Evaluation of the prescription, administration and monitoring of vancomycin in adult patients admitted to a tertiary hospital

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ABSTRACT

Introduction: Vancomycin is a strategic antibiotic in the treatment of infections caused by gram-positive bacteria. Controversies regarding its dosage and monitoring are important due to the risk of nephrotoxicity and the insurgency of resistant strains. Objectives: To describe vancomycin prescription patterns for adult patients, to observe vancomycin administration, vancocinemia collection and the timing of subsequent vancomycin dose adjustment, and to evaluate the conformity between prescription, administration and monitoring of vancomycin in a University Hospital (HU). Methodology: This was a cross-sectional and prospective study that included adult patients admitted to four clinical and surgical wards and two wards of the intensive care unit (SETI) using vancomycin. Six visits were made to the Internal Medicine, Neurology and Orthopedics wards and five visits to the Vascular Surgery and SETI wards, in which 67 patients and 989 prescriptions were evaluated, data from medical records were collected and nursing and medical routines regarding vancomycin administration, vancocinemia collection and antibiotic adjustment were observed. Results: There was no difference between the units in terms of gender, baseline creatinine levels, length of hospital stay, days of vancomycin use, and weight, with a predominance of younger patients in Neurology and a higher mean age in Vascular Surgery. The loading dose was prescribed in 83.8% of the patients, while dilution and infusion time were prescribed, respectively, in 768 (77.6%) and 212 (21.4%) of the prescriptions. The SETIs had rates of adequacy of the loading dose and frequency of dilution prescription and infusion time statistically higher than those of the wards (p 0.02, p 0.04 and p <0.001, respectively). Of the total dilutions prescribed, 56.4% were adequate. Internal medicine led in the proportion of correctly prescribed dilutions (82.8%, p<0.05), as opposed to the Intensive Care Unit – Ward 1 (SETI 1) and Neurology, which had the lowest adequacy rates, of 36.4% and 36.1%, respectively. The infusion time was correctly prescribed in 169 (79.7%) records. In Neurology, the infusion time was not prescribed at any time, and in Orthopedics, it was not adequate at any time. In the other sectors, the infusion time was mostly adequate, with a discrepant trend observed between SETI Wards 1 and 2 (p 0.058). In the analysis of SETIs versus wards, there were higher rates of adequacy of the prescribed infusion time in SETIs (p 0.003). There were nine cases of cutaneous reaction to vancomycin (13.4%). An inverse relationship was observed between the appropriate prescription for infusion time and the frequency of adverse skin reaction. A total of 56 administrations were observed, with 32 (57.1%) not being in accordance with the prescribed. Of the 59 patients using the first vancomycin regimen during hospitalization for two or

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more days, 52 (88.1%) had at least one vancokineemia collected, with the 1st vankokineemia collected predominantly on the 2nd day of antibiotic therapy in all sectors. It was not possible to establish comparisons between the sectors regarding dose collections and adjustments due to the reduced number of vancocinemia collections observed. Among the 265 levels of vanchokineemia recorded, 132 (49.8%) were classified as adequate. Acute kidney injury (AKI) developed in 13 (31.7%) of the total of 41 patients evaluated for this outcome and was more frequent in SETIs compared to wards ($p<0.001$). Comparing the day of antibiotic therapy with vancomycin that each patient was on at the time of the last creatinine measurement and the values of the 1st vanchokineemia, a median number of days and higher vanchokineemia levels were found among the patients who developed AKI (p 0.06 and p 0.002, respectively). Conclusion: There are failures in the prescription, administration and monitoring of vancomycin in all sectors of this UH. The Intensive Care Service – Ward 2 (SETI 2) and the Internal Medicine were the sectors that best met the criteria for adequate prescription. There is a need to implement measures to qualify and train professionals, as well as inspection actions regarding the rigor of prescription and administration. The data from medical records were not completely reliable to what was done in practice, however, the study was not able to reduce the importance of medical records as a data collection tool.

Keywords: Vancomycin, Vanchocinemia, Monitoring, Nephrotoxicity.

