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ORIGINAL RESEARCH ARTICLE

Impact of the Implementation of a Vancomycin Protocol on Trough Serum Vancomycin Concentrations in a Pediatric Intensive Care Unit

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Abstract

Background Vancomycin is an antibiotic that is widely used in pediatric intensive care, but the safe and effective use of this drug is challenging.

Objective This study aimed to assess the impact of a vancomycin protocol on trough serum concentrations.

Methods We conducted a retrospective quasiexperimental study in patients aged ≤ 18 years in intensive care who received vancomycin for at least 5 days. Patients were divided into two groups: before and after a protocol implemented in 2017 that suggested an initial vancomycin dose of 60 mg/kg/day, target serum levels of 15–20 µg/mL, and dose adjustments. We compared patient characteristics, target serum level achievement, and vancomycin levels over time.

Results Each group contained 65 patients; most were male infants with heart disease as the main reason for hospitalization. Only 29.2% of the patients had pretreatment cultures for bacteria identification recorded, with 1.5% identified as methicillin-resistant *Staphylococcus aureus*. For the first serum levels, 10.8% of patients in the pre-protocol group and 21.5% in the post-protocol group achieved the 15–20 µg/mL target ($p = 0.153$); during the first 5 days of treatment, this proportion significantly increased from 52.3 to 73.8% ($p = 0.018$). We observed a difference between the first and fifth levels: 8.9 µg/mL (95% confidence interval [CI] − 3.1 to 21) pre-protocol and 0.4 µg/mL (95% CI − 6.1 to 6.9) post-protocol ($p = 0.175$).

Conclusions Reaching adequate trough vancomycin concentrations in critically ill pediatric patients remains a challenge, and clinical practice protocols allow better dose adjustment and control even when monitoring technologies are unavailable.

Key Points

Vancomycin is an antibiotic commonly used in critically ill children.

It is well-established that reaching trough serum concentrations of vancomycin is difficult.

Clinical practice protocols can optimize the use of vancomycin in the absence of Bayesian software.

1 Introduction

Vancomycin is the mainstay of the treatment of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA). The relationship between the area under the total drug exposure curve (AUC) and the minimum inhibitory

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concentration (MIC) for a microorganism best predicts vancomycin activity, and the AUC/MIC ratio must reach a minimum value of 400 mg·h/L to ensure effectiveness in the treatment of severe MRSA infections [1]. Therefore, AUC-guided therapeutic monitoring of vancomycin, preferably with Bayesian estimation, is recommended for all pediatric age groups, based on developmental changes of vancomycin clearance documented from the newborn to the adolescent [2].

However, in the majority of clinical services in Brazil, routine calculation of the AUC/MIC ratio is not possible, so the most accurate and practical way to guide vancomycin dosages on a daily basis is to use trough serum vancomycin concentrations. Based on the latest practice guideline, minimum vancomycin concentrations of 15–20 µg/mL were required to effectively treat severe infections and are also an accepted target for the pediatric population [3]. Despite this, recent data suggest, by Bayesian estimation, that trough serum concentrations around 10 µg/mL correlate to AUC > 400 mg·h/L [4].

Even though international guidelines for the safe use of vancomycin in adults and children exist [3, 5], significant deviations from these guidelines and inconsistent dosing practices still occur, and subtherapeutic initial doses and long delays in reaching therapeutic levels remain frequent. For many prescribers, the fear of causing kidney injury overrides the concern of underdosing patients [6].

Geerlof and Boucher [7] evaluated vancomycin doses and serum levels in pediatric patients and found vast differences in all age groups. Initial vancomycin doses ranged from 19.5 to 82 mg/kg per day, and minimum initial concentrations ranged from 1.2 to 34.8 µg/mL. Similarly, Miloslavsky et al. [6] described significant heterogeneity in prescribed doses and intervals, with a general trend for higher total daily doses, resulting in higher average minimum concentrations. However, few studies have evaluated doses and serum levels in the context of the use of guidelines in the treatment of pediatric patients.

