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Journal of Hospital Pharmacy and Health Services

Original Paper

Open Access

Intermittent versus continuous infusion of vancomycin in pediatrics: which is the most effective and safest option?

Beatriz Dias ANDRADE[1], Bianca SESTREN[2], Heloísa Gomm BARRETO[3], Fábio Araújo MOTTA[2], Marinei Campos RICIERI[2]

[1]Programa de Residência Multiprofissional em Saúde da Criança e do Adolescente, Faculdades Pequeno Príncipe, Paraná; [2]Programa de Gerenciamento de Antimicrobianos, Hospital Pequeno Príncipe, Paraná; [3]Farmácia Clínica, Hospital Pequeno Príncipe, Paraná.

Corresponding author: Andrade BD, bedias@id.uff.br

Submitted: 28-02-2025 Resubmitted: 16-05-2025 Accepted: 16-05-2025

Double blind peer review

Abstract

Objectives: To describe and analyze vancomycin serum levels achieved by intermittent and continuous infusion, as well as clinical and microbiological outcomes and the occurrence of adverse events in pediatric patients with probable or confirmed infections by penicillin-resistant Gram-positive bacteria. **Methods:** Quantitative, observational study with retrospective and prospective data collection conducted from August 2021 to August 2024 in a pediatric hospital. Analyzed parameters included serum levels obtained after transitioning from intermittent to continuous infusion; treatment-related nephrotoxicity; clinical and microbiological outcomes; and adverse events. **Results:** Seventy-one patients were included; most were infants (63.4%), male (61.9%), and had a neurological comorbidity (49.3%), with initiation of continuous infusion in an intensive care unit (57.7%). Most infections involved the central nervous system, and the most frequently isolated bacteria were coagulase-negative *Staphylococcus*. Median serum level during intermittent infusion was 9.4 mg/L and during continuous infusion was 17.7 mg/L (reference range: 8–25 mg/L). Vancomycin level monitoring was performed 2.6 times less often during continuous infusion. Microbiological and clinical cure was observed in 76.3% of antibiogram-guided treatments, and clinical cure in 62.2% of empirical treatments. There were no deaths or initiation of renal replacement therapy within 30 days after antibiotic completion. Nephrotoxicity was less frequent with continuous than intermittent infusion (56.3% vs. 64.8%), with a 4.86-fold higher risk of acute kidney injury during intermittent infusion, and a 1% increase in the risk of nephrotoxicity for each unit decrease in creatinine clearance. More adverse events occurred with continuous than intermittent infusion, primarily process errors. In most patients, infusion was administered via a venous access dedicated exclusively to vancomycin, and no infusion reactions were observed. **Conclusion:** The analysis indicated that continuous vancomycin infusion was an effective alternative with manageable adverse events in the study population and demonstrated a more favorable renal safety profile. However, implementation of continuous infusion requires strict adherence to institutional protocols, ongoing staff training, and process monitoring by the clinical pharmacy to minimize operational errors and ensure patient safety.

Keywords: Antimicrobial Stewardship, vancomycin, clinical pharmacy.

Infusão intermitente *versus* infusão contínua de vancomicina na pediatria: qual é a opção mais efetiva e segura?

Resumo

Objetivos: Descrever e analisar os níveis séricos de vancomicina alcançados por infusão intermitente e contínua, bem como os desfechos clínicos e microbiológicos e a ocorrência de eventos adversos em pacientes pediátricos com infecções prováveis ou confirmadas por bactérias Gram-positivas resistentes às penicilinas. **Métodos:** Estudo quantitativo, observacional, com coleta retrospectiva e prospectiva realizada entre agosto de 2021 e agosto de 2024, em um hospital pediátrico. Foram analisados os níveis séricos obtidos após a transição da infusão intermitente para contínua; a ocorrência de nefrotoxicidade relacionada ao tratamento; os desfechos clínicos e microbiológicos; e os eventos adversos. **Resultados:** Foram incluídos 71 pacientes, em sua maioria lactentes (63,4%), do sexo masculino (61,9%) e com comorbidade neurológica (49,3%), com início da infusão contínua em unidade de terapia intensiva (57,7%). A maioria das infecções acometeu o sistema nervoso central, sendo que as bactérias mais isoladas foram *Staphylococcus* coagulase negativo. A mediana dos níveis séricos foi de 9,4 mg/L na infusão intermitente e 17,7 mg/L na contínua (valor de referência: entre 8 e 25 mg/L) O número de coletas de vancocinemias foi 2,6 vezes menor durante a infusão contínua. Observou-se cura microbiológica e clínica em 76,3% dos tratamentos guiados por antibiograma, e cura clínica em 62,2% dos empíricos. Não houve óbitos nem necessidade de terapia renal substitutiva até 30 dias após o término do antibiótico. A nefrotoxicidade foi menos frequente na infusão contínua do que na intermitente (56,3% vs. 64,8%), com 4,86 vezes mais chance de desenvolvimento de injúria renal aguda na infusão intermitente, além

