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OBJECTIVE Subtherapeutic vancomycin trough concentrations are common in children and may be associated with suboptimal therapeutic response. Our objective was to determine if vancomycin loading doses safely increase the frequency of target trough attainment in hospitalized children.

METHODS Patients (≥6 months and <18-years-old) who received a vancomycin loading dose between February 1, 2018, and January 30, 2019, were retrospectively enrolled. These patients were compared to a convenience cohort of patients hospitalized between January 1, 2015, and December 31, 2015, who received vancomycin without a loading dose. Target trough concentrations were defined as >15 mg/dL for invasive infections and >10 mg/dL for non-invasive infections.

RESULTS A total of 151 patients were enrolled, with 77 in the control arm and 74 in the loading dose arm. There was no significant difference in the frequency of comorbidities or need for intensive care unit admission between the two arms. Those receiving a vancomycin loading dose were older (mean age 9.1 vs 5.2 years, $p < 0.0001$). Patients given a loading dose achieved higher mean initial trough values (13.0 mg/dL vs 9.2 mg/dL, $p < 0.0001$), were more likely to have an initial trough at or above target (37.0% vs 10.4%, $p = 0.0001$), were more likely to reach target trough values at any point during therapy (52.1% vs 32.9%, $p = 0.0081$), and attained a target trough concentration more quickly (mean 41.1 hours vs 58.8 hours, $p = 0.0118$). There were no significant differences in the frequency of serum creatinine elevation or oliguria at the end of therapy.

CONCLUSIONS Vancomycin loading doses may improve the ability to safely obtain target trough values in hospitalized children.

ABBREVIATIONS AUC/MIC, area under the curve/minimum inhibitory concentration; ICU, intensive care unit; MRSA, Methicillin-resistant *Staphylococcus aureus*

KEYWORDS pediatric; pharmacokinetics; target attainment; therapeutic drug monitoring; vancomycin

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Introduction

Vancomycin is a large glycopeptide antibiotic that directs its activity against the bacterial cell wall.[1] It is commonly used in the treatment of serious Gram-positive infections,[2–4] including those due to methicillin-resistant *Staphylococcus aureus* (MRSA).[1,5] Despite having been in clinical use for more than 60 years, it still retains potent activity against most strains of *S aureus* and other Gram-positive pathogens[6] and is considered a first-line agent for use in hospitalized children infected with these organisms.[7] Clinical and animal data[2,8–10] suggest that vancomycin killing is not concentration dependent, and pharmacokinetic/pharmacodynamic data[2,3,11,12] suggest that, as a result, the area under the curve/minimum inhibitory concentration (AUC/MIC) may be the best predictor of clinical response, particularly for lung infections. The data for this parameter are more robust in adults, but it has also demonstrated utility in children.[7] However, it is often logistically difficult to calculate this value given the multiple blood specimens required (particularly in children, in whom repeated venipunctures are often challenging) and the need for an accurate MIC from an organism in a timely fashion. In addition, the lack of data associating AUC/MIC to outcomes in children and a lack of formal recommendations for how to use this parameter in children conspire to make adoption of this approach in pediatrics difficult.[4] As a result, serum trough minimum concentrations of vancomycin are often used as a surrogate for AUC/MIC to gauge the appropriateness of dosing.[2,13] In adults the trough concentrations are ideally 10 to 15 mg/dL for skin and soft tissue infections and 15 to 20 mg/dL for more severe infections.

