

Vancomycin loading dose in a neonatal intensive care unit: experience with therapeutic drug monitoring

Dosis de carga de vancomicina en una unidad de cuidados intensivos neonatales: experiencia con monitorización de niveles plasmáticos

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What do we know about the subject matter of this study?

The use of vancomycin loading doses in newborns is controversial. Although it increases the likelihood of achieving early therapeutic concentrations, some regimens do not incorporate it due to the limited evidence available in this highly vulnerable and heterogeneous population.

What does this study contribute to what is already known?

This was a retrospective study in a high-complexity NICU with 52 neonates, most of whom were extremely premature. 86% achieved the pharmacokinetic/pharmacodynamic target with vancomycin loading doses, without a significant increase in toxicity. A total of 19.2% had supratherapeutic plasma concentrations, which was associated with the presence of renal failure before the start of treatment. This study provides evidence on the safety of this strategy in neonates, reinforcing its clinical usefulness with adequate plasma monitoring and individualized therapeutic interpretation.

Abstract

Vancomycin is an antimicrobial widely used in hospitalized newborns (NB), with different dosing schedules that may or may not recommend the use of loading doses, depending on gestational age (GA), weight, and renal function. **Objective:** To evaluate the use of plasma levels after a vancomycin loading dose and its impact on achieving the target area under the curve/minimum inhibitory concentration (AUC/MIC) in a neonatal intensive care unit (NICU). **Patients and Method:** Retrospective, descriptive, and observational study in NBs hospitalized between December 2022 and December 2023, in a high-complexity NICU. All NBs with empiric/targeted vancomycin indication were included, who received loading doses with baseline plasma concentration (Pc) monitoring, according

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to local protocol. Demographic and clinical data were recorded. Renal failure was considered when creatinine increased by 0.3 mg/dl in 48 hours and/or urinary output ≤ 1 ml/kg/day. The PrecisePK® software was used to estimate pharmacokinetic parameters and the AUC. **Results:** 52 vancomycin Pc samples were analyzed, of which 73.1% reached optimal values between 10-20 mcg/ml, 19.2% Pc samples were supratherapeutic (> 20 mcg/ml), and 86% of patients achieved an AUC between 400-600 mg/L. The main risk factor for supratherapeutic Pc was renal failure before treatment ($p = 0.001$). **Conclusions:** This study indicates that the loading dose of vancomycin achieves optimal AUC in 86% of cases. It is recommended to closely monitor with basal Pc following the administration of a loading dose, particularly in patients with renal failure.

Introduction

Antibiotics are widely used in Neonatal Intensive Care Units (NICUs)¹, including vancomycin, a tri-cyclic glycopeptide that inhibits cell wall synthesis in Gram-positive microorganisms², with distribution is influenced by total body water and elimination primarily through the kidneys^{2,3}. Its adverse effects include nephrotoxicity and ototoxicity, which increase with high plasma concentrations (PC) and prolonged use of other drugs with the same toxicity profile²⁻⁴.

The pharmacokinetic/pharmacodynamic (PK/PD) target for vancomycin is to achieve an area under the curve to minimum inhibitory concentration (AUC/MIC) ratio between 400-600 mg*h/L, a parameter defined in studies in adults with methicillin-resistant *Staphylococcus aureus* (MRSA) infections and extrapolated to newborns (NB) who commonly have coagulase-negative *Staphylococcus* (CoNS) infections^{3,5}. However, recent research on CoNS suggests that an AUC/MIC between 240-480 mg*h/L may be sufficient for clinical efficacy in neonates, although there is still no consensus on modifying the target PK parameters⁶.

The PK of vancomycin in NB is variable due to differences in weight, maturation, and target organ function, which complicates the optimization of vancomycin dosage⁷⁻¹¹. The literature describes different dosing regimens^{12,13} and PK models^{5,14} for NBs that consider variables such as weight, gestational age (GA), corrected gestational age (CGA), and serum creatinine (Cr) as a marker of renal function.

The efficacy and safety of the loading dose in neonatology remains controversial, in contrast to pediatric and adult patients, where it has already been established^{2,4}. This is due to limited clinical evidence, given the ethical and practical complications hindering data collection, as well as renal maturation and variability in distribution volume⁵.

A recent meta-analysis in the neonatal population revealed that, when loading doses are used, the probability of achieving optimal levels on the first day of treatment with vancomycin increases from 43% to

89%, especially in NB less than 29 weeks GA, which is related to better clinical outcomes, through a reduction in total treatment days from 10 - 5 days¹⁵.