de aumento de 1% no risco de nefrotoxicidade para cada unidade de diminuição na depuração de creatinina. Foram registrados mais eventos adversos durante a infusão contínua, principalmente relacionados a erros de processo. Na maioria dos pacientes, observou-se o uso de acesso venoso exclusivo para a vancomicina e ausência de reações infusionais. **Conclusão:** A análise conduzida indicou que a vancomicina em infusão contínua foi uma alternativa eficaz e com eventos adversos manejáveis na população investigada, além de apresentar um perfil de segurança renal mais favorável. Por outro lado, a implementação da infusão contínua requer a adoção rigorosa de protocolos institucionais, capacitação contínua da equipe e monitoramento do processo pela farmácia clínica, a fim de minimizar erros operacionais e garantir a segurança do paciente.

Palavras-chave: gestão de antimicrobianos, vancomicina, farmácia clínica.

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Introduction

Vancomycin is a broad-spectrum antimicrobial agent used in the empirical or targeted treatment of infections caused by penicillin-resistant species of *Staphylococcus*, *Streptococcus*, and *Enterococcus*[1].

The 2020 guidelines for therapeutic drug monitoring of vancomycin recommend calculating the area under the concentration-time curve (AUC_{0-24h}) as the main pharmacokinetic/pharmacodynamic (PK/PD) parameter associated with the drug's efficacy outcomes. The target AUC is 400–600 mg·h/L for the treatment of serious infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), assuming a minimum inhibitory concentration (MIC) of 1 mg/L[2]. Although prospective data in pediatrics are scarce, the same AUC PK/PD target has been suggested for children, including neonates[2].

Monitoring based solely on trough levels (C_{trough}), as previously recommended in the 2009 guidelines, has been discontinued due to its association with an increased risk of nephrotoxicity and the lack of robust evidence for efficacy[3]. That approach recommended achieving trough levels of 15–20 mg/L as a requirement to reach AUC/MIC values of 400–600 mg·h/L, with serum level collection typically performed before the 4th or 8th dose in children, considering a vancomycin regimen of 60–80 mg/kg/day[3].

Studies highlight the discrepancy between (C_{trough}) and AUC estimation, indicating that relying solely on (C_{trough}) in clinical practice may lead to inappropriate dose adjustments[4]. In pediatrics, underexposure rates of up to 75.0% have been observed with intermittent infusion, increasing the risk of therapeutic failure and bacterial selective pressure[5]. On the other hand, although data are still limited, dose adjustment based on AUC has shown microbiological cure and clinical improvement in children[6].

In this context, Cojutti & Pea (2025) emphasized the "urgent" need to adopt alternative strategies for monitoring vancomycin serum levels. Continuous infusion (CI), characterized by administering the total daily dose over 24 hours, emerges as a viable approach to overcome this limitation. Steady-state serum levels correlate directly with the area under the curve (AUC) and can be estimated simply by multiplying the value by the 24-hour interval[2]. In Brazil, where many institutions face resource constraints, continuous infusion represents a feasible alternative for therapeutic drug monitoring in the absence of specialized software[2,5].

Additionally, continuous infusion is associated with a faster achievement of therapeutic concentrations, reduced serum level fluctuations, and a lower risk of acute kidney injury (AKI), as it helps avoid AUC values exceeding 600 mg·h/L, which are linked to nephrotoxicity[2,8]. Other benefits of CI include a reduction in the total daily dose, the need for only one blood sample (as AUC estimation via (C_{trough}) requires two), and a lower incidence of infusion-related reactions[9,10]. Beyond these operational advantages, CI has also been associated with improved clinical outcomes, such as in the treatment of coagulase-negative *Staphylococcus* bacteremia in neonates[11]. These benefits have also been observed in pediatric and neonatal onco-hematological populations[12-14].

The lack of real-world studies on the use of continuous infusion vancomycin in pediatric populations, especially in the Brazilian context, highlights the need to systematize clinical and operational data on this therapeutic strategy. Including pediatric patients across varying levels of care — from intensive care units to general wards — allows for the generation of relevant information on both the safety of the process and the optimization of clinical outcomes.

In this regard, the present study aims to describe and analyze vancomycin serum levels obtained through intermittent and continuous administration, as well as to assess clinical and microbiological outcomes and the occurrence of adverse events in pediatric patients with suspected or confirmed infections caused by penicillin-resistant Gram-positive bacteria.

Methods

This is a quantitative, observational study based on data obtained from electronic medical records and the laboratory information system of pediatric patients aged 0 to 18 years.

