ORIGINAL ARTICLE
ARTIGO ORIGINAL

Risk of acute kidney injury and cost-effectiveness analysis comparing vancomycin and linezolid for the treatment of pediatric patients infected with Gram-positive bacteria

Risco de lesão renal aguda e custo-efetividade comparando vancomicina e linezolida para o tratamento de pacientes pediátricos infectados por bactérias Gram-positivas

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Keywords:
vancomycin, linezolid, acute kidney injury, cost-effectiveness evaluation, pediatric

ABSTRACT

Objective: This study aimed to compare the occurrence of acute kidney injury (AKI) in pediatric patients who used vancomycin (VAN) or linezolid (LNZ) to treat Gram-positive coccus (GPC) infections and to assess which treatment (VAN or LNZ) is the most cost-effective considering a pediatric hospital perspective. **Methods:** A retrospective cohort was performed to evaluate the occurrence of nephrotoxicity in pediatric patients without previous AKI, with GPC infections that used LNZ, or VAN monitored by serum VAN levels. Initially, descriptive analysis and Fisher and chi-square test were performed for this comparison. Then, a cost-effectiveness analysis was conducted through a decision tree model. The outcomes of interest were the rate of AKI related to the drug and the rate of admission to the intensive care unit (ICU) and cure. **Results:** In patients without previous acute kidney injury (AKI), 20% developed nephrotoxicity associated with VAN versus 9.6% in the LNZ group (p = 0.241). As there was no difference in nephrotoxicity between VAN andlinezolid (LNZ), vancomycin (VAN) monitored by serum VAN levels can optimize and rationalize the treatment. The nephrotoxicity risk criterion should not guide the prescription for LNZ. Furthermore, the average global cost of treatment with VAN was approximately R$ 43,000, while for LNZ, it was R$ 71,000. **Conclusion:** VAN was considered dominant (lower cost and greater effectiveness) over LNZ for treating patients with GPC infection.

Palavras-chave:
vancomicina, linezolida, insuficiência renal, avaliação de custo-efetividade, pediatria

RESUMO

Objetivo: Este estudo objetivou comparar a ocorrência de lesão renal aguda (LRA) em pacientes pediátricos que usaram vancomicina (VAN) ou linezolida (LNZ) para tratar infecções por cocos Gram-positivos (CGP) e avaliar qual tratamento (VAN ou LNZ) é o mais custo-efetivo considerando a perspectiva de um hospital pediátrico. **Métodos:** Foi realizada uma coorte retrospectiva para avaliar a ocorrência de nefrotoxicidade em pacientes pediátricos sem LRA prévia, com infecções por CGP que utilizaram LNZ ou VAN, combinada com vancocinemia. Para essa comparação, inicialmente foram realizados análise descritiva e testes de Fisher e qui-quadrado. Em seguida, foi realizada uma análise de custo-efetividade por meio de um modelo de árvore de decisão. Os desfechos de interesse foram a taxa de LRA relacionada ao medicamento e a taxa de internação em unidade de terapia intensiva e cura. **Resultados:** Nos pacientes sem LRA prévia, 20% deles desenvolveram nefrotoxicidade associada à VAN *versus* 9,6% no grupo LNZ (p = 0,241). Como não houve diferença na nefrotoxicidade

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entre VAN e LNZ, a VAN combinada com a vancocinemia pode otimizar e racionalizar o tratamento, e a prescrição de LNZ não deve ser guiada pelo critério de risco de nefrotoxicidade. Além disso, o custo médio global do tratamento com VAN foi de aproximadamente R$ 43.000, enquanto para LNZ foi de R$ 71.000. **Conclusão:** Assim, a VAN foi considerada dominante (menor custo e maior eficácia) sobre a LNZ para o tratamento de pacientes com infecção por CGP.

Introduction

Gram-positive coccus (GPC), mainly *Staphylococcus* sp., are responsible for serious infections in the community and hospital settings. Resistance to antibiotics by these pathogens has increased in the last decade, and the treatment of resistant bacterial strains, for example, methicillin-resistant *Staphylococcus aureus* (MRSA), represents substantial economic expenditure for the health system (Wilke *et al*., 2017).

Coagulase-negative *Staphylococcus* (CoNS) is the most frequent etiological agent (18%) for bloodstream infection (BSI), especially in the pediatric group (Wang *et al*., 2020). Among GPC, MRSA represented a 54% prevalence in hospitalized critically ill pediatric patients (Larru *et al*., 2016). Regarding MRSA, this bacterium increased by 6.9% between 2012 and 2016 USA (Anvisa, 2019).

Currently, different antimicrobials are available for the treatment of BSI. In 1958, the FDA approved the use of the glycopeptide vancomycin (VAN), and for many years, it was established as the gold standard for treating MRSA (Micek, 2007). With the emergence of VAN-resistant strains, new antibiotics such as linezolid (LNZ) and daptomycin were developed as alternatives for treating GPC (Logman *et al*., 2010).