Given that vancomycin dosing in NB remains a clinical challenge, this study aims to evaluate the use of plasma levels after vancomycin loading doses and their impact on achieving the AUC/MIC target in a NICU.

Patients and Method

This was a retrospective, descriptive, observational study conducted between December 2022 and December 2023 in the high-complexity NICU at the *Hospital Barros Luco Trudeau*.

All patients who received empirical or targeted treatment with vancomycin and started loading doses [Table 1 (a)¹⁰ and (b)¹⁶] depending on renal function, infused over 60 minutes, with baseline PC measure before the fifth dose in both cases, were included. Staff were systematically trained to correctly record the time of administration and sample collection of the vancomycin PC.

Renal failure before, during, or after treatment was considered an increase in Cr of 0.3 mg/dL from baseline within 48 hours and a urine output (UO) of 12 or 24 hours ≤ 1 mL/kg/day¹⁷.

Vancomycin PC was determined in the hospital's biochemistry laboratory using an electrochemiluminescent immunoassay on a Cobas 501® analyzer, following the manufacturer's specifications and using internal quality controls to ensure results accuracy.

Patients with PC outside the established time frame and PC samples collected for adjustment or control measurement were excluded from the second sample onward.

Anthropometric variables were collected from the clinical record, including GA, weight, and length. Microbiological data were obtained from the hospital microbiology laboratory database. The MIC used for PK analysis was 1 mcg/ml, considering empirical treatment.

At the time of PC sampling, variables such as weight, CGA, Cr, and 24-hour diuresis obtained from diaper weight (ml/24 hours) were considered, assuming a urine density of 1 mg/ml. Urinary output (UO) was defined as diuresis expressed in ml/kg/24 hours, and creatinine clearance was obtained using the revised Schwartz equation $[ClCr = k \times \text{length (cm)}/Cr \text{ (mg/dl)}]$ ¹⁷. If any of the variables were not measured on the day the PC sample was collected, the last measured value was used.

The concomitant use of aminoglycosides (amikacin) during vancomycin treatment was considered.

The occurrence of adverse events such as red man syndrome was evaluated through direct observation of patients and renal failure with Cr monitoring on the fifth day after the end of vancomycin treatment.

used to estimate PK parameters, where the population used had a median and interquartile range (IQR) of 39 weeks GA (32-42) and a weight of 2.9 kg (1.6-3.7), respectively^{4,8}.

The therapeutic range was considered as PC between 10–20 mcg/mL and AUC/MIC between 400–600 mg *h/L².

The demographic and clinical data of the NB were entered into the software and AUC_{0-24h} was obtained $[AUC_{0-24h} = (24 \times \text{dose}/mg)/(Cl)]$ and the population PK parameters as follows: distribution volume ($Dv = 0.6 \times \text{weight}$), drug clearance $[Cl = 0.345 \times ((\text{weight}/2.9) \times 0.75) \times Fmat \times (1/Cr) \times 0.267]$, where $Fmat = 1/[1 + (CGA/34.8) - 4.53]$ is a sigmoid maturation function; elimination constant ($Ke = Cl/Dv$); and half-life $[t_{1/2} = \ln(2)/ke]$.

Pharmacokinetic analysis

PrecisePK® software with the Frymoyer model was

Statistical analysis

The data were tabulated into a Microsoft® Excel

Table 1a. Vancomycin dosing according to postnatal age and weight in patients without renal failure¹⁰

Postnatal age (days)	Weight (grams)	Loading dose (mg/kg)	Maintenance dose (mg/kg/dosis)	Interval (hours)
≤ 7	≤ 700	16	5	8
	700 – 1.000	16	7	8
	1.001 – 1.500	16	9	8
	1.501 – 2.500	16	10	6
	≥ 2.501	16	12	6
8 – 14	≤ 700	20	7	8
	700 – 1.000	20	9	8
	1.001 – 1.500	20	12	8
	1.501 – 2.500	20	10	6
	≥ 2.501	20	12	6
≥ 15	≤ 700	23	8	8
	700 – 1.000	23	14	8
	1.001 – 1.500	23	15	8
	1.501 – 2.500	23	13	6
	≥ 2.501	23	15	6

Table 1b. Vancomycin dosing according to corrected gestational age (CGA) and creatinine in patients with renal failure¹⁶