The study was conducted at a pediatric-only hospital in the state of Paraná, Brazil, with 369 beds — 76 of which belong to the Intensive Care Unit (ICU), including cardiac, neonatal, surgical, and general ICUs. It is a philanthropic, high-complexity institution, with 60% of care provided through the Brazilian Unified Health System (SUS).

The study population consisted of inpatients in wards and ICUs who received vancomycin via continuous infusion, preceded by intermittent infusion. Patients were identified through a report of once-daily vancomycin dispensing, provided by the hospital pharmacy. Retrospective data collection took place from August 2021 to January 2024, followed by prospective inclusion of patients until August of the same year.

Included in the study were patients undergoing treatment for suspected or confirmed infections caused by resistant Gram-positive bacteria, who had received vancomycin through continuous infusion, following intermittent infusion, and underwent serum monitoring through vancomycin levels.

Excluded from the study were patients undergoing dialysis; extracorporeal circulation or renal replacement therapies; those who used vancomycin for less than 48 hours; or those who did not undergo vancomycin serum level monitoring.

Collected data included clinical and demographic information, vancomycin infusion regimen details, clinical and microbiological outcomes (clinical failure, clinical cure, and microbiological cure), adverse events related to antibiotic use, and serum creatinine levels before, during, and after treatment.

Clinical failure was defined as death resulting from the infection, worsening or lack of improvement in clinical and laboratory parameters, or bacterial growth in follow-up cultures. Clinical cure was defined as the resolution of signs and symptoms associated with infection and normalization of laboratory tests in the absence of microbiological cultures. Microbiological cure was defined as negative microbiological cultures during infection control while on active antibiotic therapy[17].

Nephrotoxicity was assessed according to KDIGO (Kidney Disease: Improving Global Outcomes) criteria, based on increases in serum creatinine of ≥ 0.3 mg/dL or 1.5–2.0 times the baseline value (Stage 1); 2–3 times the baseline value (Stage 2); or ≥ 3 times the baseline, serum creatinine ≥ 4.0 mg/dL, or the need for renal replacement therapy (Stage 3). Renal creatinine clearance was calculated using the Schwartz formula. Baseline serum creatinine was defined as the lowest value obtained during hospitalization, in order to minimize the influence of elevated values due to dehydration or sepsis

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prior to starting antibiotic therapy[19,21,22]. Acute kidney injury (AKI) was attributed to vancomycin based on the temporal relationship between the start of therapy and the peak serum creatinine value.

The Common Terminology Criteria for Adverse Events (CTCAE) methodology was used to categorize adverse events. Infusion reactions were classified into five grades, in ascending order of severity: grade 1 (infusion does not need to be stopped); grade 2 (pause in infusion and response to symptomatic treatment); grade 3 (longer-lasting and recurrent reactions); grade 4 (serious consequences requiring intervention); and grade 5 (death). Infectious enterocolitis included >3 episodes of diarrhea in 24 hours, moderate abdominal pain, and oral treatment (grade 2); need for intravenous treatment, invasive interventions, and systemic signs such as hypovolemia and fever (grade 3); serious consequences requiring intervention (grade 4); or death (grade 5).

Descriptive analysis was performed on clinical and demographic data using mean, median, standard deviation, interquartile range, and absolute frequencies. Continuous variables were tested for normality (Shapiro–Wilk, α=0.05) and variance homogeneity (Levene, α=0.05). For normally distributed data with homogeneous variances ($p > 0.05$), Student's t-test was applied for independent samples. When assumptions were not met (Shapiro–Wilk $p < 0.05$), Mann–Whitney U test (for two groups), Wilcoxon Rank-Sum (for paired samples), or Kruskal–Wallis test (for more than two groups) were used. Logistic regression analysis was conducted to identify factors associated with outcomes. The predictive accuracy of the model was evaluated using the Receiver Operating Characteristic (ROC) curve. A 95% confidence interval was adopted, and p-values < 0.05 were considered statistically significant. All analyses were performed using IBM SPSS Statistics software, version 20.

The study was approved by the Research Ethics Committee of Faculdades Pequeno Príncipe, CAAE number: 75306123.4.0000.5580, and was conducted in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. Informed consent or assent was obtained from prospectively included patients.

Results

A total of 71 patients were included, corresponding to 75 anti-infective treatments administered during the study period (Table 1). Most patients (93.4%; n = 70) were transitioned from intermittent to continuous vancomycin infusion due to failure to reach therapeutic serum levels or pharmacokinetic/pharmacodynamic targets, according to institutional protocols.

During continuous infusion, the majority of patients were infants (63.4%; n = 45), male (61.9%; n = 44), and had neurological comorbidities (49.3%; n = 37), with most being hospitalized in pediatric intensive care units (57.7%; n = 41).