INTRODUCTION

VANCOMYCIN

Vancomycin is a glycopeptide antibiotic produced by *Streptococcus orientalis*, approved by the *Food and Drug Administration* (FDA) in 1958 for the treatment of infections caused by gram-positive bacteria. It inhibits the peptideoglycan cross-linking process by binding to the D-alanyl-D-alanine terminal end of precursor units of the cell wall of gram-positive bacteria, thus exerting a bactericidal role (AZEVEDO, 2015; OLIVEIRA, 2016).

It has a distribution half-life, α half-life, from about 30 minutes to 1 hour and a half-life of elimination, and a half-life β, from approximately 6 to 12 hours (ALMEIDA, 2011). It is poorly metabolized and is excreted almost exclusively by the renal route, and its clearance is closely associated with the glomerular filtration rate. In the blood, about 50% is bound to plasma proteins (AZEVEDO, 2015). Its penetration and bioavailability may vary according to the site and inflammatory state (ALMEIDA, 2011; STEINMETZ et al., 2015).

Its absorption through the gastrointestinal tract is limited and intramuscular administration should be avoided due to the risk of muscle necrosis, so that the predominant route of administration is intravenous, in the pharmaceutical form of lyophilized powder (ISOPPO, 2013). Due to its strategic position in the parenteral treatment of infections by multidrug-resistant gram-positive cocci, especially *methicillin-resistant Staphylococcus aureus* (MRSA), in recent decades, vancomycin has had its use widely spread in the hospital environment, due to the increasing incidence of sepsis, which already exceeds 750 thousand cases/year in the United States of America (USA), corresponding to 2% of hospital admissions and 10% of admissions to the Therapy Unit Intensive care unit (ICU) and increased frequency of septic shock cases attributed to gram-positive bacteria, especially methicillin-resistant *Staphylococcus aureus* (MARTINS, 2016).

Thus, vancomycin has remained, for more than 60 years, as the treatment of choice for infections caused by MRSA, whose worldwide incidence has increased substantially in the last 30 years, representing 4.6-19% of healthcare-associated bloodstream infections associated with high mortality, in addition to having been an important cause of community-acquired infections since the late 1990s.

However, in recent years, isolates of *S. aureus with* intermediary-susceptible vancomycin resistance (vancomycin intermediarycin *(*VISA) or even resistant to this antibiotic (*vancomycin-resistant S. aureus,* VRSA) have been identified. Although infections by these organisms are infrequent, such findings have increased the fear that these bacteria will become more prevalent if vancomycin exposure pressure remains (LEVINE, 2006; ZANOTTO et al., 2014).

More worrisome are the records of therapeutic failure with vancomycin in the treatment of infections by S. *aureus isolates* with a minimum inhibitory concentration (MIC) less than or equal to

2µg/ml, considered within the range of susceptibility, according to the criteria adopted by the *Clinical and Laboratory Standards Institute* (CLSI) in 2006 (CLSI, 2013). This population, considered to have intermediate hetero-resistance to vancomycin (hVISA), reflects the heterogeneity of a S. *aureus isolate* with strains with intermediate resistance and vancomycin-sensitive strains (HIRAMATSU, 2001). According to Howden et al. (2010), it is estimated that hVISA represents 60% of MRSA isolates considered sensitive by conventional methods.

Another controversy involving vancomycin, in addition to its effectiveness, is its safety. Vancomycin's use was initially restricted, as it was associated with a high incidence of adverse effects, which are now known to result, for the most part, from the impurities present in the first formulations of the medication (AZEVEDO, 2015; ALMEIDA, 2011).

The adverse effects that remained with the new formulations are mainly due to the speed of infusion and the concentration such as skin *rash*, red man syndrome, fever and phlebitis. To avoid such reactions, it is recommended to administer a solution with a maximum concentration of 5mg/mL and an infusion of up to 17mg/min, with a minimum duration of 60 minutes for intermittent administration schedules (SÍLVA JÚNIOR, 2015; HOEFEL et al., 2008; MATSUMOTO et al. 2013; DRISYAMOL; MAHESH, 2016).