Despite standard dosing based upon accepted references,[14] initial vancomycin trough values in children are often subtherapeutic or below target goals.[15] Orr et al[15] reported that 79.2% of appropriately dosed pediatric oncology patients had subtherapeutic initial vancomycin trough concentrations, while Hsu et al[16] detailed

a cohort of children with MRSA bacteremia, 73.0% of whom had a median vancomycin trough concentration of <10 mg/dL. Hoang et al[17] described a cohort of 188 children, 61.0% of whom failed to achieve target trough concentrations following vancomycin dosing, while Durham et al[18] reported that only 6.8% of 74 children receiving vancomycin at 60 mg/kg/day divided every 6 hours achieved a trough concentration of 15 to 20 mg/dL. Randolph et al[19] also reported that among 170 children receiving vancomycin for an MRSA coinfection following influenza disease, 78.0% failed to achieve an initial trough value of 10 mg/dL. More concerning are recent reports associating subtherapeutic vancomycin trough concentrations with poor clinical outcomes. Hsu et al[16] found that a longer duration of MRSA bacteremia was associated with a vancomycin trough concentration of <10 mg/dL within the first 72 hours of therapy. Children with vancomycin trough values of <10 mg/dL in this cohort were 3 times as likely to have MRSA bacteremia lasting more than 3 days than were those children with trough concentrations of >10 mg/dL.[16] Yoo et al[20] documented similar findings in a study of 46 children with MRSA bacteremia, in which those children with vancomycin trough values of <10 mg/dL were significantly more likely to experience a bacteremia lasting greater than 2 days (although this finding did not remain significant in multivariable analysis). Hamdy et al[21] documented that every 1-day increase in MRSA bacteremia duration results in a 50.0% increase in the odds that a complication will appear, which argues for a need for rapid clearance of bacteremia.

These findings suggest a need to further investigate strategies to more consistently and rapidly achieve target vancomycin concentrations in children. Recently, studies[3,22–24] have demonstrated that vancomycin loading doses may improve the likelihood of attaining early target trough concentrations in adult patients. However, there are limited data regarding the safety and efficacy of this approach in children. To our knowledge, only one study has investigated the use of vancomycin loading doses in pediatric patients. Demirjian et al[25] did not demonstrate any benefit with loading doses in a 2013 randomized controlled trial in children. However, the study did not appear powered to address the question, with only 19 children enrolled in the loading dose group (46 overall), with the primary outcome an 8-hour serum concentration, prior to steady-state attainment. An abstract[26] presented in 2014 reported a median trough concentration of 10.9 mg/dL in an uncontrolled study of vancomycin loading doses in 19 children aged 3 months to 18 years. However, this study was limited by a small sample size and lack of a control group.

Given the apparent success of vancomycin loading doses in adult medicine, this practice should be evaluated more thoroughly for use in children. To this end, we conducted a retrospective study of hospitalized children receiving vancomycin to investigate the relationship between receipt of a loading dose and the frequency of safely attaining the initial target trough concentrations.

Materials and Methods

We implemented a pediatric vancomycin loading dose protocol at the University of New Mexico Hospital on February 1, 2018. The recommended pediatric loading dose of 20 to 25 mg/kg/dose was determined based on extrapolation from adult loading dose data and preliminary data on the frequency of subtherapeutic vancomycin trough values (below target concentrations) requiring dose corrections to the 20 to 25 mg/kg dose range in children at our institution.[3,14,24] While the protocol recommended use of a loading dose, administration of a loading dose was ultimately at the discretion of the treating clinicians.

We conducted a retrospective cohort study of children hospitalized in the first year following implementation of these new vancomycin loading dose guidelines (February 1, 2018, to January 31, 2019), with comparison to a convenience cohort of children receiving vancomycin without a loading dose (January 1, 2015, to December 31, 2015).

Eligible subjects were hospitalized at our institution during the relevant time periods and were between the ages of 6 months and 18 years. Those under 6 months of age were excluded, as glomerular filtration rate reaches adult values by this age, thus providing a more comparable cohort.[27] Subjects also had to have received vancomycin for at least 24 hours followed by an appropriately collected trough. Appropriate troughs were defined as being collected within 1 hour of the next scheduled dose and were obtained at presumed steady state (within 1 hour of the 24-hour dose; e.g., within 1 hour of the third dose for every 8-hour dosing; within 1 hour of the fourth dose for each 6-hour dosing) per Infectious Disease Society of America guidelines.[3,14] Our hospital has no defined protocol for monitoring vancomycin trough values after the first 24 hours. Once a target trough value is obtained, routine monitoring of trough concentrations would occur every 5 to 7 days, unless unstable renal function was a concern, in which case more frequent trough concentrations would be obtained on a case-by-case basis. If given, the loading dose was counted as the first dose administered.