The main infectious foci were the central nervous system (56.1%; n = 42) and the respiratory system (17.3%; n = 13). All patients initially received vancomycin via intermittent infusion, with a mean initial dose of 56.8 mg/kg/day and a final dose of 66 mg/kg/day, representing a 16.2% increase. Infusions were administered over 60 minutes.

For intermittent infusion, serum levels were collected up to 30 minutes before the next dose; for continuous infusion, levels were measured at any time after 24 hours of initiation, preferably from a venous access different from the one used for antibiotic infusion.

Continuous infusion was initiated without a loading dose, with a mean initial dose of 63 mg/kg/day and a final dose of 61.8 mg/kg/day, representing a slight reduction of 1.9%. After switching to continuous infusion, 80.3% (n = 57) of patients reached the therapeutic target with the first steady-state serum level measurement. The median serum level during intermittent infusion was 9.4 mg/L (interquartile range: 6.5–13.4 mg/L), while during continuous infusion it was 17.7 mg/L (14.3–20.6 mg/L), a statistically significant difference ($p < 0.001$).

Table 1. Characteristics of patients included in the study (Paraná, 2021–2024)

Age Group (n=71 patients)	N (%)
Neonatal (0 to 28 days)	5.0 (7.0)
Infant (29 days to 2 years)	45.0 (63.4)
Preschool (3 to 5 years)	7.0 (9.9)
School-age (6 to 11 years)	10.0 (14.1)
Adolescent (12 to 18 years)	4.0 (5.6)
Sex	**N (%)**
Male	44.0 (61.9)
Body Weight (kilograms)	**Median (Interquartile Range)**
	8.0 (2.0-62.0)
Hospital Unit at the Start of Continuous Infusion	**N (%)**
Pediatric Intensive Care Unit	41.0 (57.7)
Pediatric Ward	30.0 (42.3)
Clinical Variables	
Underlying Disease[1]	**N (%)**
Neurological	37.0 (49.3)
Cardiological	6.0 (8.0)
Other Diseases	11.0 (14.7)
No Underlying Disease	21.0 (28.0)
Infection Site[1]	**N (%)**
Central Nervous System	42.0 (56.1)
Pulmonary	13.0 (17.3)
Bloodstream	10.0 (13.3)
Skin and Soft Tissue	7.0 (9.3)
Bone	2.0 (2.7)
Cardiovascular	1.0 (1.3)
Concomitant Treatment with Nephrotoxic Drugs	**N (%)**
Loop diuretics, aminoglycosides, amphotericin B, or piperacillin-tazobactam	24.0 (33.8)
Justification for Transition to Continuous Infusion[1]	**N (%)**
Failure to achieve therapeutic or target serum levels	70.0 (93.4)
Not reported in the electronic medical record	4.0 (5.3)
Laboratory deterioration	1.0 (1.3)

[1]Some patients included in the study had more than one comorbidity and/or infection site.

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Microorganisms were isolated in 58.6% (n = 44) of the treatments included in the analysis. Gram-positive bacteria were isolated in 50.6% (n = 38) of the cases, with coagulase-negative staphylococci being the main pathogens identified (Table 2). In 94.7% of the treatments, vancomycin therapy was initiated after microorganism identification and susceptibility testing results were available.

Area under the curve (AUC) values were calculated for the 38 guided treatments, based on the minimum inhibitory concentration (MIC) values for vancomycin provided in the antibiograms. In the absence of reported MIC values, a standard value of 1 was adopted by convention (Table 2).

Table 2. Microbiological Test Results (Paraná, 2021–2024)