Linezolid was released to treat pediatric GPC in 2002 (Jantausch *et al*., 2003). Since then, countless patients have been treated not only following the indications established by the FDA but also to treat bacteremia, especially for those with AKI-related risk factors or ongoing AKI (Kaplan *et al*., 2003; Moschovi *et al*., 2010; Sicard *et al*., 2020). Otherwise, daptomycin was only officially released for pediatric use in 2018, with bacteremia as a primary indication, though it had considerably higher costs than VAN.

Nephrotoxicity is one of the most reported adverse events for vancomycin. The toxicity mechanism is not fully understood, and acute kidney injury (AKI) development is contradictory (Feiten *et al*., 2019). To optimize VAN therapy and avoid AKI, monitoring the serum level of vancomycin is essential to manage the risk of nephrotoxicity. Concerning LNZ, an alternative to VAN, the use for more than 14 days may eventually cause bone marrow suppression, especially thrombocytopenia (Ikuta *et al*., 2011).

However, the clinical impact of alternative antimicrobials for treating GPC and assessing the real risk of nephrotoxicity is unclear, especially in the pediatric population, because publications in this area are very scarce (Spaulding *et al*., 2019). In addition, safety comparisons between alternative drugs for GPC treatment can benefit antimicrobial stewardship policies, thus enabling a cost-effective delivery analysis (Scheetz *et al*., 2009).

Therefore, this study aimed to compare AKI occurrence in pediatric patients who used VAN or LNZ to treat GPC infections. Furthermore, the study seeks to assess which treatment (VAN or LNZ) is the most cost-effective against GPC related to BSI from the point of view of a pediatric hospital in the southern region of Brazil.

Methods

Study design and criteria inclusion

A retrospective cohort of a pediatric population (<18 years) with bacteremia was conducted with laboratory and clinical confirmations. Clinical confirmation was established as an analysis of clinical worsening, description of sepsis or septic shock, and other laboratory worsening parameters (such as C-reactive protein). Additionally, clinical criteria helped to address cases of contamination or infection.

The study considered hospitalized patients from January 1st, 2015, to December 31st, 2018, in a pediatric hospital in the southern region of Brazil with 372 beds (60 ICUs), approximately 24,000 admissions/year, and 32 subspecialties. This study was approved by IRB (Protocol No. CAAE 53051516.2.0000.0097).

The inclusion and exclusion criteria applied to obtain the final study population are shown in Figure 1.

Sample for nephrotoxicity

The sample size was based on the occurrence of the primary outcome (nephrotoxicity) in patients exposed to VAN or LNZ. As this estimate is poorly addressed in the literature (Feiten *et al*., 2019) in terms of quality of outcomes report, AKI measurement and powered sample for the hypothesis of VAN being more nephrotoxic than LNZ, we made some assumptions based on the estimations from a systematic review (Fiorito *et al*., 2018). In this review, they found that 202/1863 (in patients with levels <15 µg/mL) had AKI; while 23/144 patients admitted to the ICU (with levels <15 µg/mL) presented AKI (11-16% = -5%, 95% CI -11 to 1.1%). Therefore, considering that most AKI related to LNZ is due to shock, we assume that the incidence of nephrotoxic events in LNZ is 5%, and that of VAN is 11%. With a 10% margin of error and 95% confidence interval in the estimates, the minimum sample size was 16 and 26, respectively, for LNZ and VAN. As the sample available was larger than this, we included 90 patients, 59 of whom were exposed to VAN and 31 to LNZ.