At first, considered highly nephrotoxic with an incidence of more than 50%, after its purification, the occurrence of vancomycin-induced kidney injury decreased significantly (MEANEY; HYNICKA; TSOUKLERS, 2014). Different definitions have been described for such diagnosis, with several recent studies using the acute kidney injury (AKI) criteria of RIFLE, AKIN, and KDIGO (SAWADA et al., 2018).

In monotherapy, this glycopeptide is indicated as a cause of kidney injury in 0 to 5% of patients, whereas when associated with other drugs with nephrotoxic potential such as aminoglycosides or piperacillin-tazobactam, this ratio rises to 35% and 42%, respectively (ALMEIDA, 2011; MIN et al., 2011). The mechanism involved is not well known and seems to be secondary to the increased urinary excretion of oxidizing compounds such as malonialdehyde (MDA) and N-acetyl-B-D-glucosaminidase (NAG) and their toxic action to the mitochondria of renal tubular cells, leading to an increase in oxygen consumption by these cells (AZEVEDO, 2015).

Such nephrotoxicity is dose-dependent and correlates with some risk factors, such as: therapy lasting 7 days or more, age over 75 years, severe hypoalbuminemia (albumin less than 2.5g/dL) and concomitant use of nephrotoxic medications, including intravenous contrast or those that alter renal function, such as angiotensin-converting enzyme (ACE) inhibitors; angiotensin II receptor blockers (ARBs II) and loop diuretics (NORTON et al., 2013; AZEVEDO, 2015).

MONITORING

The controversy between the application of lower doses of vancomycin, with greater chances of therapeutic failure and generation of bacterial resistance, and the use of higher doses, with the risk of more serious adverse effects, such as acute kidney injury, has raised the need for studies and development of administration protocols based on the monitoring of the drug (RYBAK et al., 2009; YE; TANG; ZHAI, 2013; ZANOTTO et al., 2014; DOMBROSKI; SILVA; SILVEIRA, 2015; YE et al., 2016).

The idea of monitoring is based on the fact that the administration of equal doses at regular intervals suffers individual differences in absorption, metabolism, excretion and bioavailability, so that the therapeutic response becomes dependent on the serum concentration of the medication and not on the dose administered (DOMBROSKI; SILVA; SILVEIRA, 2015).

Vancomycin monitoring is especially indicated for the population at higher risk of developing vancomycin-induced nephropathy or in whom individual characteristics make their serum level unpredictable, facilitating both the occurrence of renal injury and treatment failures. The main indications would be: use of high doses of the medication, vancomycin therapy for more than three days, concomitant use of other nephrotoxic agents, severe infections, hemodynamic instability, ICU patients, unstable renal function, hemodialysis, obese, elderly, among others (MATSUMOTO et al., 2013; DOMBROSKI; SILVA; SILVEIRA, 2015; YE et al. 2016).

The most appropriate pharmacological parameter for monitoring vancomycin is the area under the curve (AUC) by the minimum inhibitory concentration (AUC/MIC), by correlating the serum concentration of the drug and the time it remains above the MIC, since vancomycin is an antibiotic concentration and time-dependent (DROEGE; VAN FLEET; MUELLER, 2016). AUC/MIC≥400 values are associated with better outcomes, however, due to the lack of practicality in bedside use, AUC measurement is not routinely recommended and should be replaced by the measurement of the serum concentration in the trough, i.e., before administration of the next dose (YE et al., 2016).

Thus, it is recommended to monitor the medication by means of blood dosage at a time of stable equilibrium, called '*steady-state*', in which the rate of excretion is similar to the rate of bioavailability, so that the serum concentration of the drug is constant. For vancomycin, this state is achieved after 4-5 half-lives, i.e., 24 to 48 hours after administration of the first dose in patients with normal renal function, whose elimination half-life ranges from 6 to 12 hours (MATSUMOTO et al., 2013; YE et al., 2016).

For patients with altered renal function who have an increased half-life, there are several guidelines regarding the appropriate timing of vancocinemia collection. (MATSUMOTO et al., 2013; PHILLIPS; GORDON, 2015; SPADARO et al., 2015; DOMBROSKI; SILVA; SILVEIRA, 2015; YE et al., 2016).