≤ 28 weeks			> 28 weeks		
Loading dose: 20 mg/kg (infusion rate 2 hours)					
Serum creatinine (mg/dL)	Maintenance dose (mg/kg/dosis)	Interval (hours)	Serum creatinine (mg/dL)	Maintenance dose (mg/kg/dosis)	Interval (hours)
< 0,5	15	12	< 0,7	15	12
0,5 – 0,7	20	24	0,7 – 0,9	20	24
0,8 – 1	15	24	1 – 1,2	15	24
1,1 – 1,4	10	24	1,3 – 1,6	10	24
> 1,4	15	48	> 1,6	15	48

database, ensuring patient confidentiality. Statistical analysis was performed in STATA® v.17, using the following strategies:

- Continuous variables: Distribution was evaluated using the Shapiro-Wilk test. Data with non-normal distribution were expressed as median and IQR (p25-p75). Comparison between groups was performed using Student's t-test or Mann-Whitney test, as appropriate.
- Categorical variables: These are expressed as frequencies and percentages. Differences between groups were analyzed using the χ^2 independence test or Fisher's exact test.
- Proportion test using χ^2 : This was applied to identify factors associated with supratherapeutic plasma concentrations (> 20 mcg/mL), considering a significance level of $p < 0.05$.

Ethics

This study was approved by the Ethics Committee of the South Metropolitan Health Service.

Results

During the study period, 63 NB received vancomycin as empirical or targeted treatment with PC measurement in the NICU at HBLT. Eleven NB were excluded because the sampling schedule was outside the established protocol, resulting in a total sample of 52 NB. Table 2 shows the characteristics of the included NB. The median number of days of life at the start of vancomycin was 10 days (8-19 days). Of the 52 patients, 53.8% were male, with a median GA of 28 weeks (26-33 weeks), and a birth weight of 997 grams

(722-1308 g). In this group, 55.7% of the patients were preterm NB (PTNB) of ≤ 28 weeks.

The median loading dose of vancomycin was 19 mg/kg (15.9–20.8), and the maintenance dose was 9.9 mg/kg (8.8–12). The total treatment time was a median of 8 days (6–11).

The median age at the start of treatment was 10 days, with a wide IQR of 8–19 days, a dispersion that is repeated both with a median CGA of 29 weeks (28–36) and the median weight at the start of treatment of 1207 grams (922–2073).

All the patients included received targeted treatment, of which 25 were CoNS and 2 were methicillin-susceptible *Staphylococcus aureus* (MSSA), the latter being adjusted to cloxacillin when the culture result was available.

Among the total samples, 28 NB (55.1%) received concomitant treatment with amikacin throughout the course of analysis.

Plasma concentrations

Fifty-two PC samples were analyzed, with a median concentration of 13.1 mcg/mL and an IQR of 9.8–18.3 (Figure 1). Of the total samples analyzed, 73.1% (38) achieved PC between 10–20 mcg/mL, 7.7% (4) had subtherapeutic PC, and 19.2% (10) had supratherapeutic PC.

Of the NB with supratherapeutic results, 8 out of 10 did not start treatment adjusted for renal failure, of which the median Cr was 0.95 mg/dl with an IQR between 0.79 and 1.51, whereas the UO was 1.12 ml/kg/hour (0.88–1.5). This group of patients had a CGA of 28 weeks (25–29 weeks) and a birth weight of 949 grams (760–1000). Nine of these patients were PTNBs for < 28 weeks at the time of initiating vancomycin treatment.

Table 2. Demographic, clinical, and vancomycin dosing characteristics of neonates hospitalized in the HBLT NICU during the study period (n = 52) and their differences regarding plasma concentration achievement

Characteristics	Total (n = 52)		PC < 20 mcg/ml (n = 42)		PC $\geq$ 20 mcg/ml (n = 10)		p value
	N or median	% or IQR	N or median	% or IQR	N or median	% or IQR	
Male	28	54%	25	60%	3	30%	0,09
GA (weeks)	28	26-33	28	26-34	30	28-34	0,86
≤ 28 weeks	29	56%	23	55%	6	60%	0,82
BW (grams)	997	772-1308	1000	750-1314	875	704-1000	0,28
CGA at treatment initiation (weeks)	29	28-36	29	28-36	30	28-34	0,68
Peso at treatment initiation (grams)	1207	923-2072	1207	950-2084	1190	913-1500	0,64
Sc at treatment initiation (mg/dL)	0,4	0,24-0,58	0,35	0,24-0,57	0,55	0,44-0,79	0,04
UO (ml/kg/día)	4,1	3,4-4,8	3,9	3,4-4,5	4,1	3,4-4,8	0,98