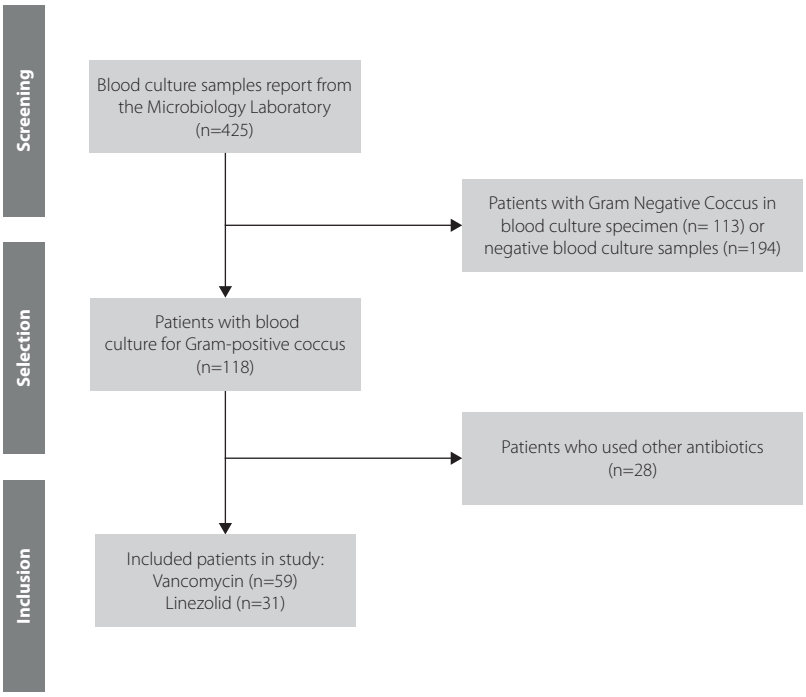


Figure 1. Flowchart of patients included according to the criteria**.**

Data extraction

For this analysis, patients with positive blood culture for GPC and who used VAN or LNZ during a treatment period longer than five days were identified (Weigelt *et al.*, 2005).

Then, the following data from the electronic medical record were collected and transcribed to Excel® (Microsoft Corp., United States): initials of the name, medical record, number of attendance, sex, age, date of birth, specialty of attendance, date of admission and date of positive blood culture, start and end date of the antibiotic used, date of hospital discharge, and laboratory results (serum levels of vancomycin, C-reactive protein and serum levels of creatinine).

Outcomes

Initially, the risk of AKI was evaluated during the treatment with VAN or LNZ. Therefore, renal function was assessed using the Acute Kidney Injury Network (AKIN) criteria. Such criteria consider among the variables an increase in serum creatinine levels (SCr), represented by SCr ≥ 0.3 $mg.dL^{-1}$ in an interval of 48 h or a 50% increase in the patient's baseline serum level over seven days (KDIGO, 2012). The cure was defined as a composite outcome of clinical, microbiological cure and mortality within 30 days from the start of treatment. Clinical cure was established as not using VAN, LNZ, or other GPC-directed antibiotics, within five days after the end of the treatment (considered failure). Additionally, no microbiological growth in blood cultures was considered a microbiological cure at the end of the treatment (Harris *et al.*, 2017).

Statistical analysis

The variables were reported with a descriptive analysis, reporting mean/median, standard deviation/interquartile (IQR), absolute counting, and percentages (%).

The comparative analysis between VAN vs. LNZ was performed using the chi-square test (x^2) and Fisher's test, considering the rejection of the null hypothesis whether $p < 0.05$.

The outcomes of clinical and microbiological cure and mortality at 30 days were plotted using the Kaplan-Meier survival curves between LNZ and VAN. Hypothesis testing (statistical difference) was made with a Log-rank test, considering not significantly $p < 0.05$.

Cost-effectiveness analysis

The cost was composed of three elements: (1) drugs, labs, and medical materials; (2) procedures; and (3) hospitalization costs (nursery or ICU). Only direct costs were included in this model. To allow a discussion with local paying sources and medical prescribers of the studied drugs, we chose to perform all cost calculations using the local currency in Brazil, the Real (R$).

Figure S1 (in supplementary material) shows the conceptual model for the microcosting technique, which considered the evolution of a BSI episode within a 30-day time horizon and included the three cost elements described above until the end of the treatment and outcome achievement (cured/uncured status). The short time horizon consisted of the

following assumptions: BSI is an acute and non-contagious disease (Bounthavong *et al.*, 2009).

Because of BSI acute clinical condition, the economic model used was the decision tree and consisted of the following mutually exclusive outcomes: AKI/non-AKI, Cure/Uncure, and ICU/non-ICU (represented in Figure 2). The result of the economic evaluation was expressed by the incremental cost-effectiveness ratio (ICER) or incremental costs for the total benefit of one patient having no acute kidney injury, not admitted to the ICU, and experiencing a clinical and microbiological cure. This composite outcome for ICER was chosen because it is of interests to patients, health care staff, and managers (payers).

Table 1. General data by treatment group

Variable	Vancomycin n = 59 (65%)	Linezolid n = 31 (35%)
Demographic characteristics		
Female	29 (49%)	10 (33%)
Male	30 (51%)	21 (68%)
Age (years)*	6 ± 6	6 ± 6
Weight (kg)*	14.88 ± 13.95	20 ± 20
Hospitalization unit		
Nursery	45 (76%)	25 (80%)
Intensive care unit (ICU)	14 (24%)	6 (19%)
Length of stay, in days *	65 ± 72	85 ± 64

Note: * mean ± standard deviation.

To assess the robustness of the model, a multivariate probabilistic sensitivity analysis (PSA) was performed using second-order Monte Carlo simulations, which considered 500 iterations varying all the probabilities and cost parameters of the model according to its 95% CI. The Monte Carlo simulation result was represented in a dispersion graph (incremental costs vs. incremental probability of cure) and acceptability curve, illustrating the likelihood of being cost-effective vs. the willingness-to-pay threshold.

