day) frequently result in low initial trough concentrations (<5 µg/ml) in children^{6, 7} and potential therapeutic failure. A modeling study in children that examined the influence of vancomycin dose and MRSA MIC (range 0.5 to 2 mcg/ml) on AUC/MIC, predicted that a dose of 40 mg/kg/day would achieve an AUC/MIC >400 -- the best measure of optimal outcome in adults^{8, 9} -- in only 66% of children whereas a dose of 60 mg/kg/day would be predicted to reach this target in >90% of children.¹⁰ Clinical studies in adults examining the influence of MRSA MIC on outcome suggest that an MRSA MIC to vancomycin >1 mcg/ml is associated with clinical failure.¹¹⁻¹³

Along these lines, our institution increased the recommended vancomycin starting dose for children with suspected invasive MRSA infections (e.g. bacteremia, osteomyelitis, meningitis, and pneumonia) and normal renal function from 45 mg/kg/day to 60 mg/kg/day. This is in accordance with the recent vancomycin dose recommendations from the Infectious Diseases Society of America (IDSA) for the treatment of invasive MRSA infections in children.¹⁴ No studies have evaluated the impact of a systematic increase in empiric vancomycin dosing in children on trough concentrations. While it was hypothesized that this increased vancomycin dose should decrease the proportion of patients with low initial troughs, it also might result in more patients with high troughs associated with potential toxicity (>20 µg/ml).

Methods

In July 2008, the University of California San Francisco (UCSF) Children's Hospital adopted a new hospital-wide empiric vancomycin dose recommendation of 60 mg/kg/d (15 mg/kg IV q6h) for children >1 month old with normal renal function and suspected invasive MRSA infections (e.g. bacteremia, osteomyelitis, meningitis, and pneumonia). Previous guidelines at UCSF Children's Hospital recommended a vancomycin dose of 45 mg/kg/d (15 mg/kg IV q8h) for non-central nervous system infections and 60 mg/kg/d (15 mg/kg IV q6h) for central nervous system infections. Vancomycin dosing guidelines are disseminated at UCSF using an antimicrobial dosing card distributed to all housestaff, clinical pharmacists and faculty physicians. Dosing recommendations are reinforced by clinical pharmacists on clinical rounds. As part of standard therapeutic drug monitoring, a trough level is drawn prior to the 3rd dose. We compared the initial vancomycin trough concentrations for all children ages 1 month-12 years at UCSF Children's Hospital before and after the dosage recommendation change during two one-year periods: July 2006-June 2007 (LD - low dose period; 45 mg/kg/day) and July 2008-June 2009 (HD - high dose period; 60 mg/kg/day).

Subjects with vancomycin trough levels were identified via a query of the medical center computerized laboratory information system, and medical records were retrospectively reviewed. Data collected included age, gender, weight, serum creatinine, hospital service, vancomycin dosage and initial vancomycin trough level. Although we did not verify the

timing of blood draw for trough concentration relative to timing of 3rd dose administration, periodic validation from the inpatient pharmacy has verified that >95% of troughs are measured at the appropriate time (data unpublished). To allow for rounding errors, a patient was considered to have received a vancomycin dose of 45 mg/kg/day or 60 mg/kg/day if the calculated mg/kg dose was within $\pm 10\%$ of either specified dose. Patients admitted to the neonatal intensive care, cardiac intensive care, nephrology, bone marrow transplant and oncology services were excluded from the study analysis as these groups represent distinct populations with known differences in vancomycin pharmacokinetics and associated dosage requirements.¹⁵ Patients with decreased renal function defined as a serum creatinine greater than our laboratory pediatric reference range (1 month-1 year, >0.7 mg/dl; 1-12 years, >0.9 mg/dl) were also excluded. If no serum creatinine level was available, the patient was presumed to have normal renal function. Children who received multiple courses of vancomycin during a one-year period were included only once for analysis (first treatment course). Because there could be differences in vancomycin pharmacokinetics between critically ill ICU patients and non-ICU patients, we also compared trough concentrations for these two populations.