In hemodialysis patients, the recommendation to collect vancocinemia in the last hour before the hemodialysis session is uniform (VANDECASTEELE; DE VRIESE, 2011; VANDECASTEELE; OF BACQUER; DE VRIESE, 2011; ISOPPO, 2013; MATSUMOTO et al., 2013; CREW; HEINTZ; HEINTZ, 2015; ELYASI; KHALILI, 2016; MAXSON; PATE; STARR, 2016). This is due to the pharmacokinetics of the medication in these individuals, in whom the pre-dialysis moment is the one with the lowest serum concentration, reflecting the trough in the best way. In these patients, contrary to what one might imagine, after a 4-hour hemodialysis session, which can remove up to 46% of this antibiotic, the serum levels of vancomycin can increase by about 16 to 36%, reflecting the redistribution phase of the medication (VANDECASTEELE; DE VRIESE, 2011).

There is a consensus that vancocinemia values in the valley, lower than 10mg/L, should be avoided because they predispose to the emergence of bacterial resistance, as well as values higher than 20mg/L because they are associated with a higher rate of nephrotoxicity (YE et al., 2016).

Patel et al. (2011) found that serum levels of 15 to 20 mg/L were related in 100% of cases with AUC/MIC ≥400 for microorganisms with MIC of 0.5 and 1 µg/ml, which, for vanchokinemias of 10 to 15 mg/L, is only true for MIC of 0.5 mg/L. Considering that, in Japan, the MIC of the main isolates is 1 µg/ml, concentrations of 15 to 20 mg/L are required in the valley (NIKI et al., 2011 apud MATSUMOTO et al., 2013). These data supported the recommendation of 10 to 20 mg/L in the trough, as well as the fact that a value lower than 15 mg/L was identified as an independent predictor of treatment failure in patients with bacteremia. infective endocarditis, osteomyelitis, meningitis, pneumonia, and severe skin and soft tissue MRSA infections (KULLAR et al, 2011; VANDECASTEELE; DE VRIESE, 2011; MATSUMOTO et al., 2013).

ADMINISTRATION PROTOCOLS

As well as the guidelines on monitoring, vancomycin administration protocols have changed and continue to change a lot in recent years, and fixed doses of 1g every 12 hours were initially recommended (GILBERT et al., 2015). Today, regimens that take into account the patient's weight seem more appropriate. Spadaro et al. (2015) still recommend loading dose of 1000mg for patients weighing less than 65kg and 1500mg for those weighing 65kg or more, although most authors recommend loading doses ranging from 25 to 30 mg/kg, with a maximum of 2g per dose, only for individuals with severe or complicated infections. with the aim of achieving early therapeutic levels in these patients (THALAKADA et al., 2012 apud ELYASI; KHALILI, 2016; MATSUMOTO et al., 2013; DOMBROSKI; SILVA; SILVEIRA, 2015; PHILLIPS; GORDON, 2015; YE et al., 2016).

Spadaro et al. (2015) also differ, with regard to the maintenance dose, especially because they consider continuous infusion more compatible with pharmacokinetics, recommending doses of 2000mg per day for patients with *creatinine clearance* greater than 50 mL/min.

Due to the lack of strong evidence demonstrating the superiority of continuous infusion, most studies still recommend intermittent regimens. Ye et al. (2016) advocate the use of Baeysian's statistical method to calculate the dose to be administered based on vancocinemia, age, serum creatinine, weight, and target concentration, which, despite being accurate, is impractical for daily clinical application. Phillips and Gordon (2015) still recommend fixed maintenance doses, not adjusted according to weight, of 1.5g every 12 hours for patients with CrCl >90mL/min, but do not describe how the adjustment should be performed. Dombroski, Silva and Silveira (2015) recommend doses of 15 to 20 mg/kg every 8 or 12 hours, similar to that recommended by Matsumoto et al. (2013), however, this last study reinforces the importance of a minimum interval between doses of 8 hours, and the recommendations for monitoring vancomycin are dependent on the frequency of administration and trough values of 15 to 20 mg/L do not guarantee AUC/MIC≥400 for regimens every 6 to 8 hours.