We conducted this study to evaluate the impact of a vancomycin protocol on trough serum vancomycin concentrations. Our main objectives were to compare the prevalence of serum levels within the therapeutic target of 15–20 µg/mL at first dose and over the first 5 days of treatment, as well as the time required to reach a therapeutic level, between two distinct periods: before and after the introduction of the protocol.

2 Methods

This was a retrospective quasiexperimental study in patients admitted to the pediatric intensive care unit (PICU) of Hospital da Criança Santo Antônio in Porto Alegre, Brazil. This is a quaternary hospital with 40 PICU beds that provides care for patients aged ≤ 18 years with highly complex pathologies, including congenital heart disease and organ transplants.

In July 2017, a vancomycin protocol was established based on the most recent evidence and according to the reality of the service. Before implementation of this protocol, dose adjustments were defined by staff. The protocol suggested an initial vancomycin dose of 15 mg/kg every 6 h, except in cases of probable sepsis with *S. aureus* (documented skin lesion or blood cultures with bacterioscopic indication of gram-positive cocci in clusters), which required a dose of 20 mg/kg every 6 h. Adjustment of initial doses could be necessary in premature newborns or patients starting treatment with an altered glomerular filtration rate. The target serum concentration for severe infections was defined as 15–20 µg/mL, collected no later than 1 h before the fourth dose. Daily monitoring was indicated for patients in the PICU. In case of supra or subtherapeutic levels at the first measurement, subsequent doses were adjusted according to hospital protocol to reach the target serum level (available in electronic supplementary material 1).

The study evaluated patients in two distinct phases: before and after protocol implementation. We defined the samples by convenience, and patients were selected consecutively from 1 January 2016 (for pre-protocol analysis) and from 1 January 2018 (for post-protocol analysis) until 65 patients were included in each group. The number of patients was determined through sample calculation according to Miloslavsky et al. [6] to find a reduction in the time needed to reach a therapeutic serum vancomycin level from 2.78 to 1.56 days before and after intervention, respectively, with 90% power and 5% significance (minimum of 28 patients in each group). We also sought an increase in the percentage of patients with adequate serum levels in the first measurement from 6.1 to 20.9%, with 80% power and 5% significance (minimum of 65 patients in each group).

We included patients aged ≤18 years who first received vancomycin in the PICU and whose treatment lasted for at least 5 days (to ensure treatment rather than prophylactic use). Patients with cystic fibrosis who received aminoglycosides along with vancomycin and those for whom data were incomplete, which would compromise our analysis, were excluded.

To assess renal function, creatinine clearance was estimated using the Schwartz formula (height in cm × K/serum creatinine, where $K = 0.413$) before treatment with vancomycin and was compared with the estimated creatinine clearance immediately after the antibiotic cycle. After calculation, we classified our results according to the "pediatric risk, injury, failure, loss, end-stage renal disease" criteria for kidney injury or failure [8].

2.1 Statistical Analysis

We expressed continuous variables as medians and interquartile ranges (IQRs). Categorical variables were reported as absolute frequencies and percentages. We used the Shapiro–Wilk normality test for continuous variables. We compared continuous variables of the two periods (2016 and 2018) using the Mann–Whitney test and categorical variables using the χ^2 test.

The first five trough vancomycin concentrations collected during treatment were analyzed according to the service protocol (first assessment of minimum serum concentration collected up to 1 h before the fourth dose and evaluation of dose adjustments collected up to 1 h before the fourth adjusted dose).

We applied the generalized estimation equation model with Bonferroni adjustment to assess the behavior of serum levels over time in each period. Given the asymmetry of serum vancomycin levels, we used the gamma model. A Kaplan–Meier curve was constructed for each group to assess the probability of reaching target concentration; curves were compared using the log-rank test.

Data were analyzed using SPSS software, version 25.0.

This study was approved by the Ethics and Research Committee of Hospital da Criança Santo Antônio (no. 2971369).