PC: Plasma concentrations, GA: Gestational age, BW: Birth weight; CGA: Corrected gestational age; Sc: Serum creatinine; UO: Urinary output

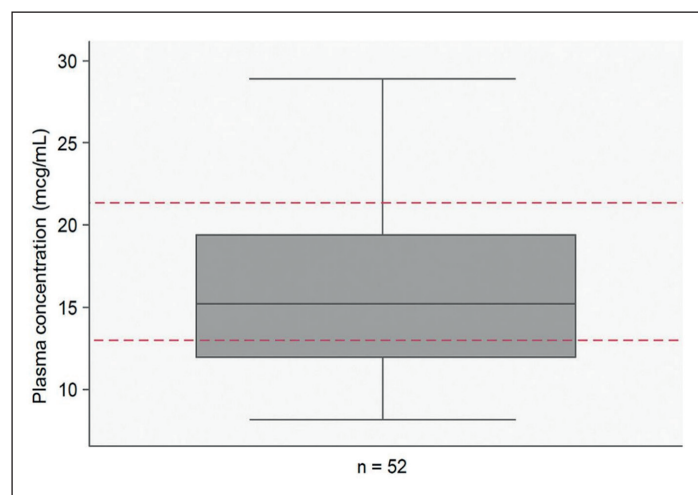


Figure 1. Box-and-whisker plot showing the distribution of the plasma concentrations (C_p) obtained and the target therapeutic range (10-20 mcg/mL) ($n = 52$).

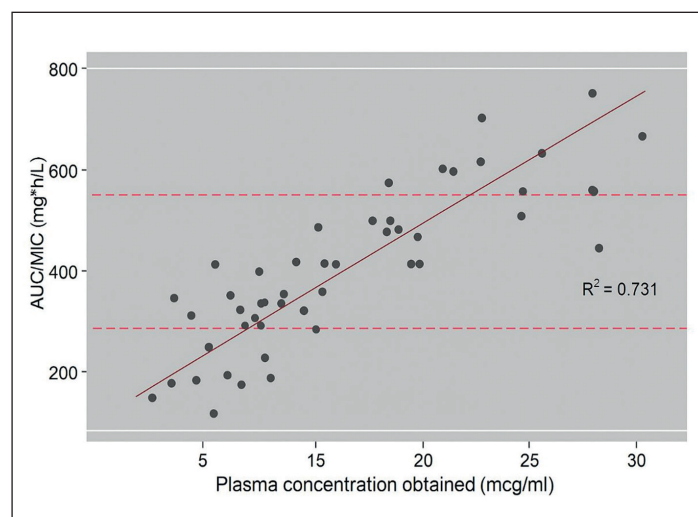


Figure 2. Plot showing the relationship between the area under the curve/minimum inhibitory concentration (AUC/MIC) ratio and the vancomycin plasma concentration obtained.

Clinical and laboratory variables were analyzed according to a PC, differentiating between ≤ 20 mcg/mL and > 20 mcg/mL. No significant differences were observed between the two groups, except for serum creatinine at the start of treatment, which was significantly higher in the group with supratherapeutic PC ($p = 0.04$) (Table 2).

AUC and PC relationship

Using PrecisePK® software, it was observed that 86% (45 patients) of the total sample was within the desired therapeutic range (400-600 mcg/mL), while 14% (7 patients) was above the desired range, which was associated with supratherapeutic PC.

The median of individual PK parameters for the sample was calculated, yielding $D_v = 0.7$ L, $Cl = 0.08$ L/h, $k_e = 0.112$ 1/h, $t_{1/2} = 6.1$ h, and AUC_{0-24}/MIC was 467.6 mg*h/L (407.4–560.7 mg*h/L).

A positive linear relationship was observed between AUC and PC with $r^2 = 0.731$. A baseline PC between 7 and 18 mcg/mL has a high probability of reaching the target PK/PD (400-600 mg*h/L) (Figure 2).

With respect to the relationship between risk factors and obtaining supratherapeutic PC levels using a proportion test, renal failure was significantly associated (70% vs. 17%, $p < 0.001$). No significant associations were observed with other clinical variables such as weight, CGA, or amikacin use (Table 3).

Safety

None of the patients in the study presented with red man syndrome after vancomycin administration.