Data for eligible subjects were collected from electronic medical records. Abstracted data included demographic information, dosing data (dose, timing in relation to trough, duration of therapy, number of dosing changes), indication for therapy, culture results (if obtained), medical comorbidities, need for intensive care unit admission, duration of hospital stay, and all trough values obtained. If available, serum creatinine and urine output values (mL/kg/hr) within 24 hours of the initial trough value and within 24 hours of vancomycin discontinuation were collected and compared to assess

for nephrotoxicity. Creatinine concentrations above age-appropriate values were considered abnormal. Although age-specific values for normal urine output are not well defined, we considered oliguria as a urine output of <1 mL/kg/hr in children between 6 months and 1 year of age and of <0.5 mL/kg/hr in older children.[28–30] An appropriate maintenance dose was defined as 40 to 60 mg/kg/day (±5 mg/kg/day) for non-invasive infections (e.g., skin/soft tissue infections without systemic involvement, lower urinary tract infections) and 60 mg/kg/day (±5 mg/kg/day) for invasive infections (e.g., meningitis, bacteremia, osteoarticular infections), per institutional guidelines.[14] Target trough concentrations were defined as 10 to 15 mg/dL for non-invasive infections and 15 to 20 mg/dL for invasive infections, as previously defined.[3,14,25,31] Although ambiguity exists with regard to the clinical significance of specific trough values, as well as the relationship between trough values and the AUC/MIC, given the frequent reliance on national guidelines and references that advocate use of a vancomycin trough in the 15 to 20 mg/dL range for serious infections, we used this as our reference point for a therapeutic or target trough value.[3,14,31,32] Data were entered into a REDCap database,[33] followed by extraction to Stata (version 11.2, 2012) for statistical analysis.

For power calculations, we estimated a 20.8% target trough attainment without a loading dose from previously published work in children,[15] with an estimated 50.0% target trough attainment with the use of loading doses (based upon previous adult and pediatric data).[22,26] Using an alpha of 0.05 and 90% desired power, we estimated we would require 108 subjects (54 in each group) in order to detect a statistically significant difference in our primary outcome (initial target trough attainment), should one exist.

Basic descriptive statistics (e.g., calculation of frequencies) were used for characterization of the cohort. A chi-square test was used to assess for significant differences between categorical variables, while comparison of mean values was conducted with Welch's unequal variances *t*-test. To analyze for the effect of age as a confounder on the attainment of a target trough, a logistic regression model was created with attainment of a target trough as the dependent variable, and a likelihood ratio test was conducted to assess for significant differences with and without the variable of interest (Wald *t*-test). Statistical significance was defined as a p value of <0.05.

Results

In the 2015 standard dosing cohort, 312 subjects were identified as having received at least one dose of vancomycin (with 77 eligible), while 307 subjects were identified in the loading dose period as having received at least one dose of vancomycin (with 74 eligible) (Figure A and B). Overall, 151 subjects were enrolled.

Subjects receiving a loading dose were older (mean age 9.1 vs 5.2 years, p < 0.0001), more likely to be female (59.5% vs 42.9%, p = 0.0208), and demonstrated higher body weights (35.5 vs 19.0 kg, p < 0.0001) than did those not receiving loading doses (Table 1). Of note, subjects excluded from the loading dose cohort for not receiving a loading dose were also significantly older than those in the control group (mean age 9.9 vs 5.2 years, p = 0.005, median 10.2 years, IQR 5.0 to 6.9 years). There were no significant differences between the groups in terms of race, ethnicity, the frequency of MRSA isolation, the presence of medical comorbidities, or the frequency of intensive care unit admission (Table 1). The most common medical comorbidities were oncologic disorders (n = 22, or 14.6% overall) followed by short bowel syndrome (n = 17, or 11.3% overall), while the most common organism isolated was *S aureus* (n = 26, 42.6% of all organisms cultured), with blood the most common site of isolation (n = 37 and 38.9% of all cultures).