Differences between treatment periods were compared by use of Student's t-test or Wilcoxon rank-sum test for continuous data and Pearson chi-square test for categorical data. The data were analyzed using STATA 10 (StataCorp LP, College Station, TX). Continuous data are reported as mean $\pm$ SD, and categorical data are reported as counts (%).

Results

Subject demographics were similar between the two study periods (Table 1). A serum creatinine was not available for 18% of patients during both periods, and these subjects were assumed to have normal renal function and included in the analysis. Subgroup analysis of subject demographics divided by ICU and non-ICU patients showed no difference between study periods (Data not shown). After the hospital-wide increase in vancomycin dose recommendation to 60 mg/kg/day, the vancomycin starting dose in patients increased (LD 49 ± 8 mg/kg/d vs HD 58 ± 10 mg/kg/d; $p < 0.001$). The proportion of patients treated with a vancomycin starting dose of 60 mg/kg/d increased from 31% to 71% (LD vs HD; $p < 0.001$). Seven patients were prescribed a starting dose >60 mg/kg/day during the HD period while only one patient was prescribed this during the LD period.

The mean initial vancomycin trough level increased from 7 ± 5 μ g/ml during the LD period to 9 ± 5 μ g/ml during the HD period ($p < 0.001$). Figure 1 compares the distribution of initial vancomycin trough levels between the two periods. The percentage of children with an initial vancomycin trough <5 μ g/ml declined significantly after the new dosage recommendations from 38% during the LD period to 17% during the HD period ($p < 0.002$). The percentage of patients with a trough concentration of >20 μ g/ml was low during both years and did not change (LD period 2% vs HD period 2%; $p = 0.9$).

A subgroup analysis was performed to compare ICU patients and non-ICU patients. Figure 2 compares the distribution of initial vancomycin trough levels between the two periods categorized according to ICU status. In non-ICU patients, the initial mean vancomycin trough level increased from 6 ± 4 μ g/ml during the LD period to 9 ± 5 μ g/ml during the HD period ($p < 0.001$). For ICU patients, the initial mean vancomycin trough level did not increase significantly when comparing the LD to HD periods (LD 8 ± 5 μ g/ml vs HD 10 ± 5 μ g/ml; $p = 0.3$). Within the LD period, the initial mean vancomycin trough level was higher in ICU compared to non-ICU patients ($p = 0.03$), but there was no difference in vancomycin trough level between ICU and non-ICU patients during the HD period ($p = 0.7$).

Discussion

Recent national guidelines from the Infectious Disease Society of America recommend a higher vancomycin dose of 60 mg/kg/day in children with invasive MRSA infections,¹⁴ and our study provides, to our knowledge, the first data on the impact of this increased empiric vancomycin dosing on vancomycin trough concentrations. A hospital-wide change in the vancomycin dose recommendation from 45 mg/kg/day to 60 mg/kg/day for invasive MRSA infection resulted in a >50% decrease in the proportion of children with an initial vancomycin trough < 5 µg/ml, while not changing the proportion of patients with a trough concentration >20 µg/ml. Our results indicate that implementing this dosing change is feasible in a tertiary care children's hospital and that it significantly increases vancomycin exposure as measured by serum troughs with no increase in the rate of troughs potentially associated with toxicity (e.g. levels >20 µg/ml).

Subgroup analysis indicated that the change in the recommended vancomycin starting dose predominantly influenced vancomycin trough concentrations for non-ICU patients (Figure 2). The fact that little change was observed for ICU patients seems to reflect the fact that trough concentrations for this population were already higher during the LD period. It is possible that ICU patients during the LD period had lower vancomycin clearance related to more severe illness that contributed to higher troughs even with lower dosing. This apparent difference between the ICU and non-ICU patients was not evident during the HD period, and the 60 mg/kg/day dose achieved similar vancomycin trough concentrations in the two groups.