In 43 patients (82.7%), the median Cr on the fifth day after the end of vancomycin treatment was 0.3 mg/dL (0.12–0.5); therefore, no patients presented with renal failure at the end of the antibiotic treatment.

It was not possible to follow up the entire sample because 9 patients died during vancomycin treatment. All these patients were PTNBs < 28 weeks of GA, who died from complications associated with such a condition.

Table 3. Risk factors for supratherapeutic vancomycin plasma concentrations associated with the use of loading dose

Variable	$C_p < 20$ mcg/mL ($n = 42$)	$C_p \geq 20$ mcg/mL ($n = 10$)	p value
Weight < 1500 grams	27 (64%)	7 (70%)	0,733
Corrected gestational age < 32 weeks	26 (62%)	7 (70%)	0,633
Renal failure	7 (17%)	7 (70%)	0,001
Concomitant use of aminoglycosides	22 (52%)	8 (80%)	0,112

PC: Plasma concentrations y p value $< 0,05$

Discussion

The use of vancomycin loading doses in NB has proven to be an effective strategy for achieving optimal PC in 73.1% of cases. However, when evaluating the established PK/PD targets, the results improved, reaching adequate AUC/MIC values in 86% of the cases.

These findings reinforce the importance of loading doses in neonatology, given that conventional regimens without this strategy fail to achieve therapeutic targets in 50% of cases⁷. This is particularly relevant in the context of late-onset sepsis, one of the leading causes of morbidity and mortality in the NICU, which especially affects PTNBs due to immunological immaturity and barrier immaturity, such as the skin, characteristic of this population. It has been documented that at least 10% of NB hospitalized in the NICU receive vancomycin at some point during their hospitalization⁵⁻⁹.

In the national literature, the study by Khlan et al. showed that only 47% of NB achieved the therapeutic target of AUC_{0-24h}/MIC , whereas 38% had subtherapeutic concentrations⁷. This suggests that optimizing dosing is a challenge in this population and that current models should consider variables such as weight, CGA, and renal function to improve accuracy.

The results of the study by Khlan et al. differ, mainly due to the dose used, which varies significantly from that used in this study, as it does not include a loading dose, has intervals of up to 18 hours, and does not consider weight, only the GA.

In pediatric² and adult¹⁸ populations, the loading dose has been shown to improve clinical outcomes by reducing mortality and complications associated with infection, allowing optimal PC level achievement, and decreasing the total number of days of treatment¹⁸.

Although the use of a higher initial dose could increase the theoretical risk of toxicity, especially renal toxicity, this risk can be reduced with adequate monitoring of PC, which showed no significant increase in the incidence of nephrotoxicity^{18,19}. This benefit has also been documented in NB, especially those born before 29 weeks of gestation, where the probability of achieving the therapeutic target improves from 43% to 89%¹⁵.

In the national context, adjusted recommendations for vancomycin dosing in NB have been proposed, such as those by the Advisory Committee on Neonatal Infections²⁰. However, these guidelines have not yet incorporated specific recommendations for patients with renal failure, which represents a gap in treatment optimization²⁰.

In this study, despite the use of dosage regimens adjusted according to renal function, 19.2% of PC lev-

els were found to be supratherapeutic, which was related to 14% of the sample above the PK/PD target. These results were observed in patients who had renal failure at the start of treatment and in whom the correct dosage regimen was not used, due to the difficulty of establishing this diagnosis early on, whether based on creatinine or urine output.

This can be explained by the classic definition of renal failure used in NB (increase Cr of 0.3 mg/dL from baseline in 48 hours and UO in 12 or 24 hours ≤ 1 mL/kg/day), which is difficult to apply in daily clinical practice, especially in extreme PTNB, since Cr in the first days of life largely reflects maternal values and does not always represent the actual renal function of the NB. Furthermore, serum creatinine is not a reliable and sensitive marker of renal function in this population, which may have hindered the timely identification of renal deterioration.

Another relevant finding was the relationship between PC and AUC. It was observed that PC levels > 7.6 mcg/mL have a high probability of reaching an $AUC_{0-24h} > 400$ mg*h/L, which is consistent with previous studies in neonatal and pediatric populations^{1,7}. However, this finding differs from the recommendations for adults, where plasma concentrations between 15-20 mcg/mL are required to achieve the PK/PD target in MRSA infections, extrapolated for CoNS².