3 Results

The study included 130 patients (65 each in the 2016 and 2018 groups) and a total of 657 trough vancomycin concentration results (280 and 377 measurements in the 2016 and 2018 groups, respectively). Of the 104 initially eligible patients in 2016, we excluded 34 because they received vancomycin for < 5 days, three because data were missing that would have compromised the analysis, one because they received concomitant treatment with an aminoglycoside, and one with cystic fibrosis. Of the 128 initially eligible patients in 2018, we excluded 59 because they received vancomycin for < 5 days, one because data were missing that would have compromised the analysis, and three because they received concomitant treatment with an aminoglycoside.

The characteristics of both groups were comparable, with a predominance of infants and boys (see Table 1). The most common reason for hospitalization was cardiac disease. At least one microorganism was identified in 38/130 patients (29.2%), and the remaining cases were characterized by empirical treatment. Among the identified bacteria, only one case in each group (5.3% of the 38 bacteria identified in both groups) was MRSA. Most sources of infection in both groups were respiratory, followed by bloodstream infections.

The height of 117/130 patients was available for this study. The height of the other 13 patients was estimated using the following regression analysis: height = 48.61 + 2.516 × weight, since weight was strongly correlated with height ($r = 0.97$, $p < 0.001$). Serum creatinine levels were available for 51/65 and 47/65 patients in the 2016 and 2018 groups, respectively, so estimated creatinine clearance was calculated for only 98 of the 130 patients included in this survey.

In the 51 patients analyzed in the pre-protocol group, four (7.8%) developed renal injury and 13 (25.5%) developed renal failure. In the 47 patients analyzed in the post-protocol group, three (6.4%) developed renal injury and eight (17%) developed renal failure. The difference between the groups was not statistically significant: $p = 0.71$ and $p = 0.41$ for renal injury and failure, respectively. Among the 65 patients analyzed in each group, 13.8% of those in the pre-protocol group and 12.3% in the post-protocol group required renal replacement therapy ($p = 1.00$). Of those who required renal replacement therapy, peritoneal dialysis was the method of choice in 88.2% of cases, followed by continuous veno-venous hemodiafiltration (11.8%).

The proportion of patients who reached the target serum level during the first 5 days of treatment significantly increased from 34/65 patients (52.3%) in the pre-protocol group to 48/65 patients (73.8%) in the post-protocol group ($p = 0.018$). Patients with initial trough vancomycin concentrations between 15 and 20 µg/mL totaled 10.8% in the pre-protocol group and 21.5% in the post-protocol group ($p = 0.153$).

The median time to reach a therapeutic serum level of 15–20 µg/mL was 2 days in both groups (IQR, pre-protocol 2.0–4.5 and post-protocol 1.0–4.2; $p = 0.98$).

The behavior of the first five serum vancomycin levels of each patient was analyzed using a generalized estimation equation. Serum levels behaved similarly between groups ($p = 0.561$). We observed a smaller oscillation between assessments in the year after protocol implementation when compared with the pre-protocol group, with a difference between the first and fifth levels of 8.9 µg/mL (95% confidence interval [CI] − 3.1 to 21) in the pre-protocol group and 0.4 µg/mL (95% CI − 6.1 to 6.9) in the post-protocol group ($p = 0.175$) (Table 2, Fig. 1).

A Kaplan–Meier curve was used to assess the probability of reaching the target serum level in each evaluated year; results were compared using the log-rank test, and no statistically significant difference was observed between curves ($p = 0.364$) (Fig. 2).