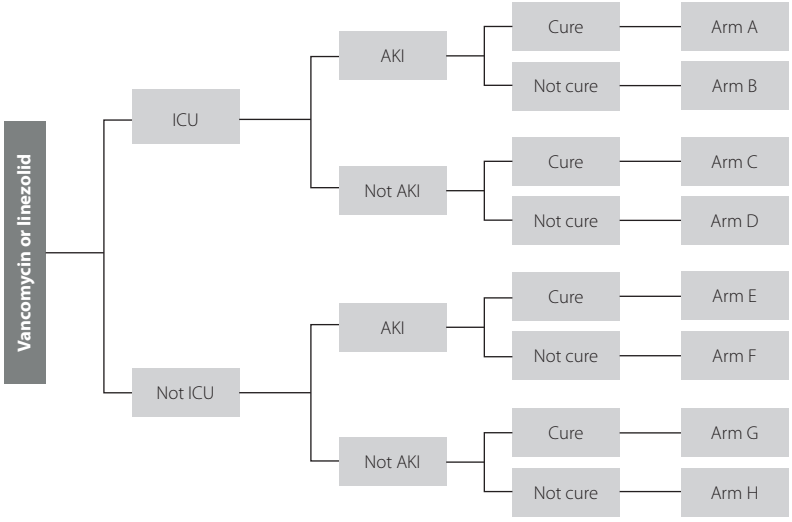
Results

For this analysis, 90 patients were included with positive blood culture and infection and treated with VAN (65%) and LNZ (35%). Different variations of demographic data are shown in Table 1.

Male patients (51%), aged six years on average, represented most patients. Patients who used LNZ (85 ± 64 days) stayed longer in the hospital than VAN-exposed patients (65 ± 72 days).

Considering the clinical findings, Table S1 (in supplementary data) shows the four isolated species of GPC in infectious blood culture, with coagulase-negative *Staphylococcus* being the most frequent pathogen (54%). *Staphylococcus aureus* was similar in both groups (p = 0.49).

Patients in the VAN group (n = 59) were treated with doses of 32-62 mg/kg/day, within the dosing schedule used and recommended by the literature (Rajon *et al.*, 2017). Of these, vancomycin serum levels during treatment days ranged from 10-16 $\mu g.mL^{-1}$.



Note: ICU, Intensive care unit; AKI, Acute Kidney Injury; **Arm A:** use of vancomycin or linezolid, ICU admission, with AKI, Cure; **Arm B:** use of vancomycin or linezolid, ICU admission, with AKI, without Cure; **Arm C:** use of vancomycin or linezolid, ICU admission, without AKI; Cure; **Arm D:** use of vancomycin or linezolid, ICU admission, without AKI, without a cure; **Arm E:** use of vancomycin or linezolid, without ICU admission, with AKI, Cure; **Arm F:** use of vancomycin or linezolid, without ICU admission, without AKI, without a cure; **Arm G:** use of vancomycin or linezolid, without ICU admission, without AKI, Cure; **Arm H:** use of vancomycin or linezolid, without ICU admission, without AKI, without a cure.

Figure 2. Decision tree model.

The primary and secondary outcomes of the study are shown in Table 2. From these data, the number of patients with AKI in the baseline (prior to treatment) was more significant in the Linezolid group (77% vs. 49%, p = 0.013). At the end of treatment with LNZ or VAN, there was no statistically significant difference in AKI between groups.

The mean initial SCr in patients using VAN was 0.40 ± 0.57 $mg.dL^{-1}$ and LNZ 1.24 ± 1.34 $mg.dL^{-1}$. At the end of the treatment, the SCr in the presence of VAN was 0.43 ± 0.68 $mg.dL^{-1}$ and LNZ 0.78 ± 0.97 $mg.dL^{-1}$, suggesting that there is a preference for prescribing LNZ to patients with high creatinine, but at the end of treatment, all patients returned to their baseline creatinine.

Among patients experiencing AKI, 1.7% required dialysis in the VAN group and 30% in the linezolid group (p = 0.0002).

More than 75% of patients treated with VAN or LNZ obtained clinical benefits (clinical/microbiological cure). However, some patients (56%) with clinical conditions were admitted to the ICU, and the proportion of these patients per treatment group is insignificant (p = 0.3711).

The analysis of the probability of survival performed by the non-parametric Kaplan-Meier method (Figure S2, in the supplementary data), indicates that patients in the LNZ group had higher survival. However, when comparing mortality rates in the period, there is no statistically significant difference between groups (Log-rank p = 0,22).