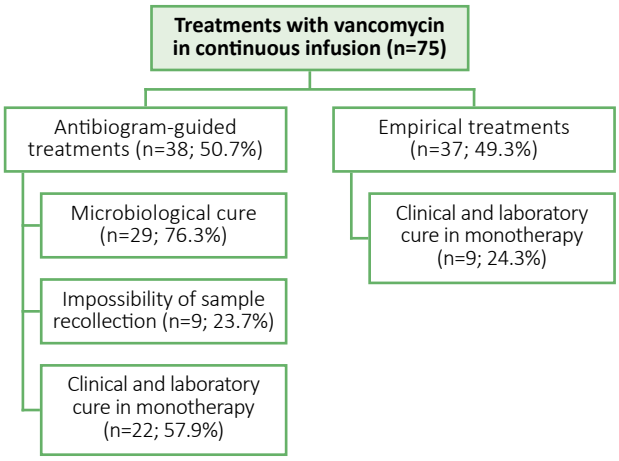
Bacterium Isolated from Biological Samples	N (%)
Coagulase-negative *Staphylococcus*	22 (57.9)
Streptococcus pneumoniae	4 (10.5)
Staphylococcus aureus	4 (10.5)
Streptococcus intermedius	3 (7.9)
Streptococcus mitis	2 (5.3)
Enterococcus faecalis	2 (5.3)
Enterococcus faecium	1 (2.6)
Infection Site with Isolated Microorganisms	**N (%)**
Central Nervous System	18 (47.4)
Bloodstream	10 (26.3)
Pulmonary	5 (13.1)
Skin and Soft Tissue	3 (7.9)
Bone	2 (5.3)
Susceptibility Profile of Isolated Microorganisms	**N (% of the species)**
Streptococcus mitis resistant to penicillins	1 (100)
Coagulase-negative *Staphylococcus* resistant to oxacillin	20 (90.9)
Methicillin-resistant *Staphylococcus aureus* (MRSA)	4 (80.0)
Streptococcus pneumoniae resistant to penicillins	1 (25)
Vancomycin Minimum Inhibitory Concentration (mg/L)	**Mean (SD)**
Staphylococcus aureus (n=4)	1 (0)
Coagulase-negative *Staphylococcus* (n=22)	1.3 (0.5)
Enterococcus spp. (n=3)	0.8 (0.3)
Streptococcus spp. (n=9)	1 (0)
Calculation of the Area Under the Curve to Minimum Inhibitory Concentration Ratio in Continuous Infusion	**Median (IQR)**
Staphylococcus aureus (n=4)	344.4 (292.8-454.8)
Coagulase-negative *Staphylococcus* (n=22)	386.4 (277.2-484.8)
Enterococcus spp. (n=3)	428.4 (379.8-661.2)
Streptococcus spp. (n=9)	444.0 (370.2-527.4)

Clinical and microbiological cure was analyzed for the 75 treatments included in this study (Figure 1). Among these, 50.7% (n = 38) were guided by antibiogram; of these, 76.3% (n = 29) achieved both microbiological and clinical cure, with vancomycin used in monotherapy in 75.9% (n = 22) of the cases.

Microbiological cure could not be assessed in 23.7% (n = 9) of the guided infections due to the inability to recollect samples for follow-up cultures. Clinical failure was observed in 13.2% (n = 5) of the treatments, and in 10.5% (n = 4) clinical outcomes could not be assessed due to changes in the therapeutic regimen (e.g., loss of venous access or serum levels above the target).

Clinical outcomes were analyzed in 37 empirical treatments, of which 62.2% (n = 23) resulted in clinical cure. Notably, only 24.3% (n = 9) of these patients received vancomycin in monotherapy. The antimicrobials most frequently used in combination were meropenem and cefepime.

Figure 1. Clinical outcomes of infections treated with continuous vancomycin infusion (Paraná, 2021–2024)



A total of 189 vancomycin serum level tests were analyzed during intermittent infusion (mean of 2.7 per patient), and 336 during continuous infusion (mean of 4.7 per patient). Values were normalized to account for differences in treatment duration. The median was 0.25 serum levels per patient/day in continuous infusion and 0.64 in intermittent infusion (Mann–Whitney U test, $p < 0.001$).

During intermittent infusion, 64.8% (n = 46) of patients presented with some degree of acute kidney injury (AKI). During continuous infusion, AKI was observed in 56.3% (n = 40), of which 80.0% (n = 32) had already developed AKI during intermittent infusion. According to the KDIGO classification applied to continuous infusion, 50.0% (n = 23) of the patients were in stage 2, and 37.0% (n = 17) in stage 3 (Table 3). No patients receiving continuous infusion required renal replacement therapy.

A statistically significant difference was observed between baseline and peak serum creatinine values during treatment in patients classified as stage 0 (no AKI), stage 2, and stage 3 ($p < 0.001$), indicating a significant change in creatinine levels during continuous vancomycin infusion. However, there was no linear increase proportional to the severity of kidney injury stages.

Binary logistic regression was performed to assess the association between creatinine clearance and the occurrence of AKI during continuous infusion. It was found that for each unit decrease in creatinine clearance, the likelihood of developing AKI increased by approximately 1.0% ($p = 0.01$).

On the other hand, the receiver operating characteristic (ROC) curve showed an area under the curve of 0.26, indicating low predictive accuracy of isolated creatinine clearance for detecting AKI in this context. Therefore, it was not possible to define a creatinine clearance threshold value with reliable predictive value for AKI. Additionally, patients receiving intermittent infusion had 4.86 times higher odds of developing AKI compared to those on continuous infusion (OR: 4.86; p = 0.002; 95% CI: 1.7–13.9).