Each group received similar initial maintenance doses of vancomycin (mean dose 57.5 vs 55.7 mg/kg/day, p = 0.736). This initial dose was deemed appropriate based upon the indication for treatment in 78.1% of loading dose subjects and 81.7% of conventional dosing subjects (p = 0.4215). The mean loading dose used was 23.4 mg/kg (median 24.4 mg/kg; IQR 20.0 mg/kg to 25.0 mg/kg). Troughs were collected a mean of 0.37 hours prior to the next dose (median 0.3 hours; IQR 0.1 to 0.6 hours for the cohort as a whole). There was no difference between the timing of trough collection between groups (0.36 vs 0.36 hours, p = 0.490). There were no significant differences in the frequency of dosing, indication for vancomycin treatment, or organism isolated between groups.

Subjects receiving a loading dose demonstrated higher mean initial trough values (13.0 vs 9.2 mg/dL, p < 0.0001) and were more likely to achieve a target initial trough (37.0% vs 10.4%, p = 0.0001) (Table 2). A significantly higher percentage of subjects who received a loading dose attained an initial trough of >10 mg/dL (64.4% vs 32.9%, p < 0.0001) and were more likely to have no troughs of <10 mg/dL during their hospital stay (57.5% vs 29.3%, p = 0.0002). Furthermore, the loading dose arm was more likely to achieve a target trough at some point during therapy (52.1% vs 32.9%, p = 0.0081). Subjects receiving a loading dose achieved a target trough significantly more quickly than did those not receiving a loading dose (mean 41.1 vs 58.8 hours, p = 0.0118). These patients also required lower maintenance doses to reach a target trough (mean dose 58.9 mg/kg vs 66.6 mg/kg, p = 0.0672), although this measure did not reach statistical significance. Subjects in the loading dose group were also less likely to require an increase in the initial dose of vancomycin (41.1% vs 57.1%, p = 0.0249).

To attempt to account for the age difference between the groups, we created a logistic regression model to