A recent study suggested that a PC of 7 mcg/mL and an AUC_{0-48h} of approximately 240 mg*h/L may be sufficient to achieve clinical cure in most NB²³. However, this threshold has not yet been conclusively validated, so in the absence of a different target, it is considered prudent to maintain the values established for MRSA.

The Frymoyer PK model was used to calculate the PK/PD parameters, which were based on a population with characteristics different from ours, with differences in GA (39 vs. 28 weeks) and birth weight (2900 g vs. 1007 g)^{4,7-9}. These discrepancies may affect the accuracy of the estimates and suggest the need to develop specific population models for NB in our context.

This model was used because this kinetic software was available, but there are other models available in the literature, such as those of Capparelli et al. and Mehrotra et al., which perform better, with lower inaccuracies (16.8% and 16.9%, respectively)²⁵.

The use of kinetic software offers multiple benefits, especially in optimizing dosing by allowing individualized adjustments, considering the physiological particularities of the NBs, which improves therapeutic efficacy and reduces the risk of toxicity. In addition, by predicting a drug's PC more accurately, the need for repeated blood draws is reduced, which is especially beneficial in this population.

This study has limitations that should be considered when interpreting its results, including the inabil-

ity to evaluate clinical outcomes, such as culture negativity or length of hospital stay. This limitation makes it difficult to establish a direct relationship between dosage and the clinical effectiveness of treatment.

In addition, the observational nature of the study does not allow a causal relationship to be established between the administration of the vancomycin loading dose and the results obtained. Since it is based on previous clinical records, this type of design entails methodological challenges, such as a lack of standardization in data collection, the possibility of selection bias, loss of information, and difficulty in prospectively controlling for confounding factors.

To improve the quality of the evidence and overcome these limitations, it would be advisable to conduct prospective, controlled studies, such as randomized clinical trials, that allow direct comparisons between a group receiving loading doses and another following a conventional regimen. This approach allows for a better estimation of the clinical impact, reducing bias and strengthening the validity of the findings.

Another relevant limitation was the heterogeneity of the sample, as NBs with very diverse clinical characteristics were included, which could have influenced the variability of the response to treatment. In addition, the grouping of patients with and without renal dysfunction without a specific subclassification may have affected the interpretation of the results in this subgroup, especially considering the impact that renal function has on the PK of vancomycin.

Among the limitations specific to NB, blood sampling stands out, especially in extremely premature and low birth weight infants, since it presents significant challenges due to their limited blood volume. Frequent blood collection can lead to iatrogenic anemia, increasing the need for blood transfusions²³. To reduce these risks, it is essential to coordinate sampling with other clinical procedures, thereby reducing the number of punctures and manipulation of the neonate. In this retrospective study, this led to the exclusion of patients due to PC samples collected at inappropriate times or changes in antibiotic administration schedules.

For this reason, healthcare personnel were trained on the importance of performing PC extractions at the appropriate times to ensure diagnostic accuracy and avoid misinterpretations, as well as using the correct dosage according to the patient's renal function.

Our findings reinforce the need to optimize vancomycin dosing in NB by individualizing doses based on weight, CGA, and renal function. In addition, we suggest advancing PC monitoring after the loading dose to avoid drug accumulation and reduce the risk of toxicity.

Given that the PK equations used in this study may not be fully representative of the Chilean neonatal population, especially in extreme PTNBs, it is recommended that specific population models be developed that consider their clinical and physiological characteristics. Future studies should also explore the relationship between plasma concentrations achieved and clinical outcomes, such as culture negativity or treatment time, to establish more accurate dosage thresholds. Conducting multicenter studies at the national level would allow for a larger sample size and generate more robust and representative evidence for this population.

Regarding PC sampling, it is proposed to evaluate micro methods for blood extraction, so that it can be monitored at appropriate times and does not necessarily involve other procedures.

Conclusions

This study provides relevant evidence on the usefulness of the vancomycin loading dose in NB, showing that it was possible to achieve the PK/PD target in 86% of cases. It is suggested that PC be monitored earlier, especially in NB with renal failure, to avoid toxicity, as these patients had 19.2% supratherapeutic PC. Individualization of the dose on the basis of weight, CGA, and renal function is essential, as suggested by recent guidelines.

In future studies, it may be beneficial to implement more advanced PK models with a Bayesian approach, as this could reduce the time needed to reach the therapeutic target and limit the number of blood sample collections in NB, compared with traditional PK equations.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: This study was approved by the respective Research Ethics Committee. The authors state that the information has been obtained anonymously from previous data.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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