The standardization of protocols for patients with impaired renal function is even more complex, since this is a very heterogeneous group. For this population, Matsumoto et al. (2013) suggest a longer interval between doses of the antibiotic, every 24 hours, while Spadaro et al. (2015), Phillips and Gordon (2015) propose regimens according to creatinine *clearance* ranges as shown in the table below (Chart 1).

Table 1 – Vancomycin doses in patients with altered renal function

Clearance de creatinina (mL/min)	***Vancomycin dose***
Spadaro et al. (2015)	
>50 AM	2000 mg/day
20 – 50	1500 mg/day
10 – 20	1000 mg/day
<10	500 mg/day
Phillips e Gordon (2015)	
>90 AM	1500 mg every 12 hours
60 – 90	1000 mg every 12 hours
20 – 59	1000 mg every 24 hours
< 20	1000 mg every 2 to 7 days

Fonte: SPADARO et al. (2015, modificado); PHILLIPS; GORDON (2015, modificado).

Among these studies, few authors have accurately described how dose adjustment should be performed according to vancokineemia values. Spadaro et al. (2015) advise, for vanchokinemic values below 15 mg/L, an increase in the daily dose of 500mg, between 15 and 25 mg/L dose maintenance, between 25 and 30 mg/L a decrease of 500mg in the daily dose and, for those above 30 mg/L, the interruption of continuous infusion for 6 hours followed by dose reduction. Dombroski, Silva and Silveira (2015), who advocate intermittent infusion, recommend an increase of 20 to 30% of the daily dose for trough levels below 15 mg/L, maintenance of the dose for levels between 15 and 20 mg/L, reduction of the daily dose by 20 to 30% for vancokinemias between 20 and 25 mg/L and suspension of the next dose when values above 25 mg/L. Other authors recommend adjustments

according to nomograms such as Ye et al. (2016), who use Baeysian's statistical method to calculate doses.

MEDICAL RECORD

It is true that, with regard to vancomycin, much remains uncertain, especially regarding the best therapeutic regimen and the form of administration and monitoring of its serum levels in the most different populations, despite the increasing number of studies on this subject since 1994 (ALMEIDA, 2011). Many of these studies are based on data obtained from medical records, and of the 16 human studies used in this project, at least 10 had their data collected from medical records.

The medical record is defined by the Federal Council of Medicine (2002), in its Resolution No. 1638, of 07/10/2002, in Art. 1, as:

> A single document consisting of a set of information, signs and images recorded, generated from facts, events and situations about the patient's health and the care provided to him, of a legal, confidential and scientific nature, which enables communication between members of the multidisciplinary team and the continuity of the care provided to the individual.

Even with such an important role in the care, research, teaching, administrative control and legal monitoring of the activities of health professionals, it is still often neglected, with few studies that evaluate the quality of information in their records (SARMENTO et al., 2011).

As already explained, the adjustment of the doses of vancomycin to be administered is very fine and is interfered with by several factors related to the patient, the medication, the form of dilution, the administration, the collection of vancocinemia and the time of adjustment, so that the absence of any data or the incorrect record lead the physician to make inappropriate decisions with clinical implications for the patient. in addition to producing misleading data for research.

OBJECTIVES

The main objectives of this study were to describe vancomycin prescription patterns for adult patients, considering dose, dilution, and infusion rate; as well as observing the administration of vancomycin, the collection of vancocinemia and the timing of subsequent adjustment of the vancomycin dose and to assess the conformity between prescription, administration and monitoring of vancomycin.

As secondary objectives, to analyze the relationship between infusion rate and the presence of skin reactions (*rash* and pruritus) and to evaluate the relationship between vanchokinemic levels and the development of acute kidney injury.

METHODOLOGY

ETHICAL PROCEDURES

The present study was carried out by means of a Free and Informed Consent Form (ICF), signed by the participant or guardian and was submitted to the Research Ethics Committee of the Botucatu School of Medicine, through Plataforma Brasil, in accordance with Resolution 466/2012 of the National Health Council, starting only after its approval under opinion No. 2,231,035.

RESEARCH METHOD

This is a cross-sectional, observational and prospective study.