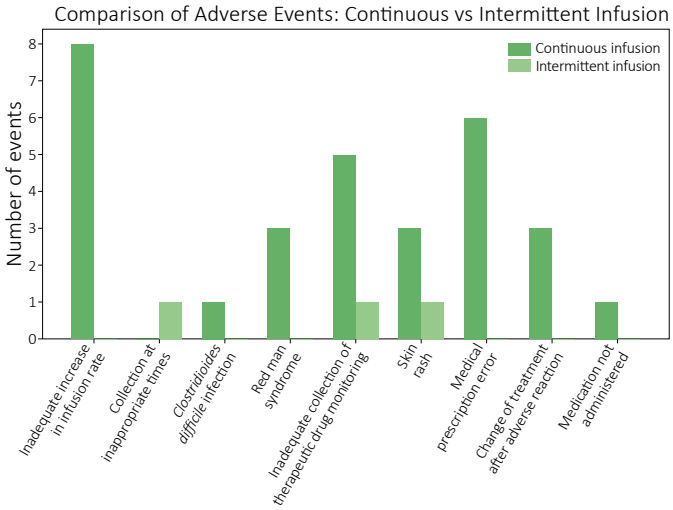
Regarding infusion-related reactions, three cases of skin rash and three cases of red man syndrome were recorded, all classified as grade 2 and related to inadequate infusion rates. Management consisted of administering antihistamines and corticosteroids, followed by resuming the infusion at the recommended rate.

There were also five incidents of blood collection for vancomycin levels from the same line used for infusion, six medical prescription errors, and one administration error. These events were mitigated through educational interventions by the clinical pharmacy team. In addition, one case of grade 2 infectious enterocolitis was documented, which was treated with oral metronidazole.

In the intermittent infusion group, one case of grade 2 skin rash, one case of blood sampling from the same infusion line, and one case of inappropriate timing for serum level monitoring were reported (Figure 2). No patients experienced long-term consequences after management of these adverse events in either infusion regimen.

The safety of continuous vancomycin infusion was also assessed through medication compatibility analysis on the first day of infusion. All patients had central venous access: 63 with a central venous catheter (CVC) and 12 with a peripherally inserted central catheter (PICC).

Figure 2. Adverse events during vancomycin infusion (Paraná, 2021–2024)



It was observed that 59 infusions (78.7%) were administered through a dedicated line without concurrent administration of other medications. Conversely, 16 infusions (21.3%) occurred through shared lines, with 13 involving medications deemed compatible according to the technical prescription review.

In the three cases where vancomycin was administered simultaneously with incompatible medications, temporary interruption of the infusion was necessary to administer the other drugs. All such incompatibility events occurred in patients admitted to Intensive Care Units.

Table 3. Analysis of nephrotoxicity during continuous infusion (Paraná, 2021–2024)

	Intermittent Infusion				Continuous Infusion		
Variable (n=71)	No AKI (n=25)	Stage I (n=7)	Stage II (n=32)	Stage III (n=7)	No AKI (n=31)	Stage II (n=23)	Stage III (n=17)
Male sex, n (%)	14 (56.0)	4 (57.1)	21 (65.6)	3 (42.9)	18 (58.1)	16 (69.6)	8 (29.4)
Age (months), median (IQR)	8 (4.0-22.0)	51 (7.0-138.0)	13 (4.0-64.0)	11 (1.0-47.0)	10 (5.0-85.0)	8 (1.0-19.0)	27 (11.0-50.0)
Weight, median (IQR)	13.9 (4.1-29.0)	15 (9.2-18.8)	9 (4.8-19.4)	5.7 (3.5-19.5)	15.9 (5.6-54.0)	5.3 (4.0-11.0)	14 (7.9-19.3)
ICU admission, n (%)	12 (48.0)	5 (71.4)	25 (78.1)	2 (28.6)	15 (48.4)	17 (73.9)	9 (52.9)
Baseline serum creatinine (mg/dL), median (IQR)	0.1 (0.1-0.1)	0.2 (0.2-0.2)	0.1 (0.1-0.2)	0.2 (0.1-0.3)	0.10 (0.10-0.20)	0.10 (0.10-0.10)	0.20 (0.10-0.20)
Maximum serum creatinine (mg/dL), median (IQR)	0.1 (0.1-0.2)	0.3 (0.3-0.3)	0.2 (0.2-0.2)	0.3 (0.3-0.4)	0.20 (0.20-0.30)	0.20 (0.20-0.20)	0.30 (0.30-0.40)
Creatinine clearance (mL/min/1.73 m²)[1], mean (SD)[2]	264.1 (99.8)	138.9 (45.3)	217.5 (115.6)	89.1 (16.1)	253.7 (129.8)	178.0 (81.9)	172.1 (90.8)
Daily vancomycin dose (mg), median (IQR)	456 (294.0-985.0)	1050 (592.0-1680.0)	528 (276.0-930.0)	456 (262.5-1560.0)	578.0 (475.5-1.260.0)	424.0 (280.0-780.0)	772.0 (568.0-1.029.0)
Vancomycin dose (mg/kg/day), median (IQR)	60 (60.0-80.0)	75 (70-80)	65 (60-80)	75 (70-80)	65.0 (60.0-75.0)	65.0 (60.0-70.0)	60.0 (47.5-70.0)
Duration of vancomycin treatment (days), median (IQR)	4 (3.0-5.0)	6 (4.0-9.0)	4 (3.0-8.0)	8 (5-19)	15.0 (9.0-18.0)	11.0 (7.0-27.0)	16.0 (12.0-22.0)
Concomitant use of other nephrotoxic drugs, n (%)	7 (28.0)	0 (0.0)	13 (40.6)	4 (57.1)	10.0 (32.3)	5.0 (21.7)	5.0 (29.4)
AUC values in continuous infusion, median (IQR)	NA	NA	NA	NA	408.0 (358.8-466.8)	405.6 (338.4-492.0)	421.2 (400.8-480.0)