Our primary endpoint was the initial vancomycin trough concentration, since trough levels are most commonly monitored in clinical practice. Based in part on correlations with AUC achievement and concerns that prolonged vancomycin exposure at low concentrations (< 10 µg/ml) may promote resistance, recent adult guidelines recommend a goal vancomycin trough of 15-20 µg/ml for invasive MRSA infections.^{9, 14, 16} It is unknown whether these goal trough concentrations are applicable for children. If we apply the guidelines for these higher trough concentrations, very few children with normal renal function would achieve “therapeutic levels” (<15% achieved a trough level between 15-20 µg/ml in the HD period of our study). To achieve this higher goal, significantly larger doses would be needed, but few data are available to support doses >60 mg/kg/day in children. Additionally, given the variability in vancomycin clearance between children, this goal represents a narrow therapeutic window that would be difficult to achieve consistently with empiric dosing. Expanding the goal trough concentration to 10-20 mg/ml would be more practical, but still only 37% of patients in our study reached this target at the initial trough level with a dose of 60 mg/kg/day.

The AUC/MIC value may be a more clinically meaningful measure of vancomycin exposure and endpoint. Animal and adult data suggest an AUC/MIC >400 best predicts successful outcomes when treating invasive MRSA infection.^(8,9) Previous modeling studies have suggested that a vancomycin starting dose of 60mg/kg/day consistently achieves this vancomycin exposure in children with invasive MRSA infections.^{10, 17} However, the calculation of AUC/MIC for individual patients is practically difficult because it requires multiple vancomycin levels for a reliable estimation, and only trough levels are routinely available at most clinical institutions including our own. Improved therapeutic drug monitoring may require more robust models for AUC extrapolation if this target is an important predictor of outcome in children with invasive MRSA infections. Until there are data supporting a specific target trough level in children, we believe vancomycin trough concentrations should be used to detect extreme outliers, i.e. those with troughs < 5 µg/ml who are obviously underdosed and those with potentially toxic troughs >20 µg/ml.

Increased vancomycin dosing raises the concern for increased nephrotoxicity and ototoxicity. Yet, the link between vancomycin exposure and toxicity has not been firmly established in children or adults.^{5, 9} Early descriptions of toxicity were confounded by issues with the vancomycin formulation (“Mississippi mud”). Establishing causality in vancomycin toxicity is further complicated by its common co-administration with known nephrotoxic drugs such as gentamicin. In the interim, monitoring of vancomycin troughs and patient renal function is recommended.

The limitations to our study include the exclusion of certain patient populations (e.g. neonates), and potential differences in patient populations between the two study periods. In addition, since we examined only a single trough level, some patients may not have been at steady-state. Finally, we did not directly evaluate the impact of the dose increase on clinical outcomes including treatment effectiveness or toxicity.

Conclusion

In summary, we found that a hospital-wide increase in the recommended empiric vancomycin dose to 60 mg/kg/day for children with suspected invasive MRSA infection resulted in more favorable vancomycin trough concentrations. Combined with previous clinical and pharmacodynamic modeling studies, these results further support implementation of this dosing strategy for pediatric patients with suspected invasive MRSA infection. Comparative effectiveness studies are needed to directly evaluate vancomycin dosing regimens and clinical outcomes for children with invasive MRSA infections.

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Figure 1.

Distribution of initial vancomycin trough levels before (LD Period) and after (HD Period) an increase in the hospital-wide vancomycin dose recommendation from 45 mg/kg/day to 60 mg/kg/day for children 1 month to 12 years with suspected invasive MRSA infection.

Figure 2.

Subgroup analysis dividing patients by a) non-ICU and b) ICU status. For each group, the distribution of initial vancomycin trough levels is presented before (LD Period) and after (HD Period) an increase in the hospital-wide vancomycin dose recommendation from 45 mg/kg/day to 60 mg/kg/day for children 1 month to 12 years with suspected invasive MRSA infection.

Table 1
Subject demographics

Demographic	LD period (N=88)	HD period (N=94)	p value
Age ^a , years	4.9 ± 4.0	5.2 ± 3.9	0.6
Weight ^a , kg	18.4 ± 12.5	21.1 ± 15.2	0.2
Female, N (%)	46 (52%)	47 (50%)	0.8
Serum Creatinine ^a (mg/dl)	0.4 ± 0.1	0.4 ± 0.1	0.4
Intensive Care, N (%)	27 (31%)	40 (43%)	0.1

^aValues are mean ± SD.

LD period; Low dose period, 45 mg/kg/day recommended

HD period; High dose period, 60 mg/kg/day recommended