Cost-effectiveness analysis

Arm G, patients who presented cure and were not admitted to ICU and did not develop AKI, was higher in the VAN group (30.5%) than LNZ (17.2%) group (NNT = 7). VAN-exposed patients showed an average cost of R$ 43,176, while for LNZ, it was R$ 70,919. Therefore, in the base case scenario (Table 3), vancomycin was considered dominant compared to LNZ (ICER = -R$ 209,227) because VAN had lower costs and more significant clinical benefits in the study model. Furthermore, we calculated the Number Needed to Treat (NNT) of 0.305 for vancomycin and 0.172 for linezolid, considering the probability of cure and not ICU, *i.e.*, the Number Needed to Treat (NNT) is 1 in 7 patients having clinical benefits using VAN.

Stratifying the values by clinical outcome (Table S2, in supplementary material) verifies higher costs for patients who have not obtained clinical/microbiological cure. This fact is represented in Arm B, which has higher values for each treatment (VAN R$ 83,678 vs. LNZ R$ 96,956) and represents the scenario in which the patient is admitted to the ICU and develops AKI and does not achieve cure. Also, the same values can be observed for Arm E, and F of treatment with linezolid since the two clinical outcomes include patients with AKI in the same admission unit.

Regarding the probabilities of each arm, shown in Table S3, in supplementary material, the Arm E of the VAN has a greater likelihood of presenting AKI in patients who are

Table 2. Data on primary and secondary clinical outcomes

Variable	Vancomycin n = 59	Linezolid n = 31	p-value
Primary outcome			
Basal AKI	29 (49%)	24 (77%)	*0.0129*
AKI during treatment (with or without previous AKI	27 (46%)	17 (55%)	0.5070
AKI at the end of treatment	23 (39%)	18 (58%)	0.1188
AKI during treatment in patients without previous AKI	12 (20%)	3 (10%)	0.2453
Secondary outcomes			
ICU admission	31 (53%)	20 (64%)	0.3711
Microbiological and clinical cure	45 (76%)	24 (77%)	1
30-day mortality	3 (5%)	0	0.5485
Patients admitted to the ICU who were undergoing treatment	8 (27%)	8 (39%)	0.3385

Note: AKI, acute kidney injury; ICU, intensive care unit.

Table 3. Base scenario of the study

Treatment	Arm G*	Global cost	Effectiveness difference	Cost different
Vancomycin	0.30	R$ 43,176	0.13	- R$ 27,743
Linezolid	0.17	R$ 70,919	-	-
ICER	Vancomycin is dominant since it is the cheapest and most effective.			

Note: ICER, incremental cost-effectiveness ratio; Arm G, is the clinical benefit of the economic model, represented by lack of admission to the ICU, absence of acute kidney injury, and microbiological cure.

not admitted to the ICU and who have a clinical and microbiological cure (VAN 16.9% vs. LNZ 10.3%). The B arm of LNZ presents a worse clinical result and higher admission to the ICU, with AKI and no clinical and microbiological cure concerning VAN (31.7% vs. 3.4%, respectively).

A multivariate analysis was conducted to assess the robustness of the model. The simulation result is represented by the supplementary material's cost-effectiveness plan presented in Figures S3 and S4 in supplementary material. That is, it illustrates the 500 Monte Carlo iterations and reiterates that the VAN is the dominant strategy in the study (more effective and less costly, that is, all simulations remained in the right lower quadrant).

When analyzing the cost-effectiveness acceptability curve (Figure S5 in supplementary material), VAN is dominant over LNZ in all willing-to-pay thresholds.

Discussion

To our knowledge, this is the first cost-effectiveness study evaluating the treatment of bacteremia by GPC in pediatric patients. With the increasing prevalence of antimicrobial-resistant microorganisms and costs of medical care, it is essential to present cost-effectiveness studies that support the action through optimized use of antimicrobials, as in this case in which the nephrotoxicity risk can lead to excessive use of linezolid, provoking an emerging resistance in the future.

The exact mechanism of renal damage induced by vancomycin is still unknown. Still, some studies indicate the occurrence of necrosis of proximal renal tubular cells related to the accumulation of vancomycin, causing oxidative stress (Rybak *et al.*, 2009). We found no AKI differences between patients treated with either VAN or LNZ, especially in those not experiencing AKI in the baseline (before the treatment starts) ($p = 0.2453$).

We emphasize that the hypothesis that VAN is associated with a higher risk of AKI is controversial since the risk of AKI can be multifactorial and not only attributed to pharmacological treatment (Bartz *et al.*, 2014; Gómez & Kellum, 2016). The systematic review by Fiorito *et al.* (2018) suggested that admission to the ICU and use of concomitant nephrotoxic drugs play an additional role in vancomycin nephrotoxicity. Serum vancomycin levels above 15 $mg.dL^{-1}$ may also contribute to AKI worsening (Fiorito *et al.*, 2018).