[1]p-value <0.05 when comparing groups. [2]23 patients were excluded from the analysis due to insufficient data. NA: Not applicable.

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Discussion

The 2020 guideline on vancomycin therapeutic drug monitoring marked a paradigm shift, replacing traditional trough level monitoring with the estimation of the area under the curve/minimum inhibitory concentration (AUC/MIC) ratio. This new approach is supported by robust evidence demonstrating the superiority of AUC/MIC as a predictor of therapeutic efficacy and safety, particularly in the adult population.

In continuous vancomycin infusion, once steady-state is achieved, serum level collection enables AUC calculation, allowing for more precise dose adjustments and reduced risk of nephrotoxicity in pediatric patients — benefits that were also observed in the present study[2,16]. This strategy represents a significant advance in pharmacotherapy, aligning with clinical demands for individualized treatment and mitigation of adverse events.

Vancomycin is preferably administered via continuous infusion as it maintains serum concentrations above the MIC 100% of the time, thereby optimizing its time-dependent effect[16]. The present study demonstrated higher median serum vancomycin levels in the continuous regimen compared to the intermittent one (17.7 mg/L vs. 9.4 mg/L, respectively). This finding aligns with studies showing a higher frequency of achieving therapeutic target levels with continuous infusion than with intermittent administration[18].

On the other hand, no significantly lower doses were observed in the continuous infusion group, which contrasts with studies reporting reductions of up to 32 mg/kg/day with this method of administration[9]. This divergence may be related to the greater infusion safety and lower nephrotoxicity associated with continuous infusion, as observed in our institution, potentially giving physicians more confidence to maintain higher doses even when serum levels exceeded 15 mg/L or MICs were <1 mg/L.

Furthermore, most infections treated in this study were focused on the central nervous system (CNS), a condition that justifies higher AUC targets due to vancomycin's hydrophilic nature and high molecular weight. Consistent with the literature, coagulase-negative *Staphylococcus* species resistant to penicillins were the most prevalent pathogens (52.6% of isolates), often implicated in neonatal infections. However, their significance in deep-seated infections remains controversial, especially when isolated only in blood cultures from long-term catheter devices[15].

Given the clinical severity of most patients, continuous infusion allowed faster attainment of target serum levels, enabled early adjustments in the 20% of patients who did not reach the target in the first vancomycin level, and ensured more stable serum concentrations. These findings support the favorable clinical profile of the continuous modality and corroborate its previously described benefits[2].

Nephrotoxicity associated with continuous infusion was lower than that observed in the intermittent regimen (56.3% vs. 64.8%, respectively). Among patients with AKI during continuous infusion, univariate analysis did not show a statistical association between AKI and the concomitant use of nephrotoxic medications. However, greater concomitant use of such medications was identified during the intermittent infusion. It is important to note, as a limitation, that some patients had already developed AKI prior to initiating continuous infusion.

Binary logistic regression analysis showed that reduced creatinine clearance was associated with an increased risk of AKI in both infusion regimens. However, the ROC curve had low predictive accuracy, making it impossible to define a reliable clearance threshold as a marker of AKI during continuous vancomycin use.

Conversely, the odds ratio—indicating a 4.86 times greater likelihood of developing AKI with intermittent infusion compared to continuous infusion—reinforces previous findings in both adult and pediatric populations, which point to continuous infusion as a regimen associated with lower nephrotoxicity[15].