Table 1 Characteristics of patients in the pre- and post-protocol groups

Characteristics	Pre-protocol, 2016 ($N = 65$)	Post-protocol, 2018 ($N = 65$)	*p*-value
Age, months, median (IQR)	7 (1.5–21.5)	9 (3–31)	0.57[a]
Sex, n (%)			0.10[b]
Male	34 (52.3)	44 (67.7)	
Female	31 (47.7)	21 (32.3)	
Weight, kg, median (IQR)	6.5 (3.6–9.5)	6.8 (3.7–12.7)	0.65[a]
Length of stay, days, median (IQR)	16 (9.5–35)	19 (9–35.5)	0.53[a]
Duration of therapy, days, median (IQR)	9 (7.0–1.0)	10 (7–11.5)	0.67[a]
PIM-2, median (IQR)	4.5 (1.5–8.6)	6.6 (2.8–10.8)	0.17[a]
Cause of PICU admission, n (%)			
Cardiac disease	34 (52.3)	48 (7.8)	
Respiratory disease	8 (12.3)	2 (3.1)	
Neurologic disease	2 (3.11)	7 (10.8)	
Infectious disease	6 (9.2)	3 (4.6)	
Organ transplant	4 (6.2)	1 (1.5)	
Oncological disease	3 (4.6)	1 (1.5)	
Noncardiac surgery	6 (9.2)	2 (3.1)	
Gastrointestinal/liver disease	2 (3.1)	0 (0)	
Others	0 (0)	1 (1.5)	
Renal replacement therapy, n (%)	9 (13.8)	8 (12.3)	1.00[b]
Bacterial culture identification, n (%)	22 (33.8)	16 (24.6)	0.33[b]
MRSA	1 (1.5)	1 (1.5)	1.00[b]
Outcome, n (%)			0.23[b]
Discharge	46 (70.8)	52 (80)	
Death	19 (29.2)	12 (18.5)	
Hospital transfer	0 (0)	1 (1.5)	

IQR interquartile range, *MRSA* methicillin-resistant *Staphylococcus aureus*, *PICU* pediatric intensive care unit, *PIM-2* pediatric index of mortality

[a]Mann–Whitney test

[b]χ^2 test

Table 2 Assessment of trough vancomycin concentration over time in the pre- and post-protocol groups

Variables	Pre-protocol, 2016[a]	Post-protocol, 2018[a]	Variation[b]	*p*-Value	Interaction effect (*p*)
Trough concentration					0.561
1st evaluation	18.1 ± 1.3 ($n = 65$)	21.1 ± 2.0 ($n = 65$)	− 3.0 (− 7.6 to 1.7)	0.208	
2nd evaluation	20.5 ± 1.5 ($n = 62$)	22.4 ± 1.3 ($n = 64$)	− 1.9 (− 5.8 to 2.0)	0.344	
3rd evaluation	18.1 ± 1.1 ($n = 57$)	21.8 ± 2.3 ($n = 60$)	− 3.6 (− 8.6 to 1.3)	0.153	
4th evaluation	17.2 ± 1.3 ($n = 37$)	19.9 ± 1.9 ($n = 53$)	− 2.7 (− 7.1 to 1.7)	0.223	
5th evaluation	27.1 ± 5.9 ($n = 24$)	21.5 ± 2.4 ($n = 43$)	5.6 (− 6.9 to 18.0)	0.383	
Variation (1st–5th) 95% CI	8.9 (− 3.1 to 21.0)	0.4 (− 6.1 to 6.9)	–	0.175	

CI confidence interval

[a]Data are presented as mean (μg/mL) ± standard error unless otherwise indicated