Our study prescribed VAN as 43.7 ± 16.0 mg/kg/day for 11 ± 7 days. VAN levels ranged from 9.6-15.8 $\mu g.mL^{-1}$, with 3 ± 2 serum measurements per patient, like that reported by the study by Shibata *et al.* (Shibata *et al.,* 2018). That may be why our VAN group did not present so many AKI events, corroborating previous literature findings that serum levels of 10-15 $\mu g.mL^{-1}$ are associated with less AKI risk (Liu *et al.*, 2011). The mean treatment period was 12 ± 7 days, with average doses of VAN 49.8 ± 13 mg/kg/day.

For patients treated with LNZ, the average dose used was 10 mg/kg/dose for 14 ± 8 days, a dose equivalent to the study by Shibata *et al.* (Shibata *et al.*, 2018).

For clinical and microbiological cures, this study demonstrated no statistical difference between patients treated with either VAN or LNZ. These results are like the study by Wang *et al.* (2015). They reported no significant differences between patients with nosocomial pneumonia treated empirically with LNZ or VAN ($p = 0.38$) or patients with confirmed culture for *S. aureus* ($p = 0.52$) (Wang *et al.*, 2015).

Regarding cost-effectiveness analysis, VAN was dominant over LNZ (less costly and more effective). Thus, with the dominant strategy's clinical benefit, the payer stops spending R$ 209,277.00 (ICER) when choosing the VAN.

Our results contradict other cost-effectiveness studies that concluded that incorporating linezolid in the treatment was cost-effective (Bounthavong *et al.*, 2009; Daniel Mullins *et al.*, 2006; McCollum *et al.*, 2007). However, in these studies, in addition to the study population being adults, patients' hospitalization receiving vancomycin was longer than those on linezolid. Moreover, in our study, vancomycin was associated with its plasma monitoring; thus, in addition to ensuring the safety of this drug, dose adjustments were made to improve clinical results and reduce hospital stays.

Patients with no clinical/microbiological cure cost approximately thrice as much as those who are cured (approximately R$ 30,000 vs. R$ 90,000). Thus, the absence of a cure can significantly increase the average hospital stay and costs, corroborating the findings of Rubio-Terrés *et al.* (Rubio-Terrés *et al.*, 2010).

Also, patients with complications: who go to the ICU and especially those with no cure are directly related to higher costs. According to Bounthavong *et al.*, this result found that the response rate to treatment was one of the most impacted variables on incremental costs.

Considerable costs are linked to the length of stay when the patient is admitted to the ICU. It is a critical variable in analyzing economic health differences between treatments for hospitalized patients. This result is reinforced by Rubio-Terrés *et al.* (Rubio-Terrés *et al.*, 2010). They reported that the risk of ICU admission is the primary determinant of the cost difference. It represents approximately 75% of the total values (from R$ 6,917 to R$ 8,703, from R$ 9,839 to R$ 11,044).

As the limitation of the study, we can consider the study design (a retrospective cohort), where the information collected was from non-modifiable medical records; the relatively small number of patients included, and no safety outcome of VAN and LNZ treatment. Moreover, caution is needed when extrapolating the results of this cost-effectiveness model to other scenarios. Nevertheless, the model considers different probabilities for each clinical outcome (in multivariate analysis). Thus, we emphasize the internal validity of the model (clinical rationale), which is valid for any

gram-positive infections resistant to methicillin. Therefore, the economic model outlined can be helpful in future research involving the studied population.

Conclusion

In our study, no statistical difference in the occurrence of AKI was reported during the treatment with VAN or LNZ in pediatric patients without previous AKI. Regarding the economic analysis performed using the decision tree model, our results demonstrated that treatment with VAN associated with therapeutic monitoring for vancomycin has a clinical and financial advantage in treating infections by GPC. The average global cost of treatment with VAN was approximately R$ 43,000, while for LNZ, it was R$ 71,000. Therefore, VAN was considered dominant (lower cost and greater effectiveness) over LNZ for treating patients with GPC infection. Furthermore, it is essential to highlight that this study's objective is not to encourage the use of vancomycin but to rationalize the use of linezolid, considering the risk of emerging resistance to oxazolidinones in the world.