The findings of this study could theoretically support a reduction in the frequency of serum creatinine testing during continuous infusion. However, creatinine is a marker with low sensitivity and a delayed response to kidney injury, especially in pediatric patients, whose muscle mass and glomerular filtration rate vary widely[23]. For earlier and more accurate assessment of renal function, validated biomarkers such as cystatin C and neutrophil gelatinase-associated lipocalin (NGAL) would be desirable, as they show promise in the early detection of tubular injury in neonates and children[24,25]. Moreover, the monitoring strategy should take into account individual risk factors (such as age, concomitant use of other nephrotoxic drugs, prior renal dysfunction, etc.) in order to optimize laboratory resource use and maximize treatment safety with vancomycin[26].

Continuous vancomycin infusion in pediatrics offers additional advantages, including once-daily dosing, fewer blood sample collections, and the ability to calculate AUC using simple rule-of-three equations. This method facilitates subsequent dose adjustment, maintaining the AUC/MIC parameter as a recognized predictor of improved clinical outcomes. In this context, a 2.6-fold reduction in vancomycin level requests per treatment day was observed in the continuous infusion group. However, this number could be further reduced through ongoing nursing education, since one of the main barriers to proper vancomycin level collection in this regimen is the possibility of drawing blood from the same intravenous line used for infusion. If done during administration, this can result in inaccurate levels that are often interpreted as toxic.

No statistically significant differences were found in the median AUC values between patients with and without acute kidney injury (AKI) during continuous infusion, supporting the hypothesis that serum concentrations of the antibiotic are not, by themselves, predictive of nephrotoxicity[18]. However, patients in this study presented other clinical conditions associated with AKI, such as admission to intensive care units (ICUs) and concomitant use of nephrotoxic drugs.

Previous pediatric studies have pointed to the unavailability of intravenous access for the administration of other medications as a limitation of continuous infusion[19,20]. In our cohort, most patients (78.7%, n = 59) were able to maintain a dedicated line for vancomycin administration. For the 13 patients who did not have exclusive access, Y-site compatibility analyses showed that vancomycin was compatible with the other prescribed drugs.

However, in three prescriptions for patients admitted to pediatric ICUs, incompatibilities between vancomycin and other medications were identified, requiring temporary interruption of the continuous infusion for administration of the other drugs. This practice may increase the risk of adverse events such as delays in reinfusion, therapeutic failure, and selection of resistant microorganisms. These findings underscore the importance of implementing a rigorous institutional protocol for vancomycin continuous infusion, preferably ensuring a dedicated intravenous line or, alternatively, the support of a clinical pharmacist to assess compatibility and infusion safety.

During the study, continuous infusion was associated with a higher frequency of adverse events compared to intermittent infusion, mainly related to process errors, such as unintended increases in infusion rate and resulting infusion-related reactions. A greater absolute number of inadequate vancomycin level collections was also observed during continuous infusion, due to use of incorrect lines or inappropriate timing.

To mitigate these events, it is recommended that periodic training sessions be conducted for medical and nursing staff, given the high turnover of professionals and the relative unfamiliarity with continuous vancomycin infusion techniques. Additionally, the clinical pharmacy team plays a critical role in guiding prescriptions and ensuring appropriate serum level requests, as a safety strategy and to rationalize the use of resources.

Due to its design, this study presents several limitations. Renal function analysis was based on the lowest serum creatinine level during vancomycin treatment, which may overestimate the diagnosis of AKI. Moreover, serum creatinine is a recognized limited marker—especially in pediatric populations—due to its low sensitivity and variability according to age and muscle mass. More accurate markers, such as cystatin C and NGAL, were not available at the institution. Furthermore, the study included patients from a single institution, predominantly neonates and onco-hematologic patients, limiting the generalizability of the findings to the broader pediatric population, which presents distinct pharmacokinetic characteristics. Additional confounding factors include concomitant use of nephrotoxic drugs and potential errors or omissions in the reviewed medical records. Given these limitations, prospective and randomized studies with larger and more representative pediatric samples are recommended to robustly compare both infusion regimens and validate the potential benefits of continuous vancomycin infusion.

Conclusion

The analysis conducted indicates that continuous vancomycin infusion constitutes an effective therapeutic alternative, with a more favorable renal safety profile compared to intermittent infusion, and manageable adverse events in the pediatric population evaluated. However, its successful implementation depends on the adoption of standardized institutional protocols, ongoing training of the involved multidisciplinary teams, and systematic monitoring by the clinical pharmacy team in order to reduce operational errors and ensure the safety and effectiveness of treatment.

Funding sources

This research received no specific funding for its development.

Contributors

BDA and MCR designed the research project, interpreted the data and results. BS, MCR, FAM, and HBG critically reviewed the manuscript, and BDA was responsible for writing. All authors approved the submitted version for publication.

Conflict of interest statement

The authors declare no conflicts of interest.

JHPHS
Journal of Hospital Pharmacy and Health Services

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