[b]Data in parentheses are 95% confidence interval

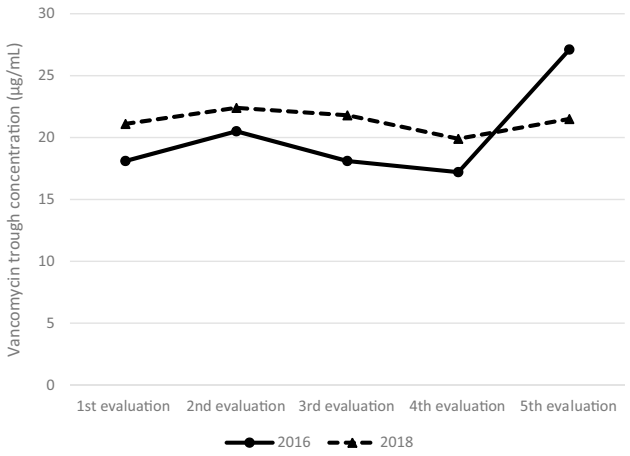
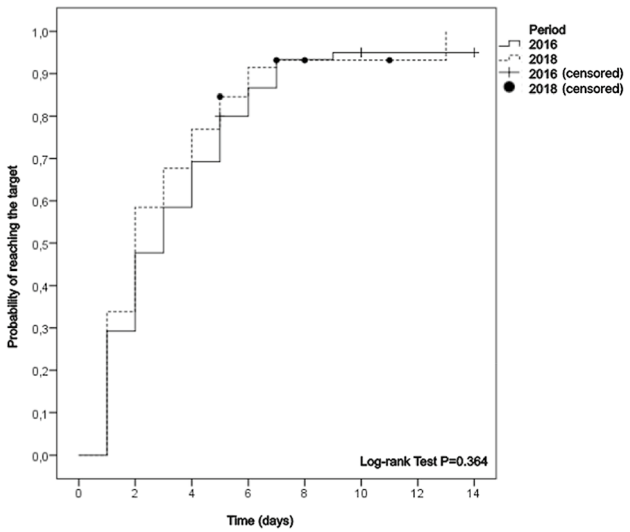


Fig. 1 Trough vancomycin concentration over time in the pre- and post-protocol groups (evaluated in 2016 and 2018, respectively)



Year		Probability of reaching the target (%)							
	Evaluation	1st	2nd	3rd	4th	5th	8th	10th	15th
2016		29.2	47.7	58.5	69.2	80.0	93.3	95.0	95.0
2018		33.8	58.5	67.7	76.9	84.6	93.2	93.2	100

Fig. 2 Probability of reaching the target serum vancomycin level in 2016 and 2018

4 Discussion

Our study found an increase in the number of patients with serum vancomycin levels within the target range during the first 5 days of treatment: 52.3% in the pre-protocol group and 73.8% in the post-protocol group ($p = 0.018$). However, no significant difference was observed between the number of patients who achieved the target levels in the first assessment in the pre- and post-protocol groups (10.8 vs. 21.5%; $p = 0.153$). In an initiative to improve the quality of care, Miloslavsky et al. [6] also reported a significant increase (from 6.1 to 20.9%; $p = 0.03$) in the proportion of patients with an initial minimum therapeutic serum concentration when comparing groups pre- and post-intervention. However, there was no significant improvement in the number of patients who achieved therapeutic serum levels throughout the treatment (36.7 vs. 46.3%; $p = 0.4$) [6].

Even with the substantial improvement in results after institution of the vancomycin protocol, the percentages of target serum concentrations remained suboptimal, reaffirming the difficulty of achieving adequate serum levels with the established initial doses (as previously revealed by other studies [6, 9–13]). Moreover, although the use of serum concentrations to monitor the use of vancomycin is practical and quick, it is not ideal. The pharmacodynamic characteristics of vancomycin mean its effectiveness is best predicted using the AUC/MIC ratio. The AUC estimate can be calculated using pharmacokinetic equations (requires the determination of at least two vancomycin levels and is a static estimate of the AUC) or, preferably, using Bayesian software (requires software purchase and additional training). The latter has multiple advantages because age, weight, renal function, and vancomycin clearance can be incorporated into the calculation of the initial dose and adjustments [2, 14]. A recent retrospective cohort study illustrated this challenge, with two-thirds of vancomycin trough concentrations outside the target range in pediatric patients in critical care, confirming the importance of validating model-based dosing advice at the bedside to enable early optimization of treatment [15, 16].

When analyzing the behavior of the first five vancomycin assessments for each patient in our study, both groups behaved similarly. However, greater stability between levels was observed in the post-protocol assessments, with a variation of only 0.4 µg/mL between the first and fifth measurements, compared with 8.9 µg/mL in the pre-protocol group ($p = 0.175$). Despite the well-established initial dose guidelines, the literature contains no description of the ideal method for performing vancomycin dose adjustments in case of off-target levels without the use of software. Therefore, our protocol included a flowchart of dose adjustments according to vancomycin levels based on experience in our service; this was probably the reason for the greater stability between measurements. It is known that the adoption of clinical practice guidelines results in significant short-term improvements in the standardization and monitoring of vancomycin doses, improving the team's adherence to international and national guidelines [17].