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Supplementary material

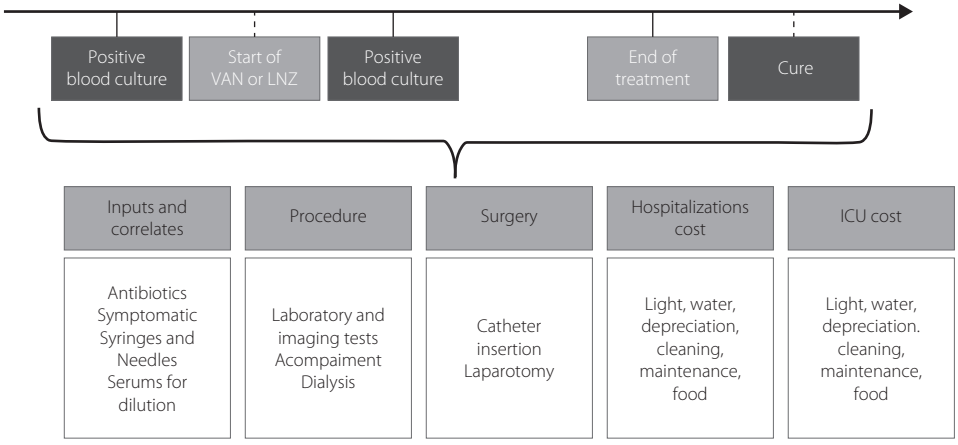

Figure S1. Conceptual model that presents the variables considered in the cost-effectiveness analysis of the treatment with vancomycin or linezolid.

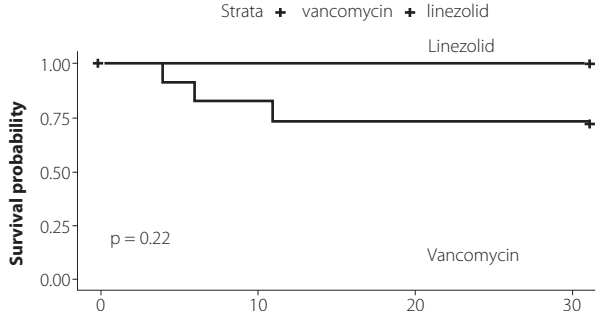

Figure S2. Survival analysis using Kaplan-Meier method.

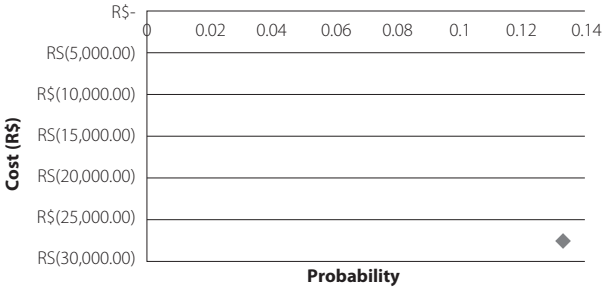

Figure S3. Cost-effectiveness plan through Monte Carlo simulation.

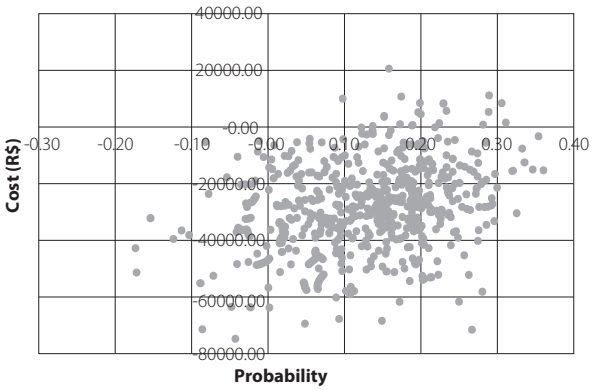

Figure S4. Cost-effectiveness plan for the dominant treatment strategy: vancomycin concentration in plasma.

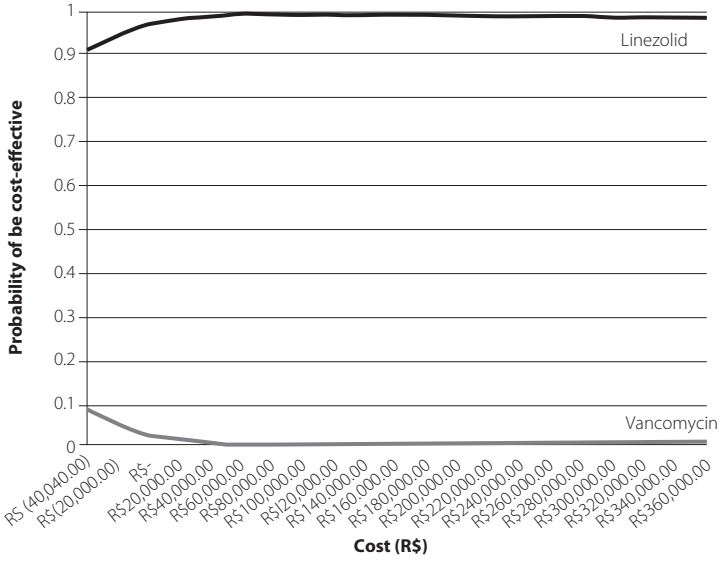

Figure S5. Cost-effectiveness acceptability curve.