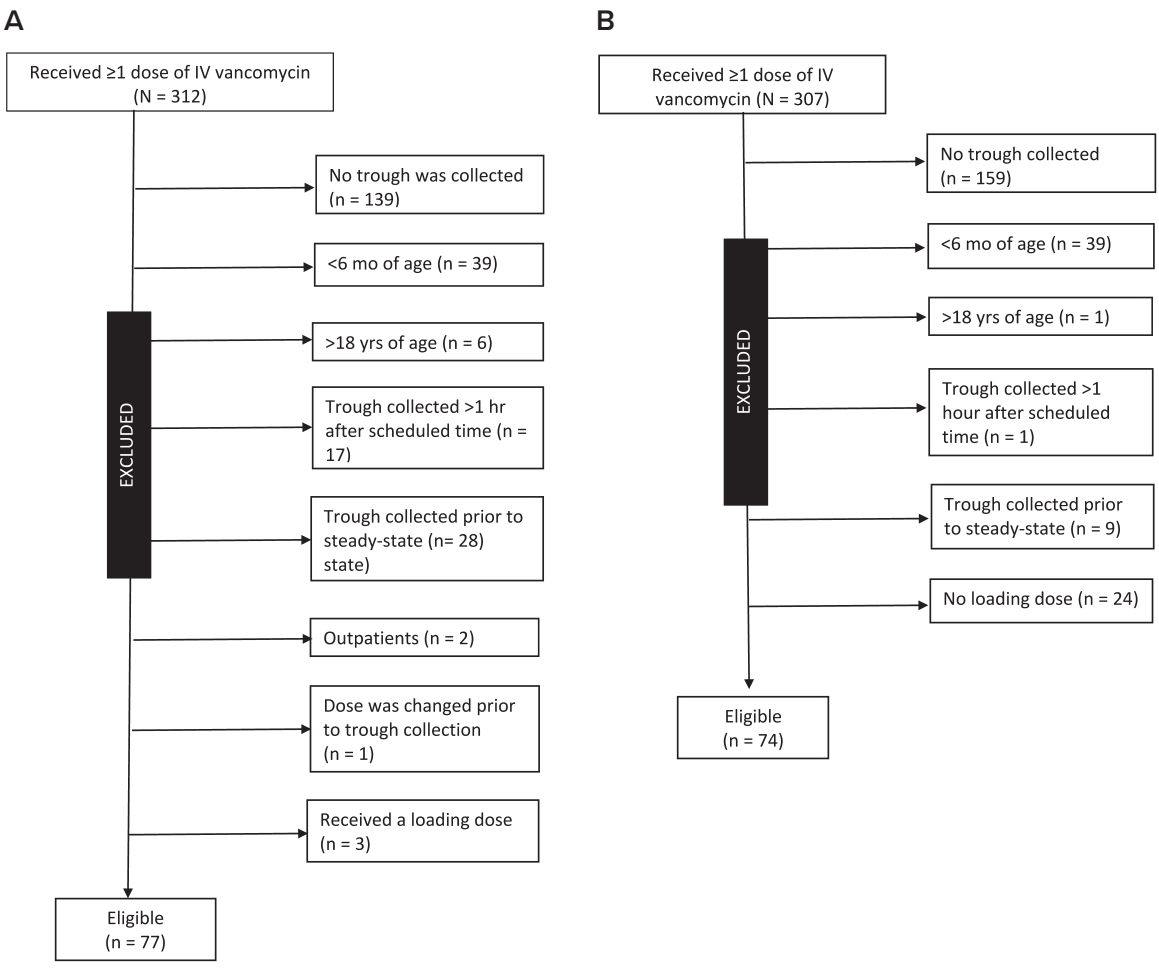

Figure. Flowchart of eligible subjects: standard dosing cohort (A); loading dose cohort (B).

control for the effect of age on our primary outcome, attainment of an initial target trough. In this model use of a loading dose was still significantly associated with the likelihood of attaining an initial target trough after controlling for age (OR = 1.14, 95% CI 1.06–1.23, p = 0.0027).

To account for the effect of potential dosing irregularities, we separately analyzed those subjects who only received appropriate dosing of vancomycin (for the stated indication). Differences persisted between the loading dose and the control groups for mean first trough value (13.2 vs 8.9 mg/dL, respectively, p < 0.0001), frequency of initial target trough attainment (36.8% vs 9.0%, p = 0.0001), and frequency of an initial trough of >10 mg/dL (66.7% vs 28.4%, p < 0.0001), although not for time to target trough attainment (42.6 vs 53.6 hours, p = 0.0839).

The percentage of subjects with creatinine elevation (6.1% in the non–loading dose group vs 2.7% in the loading dose group, p = 0.4073) or oliguria at the end of therapy (2.4% in the non–loading dose group vs 5.5% in the loading dose group, p = 0.3584) was not significantly different between groups, nor was the mean number of troughs collected per subject (1.8 in the non–loading dose group vs 2.3 in the loading dose group, p = 0.0799) (Table 2).

Supratherapeutic troughs (>20 mg/dL) were rare and not significantly different between the non–loading dose and loading dose cohorts (3.9% vs 8.2%, respectively, p = 0.136). There was no significant difference in the duration of vancomycin therapy between the non–loading dose and the loading dose groups (79.9 hours vs 80.1 hours, respectively, p = 0.4940) or in the length of hospital stay (22.3 days vs 25.5 days, respectively, p = 0.3292).