Although our sample included patients who underwent prolonged treatment with several measurements of vancomycin serum levels, only the first five measurements were analyzed to reduce the amount of missing data since all patients included in this study had at least 5 days of vancomycin treatment.

Vancomycin-related kidney injury is a concern. Several definitions of vancomycin-associated acute kidney injury are described in the literature; the most widely used is an increase in serum creatinine of > 0.5 mg/dL, a 50% increase from baseline in two or three consecutive daily measurements, or a 50% reduction in creatinine clearance from baseline on 2 consecutive days in the absence of any other defined reason [2, 5]. We did not calculate vancomycin-related renal injury using the available criteria because daily serum creatinine data were not available for all patients included in this retrospective study. Therefore, we calculated estimated creatinine clearance before and after the vancomycin treatment cycle.

The incidence of vancomycin-related renal injury varies in the literature. Van Hal et al. [18] conducted a meta-analysis and found rates of 5–43%. Pediatric studies show smaller variations, with an incidence of 11–19% [19–21]. The incidence of renal injury and renal failure after vancomycin treatment observed in both our groups was within the range described in the literature (33.3 and 23.4% in the 2016 and 2018 groups, respectively). However, this comparison should be interpreted with caution because the criteria we used differed from that in the literature. The retrospective design of our study meant we were unable to assess the recovery of renal function in these patients as data were lacking in the medical records. The literature indicates that vancomycin-induced nephrotoxicity is reversible in the vast majority of cases [18, 19, 22, 23].

It is important to note that, for 70% of the patients undergoing treatment with vancomycin in our sample, bacteria were not isolated in the cultures collected at the beginning of treatment; among those with positive cultures, only one MRSA strain was isolated in each group. In a Brazilian surveillance study, *S. aureus* was the main agent of bloodstream infections and skin and soft tissue infections (20.2 and 28.1%, respectively) and the second most common agent in pneumonia in hospitalized patients (24.9%). Approximately 30% of these *S. aureus* strains were resistant to methicillin [24]. However, in a study performed in the southern region of Brazil, the rates of MRSA isolation were between 4 and 8% of all *S. aureus* isolates and less than 2% for nosocomial isolates [25]. Thus, the actual need for the extensive use of vancomycin in empirical treatment of sepsis is questionable, and our data indicate overuse of this antibiotic.

Our study has limitations due to its retrospective design. The use of data from electronic records that were not specifically registered for a research application resulted in a significant percentage of missing data (e.g., the serum creatinine used to calculate vancomycin-related renal injury according to available criteria). Furthermore, this was a single-center study with a predominance of cardiac patients, limiting the generalizability of our results. We also believe that changes in the practices of vancomycin use were already being implemented before the protocol because of recent evidence on the theme, so the difference between periods was not more significant.

5 Conclusion

Reaching adequate trough vancomycin concentrations remains a challenge in critically ill pediatric patients, and the use of clinical practice guidelines and protocols can optimize results. The implementation of a vancomycin protocol made it possible to optimize serum levels within the target range quickly, safely, and cheaply, despite the unavailability of monitoring technologies.

Our results also indicate that a discussion of the excessive and prolonged use of vancomycin in empirical treatments is essential given the challenges with the use of this drug coupled with the low incidence of confirmed MRSA infections in our population.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40272-021-00445-3.

Declarations

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Conflict of interest Raíssa Queiroz Rezende, Cícero Armídio Gomes Dias, Claudia Pires Ricachinevsky, and João Paulo de Lucena Capelari have no conflicts of interest that are directly relevant to the content of this article.

Availability of data and material Not applicable.

Code availability Not applicable.

Author contributions All authors contributed to the study conception and design.

Ethics approval This study was approved by the Ethics and Research Committee of Hospital da Criança Santo Antônio under No. 2971369.

Consent to participate Not applicable.

Consent for publication Not applicable.

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