Table S1. Microbiological and treatment data

	Total sample (n = 90)	Vancomycin (n = 59)	Linezolid (n = 31)
Isolates microorganisms			
Enterococcus sp.	2 (2.2%)	1 (1.7%)	1 (3.2%)
Staphylococcus aureus	34 (37.7%)	24 (40.6%)	10 (32.2%)
Staphyloccocus coagulase-negative	49 (54.4%)	30 (50.8%)	19 (61.2%)
Streptococcus sp.	5 (5.5%)	4 (6.7%)	1 (3.2%)
Treatment			
Initial dose in mg/kg/day		49.82 ± 13.87	29.36 ± 11.05
Vancomycin concentration in plasma sample		3.0 ± 2.15	
Treatment time (days)		12 ± 7.43	14 ± 7.89

Table S2. Total direct costs considering clinical outcomes (each arm)

Antibiotic	Variable	Median	Q1	Q3	Standard deviation
Vancomycin	Arm A	R$ 34,183.28	R$ 27,692.78	R$ 46,662.40	R$ 12,867.73
	Arm B	R$ 83,678.62	R$ 98,680.98	R$ 98,680.98	R$ 30,004.73
	Arm C	R$ 32,856.17	R$ 30,442.60	R$ 56,932.07	R$ 18,170.36
	Arm D	R$ 68,143.70	R$ 51,545.52	R$ 74,833.65	R$ 29,713.71
	Arm E	R$ 42,658.58	R$ 25,956.30	R$ 49,375.28	R$ 15,288.60
	Arm F	R$ 29,670.99	R$ 19,007.92	R$ 32,126.38	R$ 9,419.43
	Arm G	R$ 20,736.75	R$ 11,660.77	R$ 37,055.20	R$ 23,681.60
	Arm H	R$ 149,531.88	-	-	-
Linezolid	Arm A	R$ 24,415.80	R$ 22,232.90	R$ 76,258.41	R$ 49,938.90
	Arm B	R$ 96,956.12	-	-	-
	Arm C	R$ 53,269.39	R$ 40,562.20	R$ 67,125.85	R$ 23,466.05
	Arm D	R$ 96,956.12	-	-	-
	Arm E	R$ 27,879.94	R$ 19,629.80	R$ 99,420.04	R$ 71,655.13
	Arm F	R$ 27,879.94	R$ 19,629.80	R$ 99,420.04	R$ 71,655.13
	Arm G	R$ 11,190.16	R$ 9,435.02	R$ 62,390.01	R$ 49,119.95
	Arm H	R$ 41,040.23	32,386.15	R$ 49,694.30	R$ 17,308.14

Note: **Arm A:** ICU admission, with AKI, Cure; **Arm B:** ICU admission, with AKI, without Cure; **Arm C:** ICU admission, without AKI; Cure; **Arm D:** ICU admission, without AKI, without Cure; **Arm E:** without ICU admission, with AKI, Cure; **Arm F:** without ICU admission, with AKI, without Cure; **Arm G:** without ICU admission, without AKI, Cure; **Arm H:** without ICU admission, without AKI, without Cure.

Table S3. Probabilities and costs for each arm

Antibiotic	Variable	Probability (P)	Cost (C)	Global cost (P x C)
Vancomycin (n=59)	Arm A	16.9%	R$ 36,031.18	R$ 6,103.68
	Arm B	3.4%	R$ 83,648.62	R$ 2,844.05
	Arm C	11.9%	R$ 43,257.88	R$ 5,147.70
	Arm D	6.8%	R$ 58,235.48	R$ 3,960.01
	Arm E	16.9%	R$ 37,066.02	R$ 6,278.98
	Arm F	8.4%	R$ 26,238.78	R$ 2,222.42
	Arm G	30.5%	R$ 29,584.21	R$ 9,023.18
	Arm H	5.0%	R$ 14,9531.88	R$ 7,596.21
Linezolid (n=31)	Arm A	2.8%	R$ 57,522.53	R$ 1,610.63
	Arm B	31.7%	R$ 96,956.11	R$ 30,783.56
	Arm C	24.1%	R$ 54,418.68	R$ 13,114.90
	Arm D	7.0%	R$ 96,956.11	R$ 6,786.92
	Arm E	10.3%	R$ 70,073.25	R$ 7,217.54
	Arm F	3.4%	R$ 70,073.25	R$ 2,382.49
	Arm G	17.2%	R$ 44,153.30	R$ 7,612.02
	Arm H	3.4%	R$ 41,040.23	R$ 1,411.78

Note: **Arm A:** ICU admission, with AKI, Cure; **Arm B:** ICU admission, with AKI, without Cure; **Arm C:** ICU admission, without AKI; Cure; **Arm D:** ICU admission, without AKI, without Cure; **Arm E:** without ICU admission, with AKI, Cure; **Arm F:** without ICU admission, without AKI, without cure; **Arm G:** without ICU admission, without AKI, Cure; **Arm H:** without ICU admission, without AKI, without cure.