Discussion

We found that hospitalized children who received a vancomycin loading dose were significantly more likely

Table 1. Demographic Characterization of the Study Cohort

Variable	Standard Dose Cohort	Loading Dose Cohort	p value
Enrolled	77	74	—
Age, yr			
Mean	5.2	9.1	<0.0001
Median	3.9	10	
IQR	1.7–7.3	3.9–13.4	
Sex, n (%)			0.0208
Male	44 (57.1)	30 (40.5)	
Female	33 (42.9)	44 (59.5)	
Race, n (%)			0.7210
White	48 (62.3)	50 (67.6)	
Native American	26 (33.8)	13 (17.6)	
Pacific Islander	1 (1.3)	1 (1.4)	
No answer	2 (2.6)	10 (13.5)	
Ethnicity, n (%)			0.5680
Hispanic	37 (48.1)	40 (54.1)	
Not Hispanic	39 (50.7)	30 (40.5)	
No answer	1 (1.3)	4 (5.4)	
Medical comorbidities	57 (74.0)	48 (64.9)	0.5940
ICU admission, n (%)	26 (33.8)	25 (34.3)	0.4755

to attain an initial target trough concentration and to do so more quickly than were those who did not, without any increase in nephrotoxicity. In addition, even those children not attaining initial target trough concentrations were significantly more likely to obtain a higher initial trough concentration, to attain a target trough at some point during therapy, and to reach a trough of at least 10 mg/dL. Therefore, given the prevalent use of trough concentrations for therapeutic drug monitoring in children receiving vancomycin, and the fact that subtherapeutic vancomycin troughs have been associated with poor outcomes in children,[16,19] the use of pediatric vancomycin loading doses should be considered for further study.

It should be noted, however, that even with the added benefit of a loading dose, the overall attainment of initial target trough values was still not ideal in our cohort (37.0%). This may argue for higher loading doses (e.g., 25–30 mg/kg, as has been described in adults) or higher maintenance doses following a load.[22] Concerns of nephrotoxicity with higher doses of vancomycin are less of a concern in children, in whom vancomycin-induced nephrotoxicity appears more common in the setting of coadministration with other nephrotoxic agents and/or in the setting of a severe underlying illness.[34–36]

The clinical significance of vancomycin trough values is still unclear, however, with conflicting reports in the literature[16,20,21] regarding the association between subtherapeutic trough values and poor outcomes in children. The specific trough values required for optimal outcomes are also not well validated and likely vary by pathogen and site of infection, among other factors.[3,16,20] Although trough concentrations are routinely used to aid in clinical decision making, there is evidence[37,38] that trough concentrations may not reflect meaningful clinical endpoints as effectively as do other potential markers, such as the AUC/MIC. The AUC/MIC is of unproven value in children, although more study is required to better assess associations with clinical outcomes and the ability to use this parameter with only one blood measurement.[7,32] While a consensus review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists suggests a trough of 15 to 20 mg/dL is likely necessary to reach a therapeutic AUC/MIC of >400 mg*hr/L ,[3] these data are based on adult populations, and this assumption may not be applicable to pediatric patients. Regen et al[32] found a poor correlation between vancomycin trough concentrations and estimated AUC_{24}/MIC ratios using 2 different methodologies (R^2 = 0.32 and 0.22) in a study of 65 children with MRSA bacteremia. Nonetheless, the efficacy of loading doses in children should be evaluated with different pharmacokinetic and pharmacodynamic outcomes, including the AUC/MIC.

However appealing the idea of a loading dose may

Table 2. Primary Clinical Outcomes Between Non–Loading Dose and Loading Dose Groups

Variable	Standard Dose Cohort	Loading Dose Cohort	p value
Initial trough, mean, mg/dL	9.2	13.0	<0.0001
Therapeutic initial trough, %	10.4	37.0	<0.0001
No troughs <10 mg/dL, %	29.3	57.5	0.0002
Initial trough >10 mg/dL, %	32.9	64.4	<0.0001
Time to therapeutic trough, hr	58.8	41.1	0.0118
Therapeutic trough at some point during therapy, %	32.9	52.1	0.0081
Elevated EOT creatinine, %	6.1	2.7	0.4073
Oliguria at EOT, %	2.4	5.5	0.3584
Length of hospital stay, days	22.3	25.5	0.3292
Duration of vancomycin use, hr	79.9	80.1	0.4940

EOT, end of therapy

be, alternative strategies for optimizing antibiotic use in children with severe Gram-positive infections should be pursued. For example, alternative dosing strategies for vancomycin (such as the use of continuous infusions) are promising approaches. Continuous infusion of vancomycin was shown[39] to be superior to intermittent dosing in a randomized controlled trial of 111 infants under the age of 3 months (85% target trough attainment in the continuous infusion group vs 41% in the intermittent dosing group, $p < 0.001$) and required fewer dosage adjustments and a lower mean daily dose and demonstrated a favorable safety profile. The use of a continuous infusion of vancomycin was recently shown[40] to be an effective tool for achieving goal trough values in a retrospective study of 240 older children as well. This modality is also associated with less nephrotoxicity and a more rapid time to attainment of a therapeutic concentration in adults.[40–42] Continuous infusions do present some limitations in children, however, as reliance on one venous access point for the infusion may impair the ability to administer other medications, particularly those that may interact with vancomycin. Continued study of alternative agents to vancomycin (e.g., those with a more favorable adverse effect profile and no need for serum drug monitoring) should be pursued. Ceftaroline, daptomycin, and dalbavancin are all relatively new agents with comparable coverage to vancomycin with expanding clinical data in children.[43–46] Lastly, continued emphasis on antimicrobial stewardship would likely de-emphasize the need for vancomycin in many patients, thereby eliminating concerns of dosing in at least a subset of children.

Our study has several strengths. To our knowledge, it involves the largest cohort evaluating a loading dose of vancomycin in children, and it also includes one of the most diverse cohorts. We enrolled 39 Native American children (representing 25.8% of the entire cohort), thus capturing a group typically not well described in pediatric pharmacological studies. The study has several limitations as well. Most notable is its lack of randomization, which may have led to imbalances in potential prognostic factors. Indeed, the mean age of children receiving a loading dose (2018–2019 enrollment) was significantly higher than the mean age of those in the conventional dosing arm (2015 enrollment). However, those subjects excluded from the loading dose cohort for lack of a loading dose were also significantly older than subjects in the control cohort, suggesting that the overall age of subjects receiving vancomycin at our institution may have increased. Between 2015 and 2018, a new antimicrobial stewardship program was instituted, which may have decreased the use of vancomycin in younger subjects. As a result, our results may not be generalizable to younger patients. This is of particular importance given that younger patients may be less likely to achieve target trough concentrations with standard dosing.[15,40] However, after controlling for age in our regression model, the use of a loading dose was still significantly associated with attainment of an initial target trough concentration. The difference in body weights between the 2 groups was likely related to the aforementioned age differences. Other limitations of this study include the retrospective design (which limited our ability to collect data on variables not captured in the medical record, such as the rationale for not providing a loading dose), a small sample size, and single-center enrollment. We were also unable to analyze outcomes by diagnosis (e.g., MRSA bacteremia), given the small numbers of specific diagnoses in each group. Further investigation of loading doses with prospective randomized controlled trials and larger sample sizes are warranted, as are studies of loading doses correlated to potentially better markers of clinical outcomes (e.g., AUC/MIC) in children.

Conclusions

The use of vancomycin loading doses in hospitalized children may improve the ability to rapidly achieve

target trough concentrations without a corresponding risk of nephrotoxicity. Despite this, however, the majority of subjects receiving vancomycin loading doses still demonstrated subtherapeutic trough concentrations. Additional prospective study is required to assess the effect of loading doses on newer parameters, such as the AUC/MIC, and to further validate and optimize vancomycin loading doses in children of varying ages, racial groups, and in various clinical settings.

ARTICLE INFORMATION

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