SCENARIO AND PARTICIPANTS

The study included adult patients (> 18 years old), admitted to four wards and two SETI wards of the HC-FMB, who were using intravenous vancomycin on the days when visits to these units of the hospital occurred, in the period from August 23 to November 30, 2020. There were no exclusion criteria.

The following HC-FMB units were part of the study: Internal Medicine, Vascular Surgery, Neurosurgery, Orthopedics, and Wards 1 (SETI 1) and 2 (SETI 2) of the Intensive Care Service.

The sample size was calculated for the estimation of proportions, considering that the actual prevalence of inappropriate prescriptions for one of the outcomes studied (dose, dilution, infusion rate, or time of vancokinemic collection) was 20% and the difference between the actual and estimated prevalence was up to 10%. At a significance level of 5%, the result was 61 patients.

DATA COLLECTION

At least five visits were made to each sector, during which data were collected from the electronic medical record (MV-PEP) of hospitalized patients using intravenous vancomycin and observed the nursing routine, with regard to the administration of the drug and the collection of the vancokineemia test.

The data obtained were recorded in a specific form for the research (appendix A), which consisted of:

- Medical record data regarding the patient and the prescription: name, record, estimated or measured weight, date of start of vancomycin use, day of vancomycin use, dose, dilution, infusion time, dose and dosage correction according to vancocinemia value, reaction to vancomycin (pruritus or *rash*), presence of kidney injury, creatinine dosage at admission/baseline, Vancocinemia dosages, interval between doses.

- Nursing routine: administration of vancomycin in terms of dose, dilution, scheduling and speed of infusion, collection of vancocinemia, and interval between collection of the test and administration of the next dose of vancomycin (whether or not performed in the valley).
- Medical routine: whether and when the next dose of vancomycin was adjusted.

DATA ORGANIZATION AND ANALYSIS

The data were stored in Excel spreadsheets and analyzed using the Sigmastat 4.0 program (SSI, São José, CA).

The characterization of the subjects by sector was expressed as mean and standard deviation or median with interquartile ranges for continuous variables (age, weight, baseline creatinine, day of hospitalization, day of vancokineemia) and frequency for the sex categories.

Similarly, the prescribing patterns by sector were initially described by means of medians and interquartile ranges for continuous variables (loading and maintenance doses) and frequency for categorical variables (presence of prescribing attack, dilution, and infusion rate). Subsequently, the data on prescription, administration, vancocinemia collection, and dose adjustment were categorized as adequate or inadequate, and frequency calculations were made for each sector.

For each HC-FMB unit, vankokineemia levels, as well as the day of antibiotic therapy on which patients were at the collection of the 1st vancocinemia, were described using medians and interquartile ranges.

Medians and interquartile ranges of the 1st vanchokineemia of patients who did not develop AKI and those who developed AKI in each sector were also calculated. The occurrence of AKI and skin reactions were established as outcome variables, the frequencies of which were also calculated for each sector studied.

In a second moment, the analytical stage was performed, using the ANOVA test to compare the continuous variables, except for the comparison of the levels of the 1st vancokineemia of individuals with and without AKI, in which the Mann-Whitney test was applied, both at a significance of 5% ($p<0.05$). The chi-square test was applied to categorical variables at the same level of significance. The correlation between the proper prescription of the infusion time and the development of skin reactions was established using Pearson's correlation coefficient .

DEFINITIONS

The first dose prescribed was considered an attack when it was higher than the next dose prescribed, with no collection of vanchokineemia levels that would justify adjustment. For the

purpose of evaluating the maintenance prescription, the first maintenance dose prescribed was judged.

Loading doses of 24 to 26 mg/kg and maintenance doses of 14 to 16 mg/kg, dilutions with a vancomycin concentration of less than or equal to 5 mg/mL, and infusion rates of up to 17 mg/min were determined to be adequate.

Loading and maintenance prescriptions were defined as appropriate only when they met all the criteria of dose adequacy, dilution and infusion rate.

Regarding administration, the correspondence between dose, dilution and infusion speed prescribed and performed and the time of administration of the medication was observed, with a delay of up to 30 minutes being tolerated. In situations of non-prescription of any of the parameters evaluated, the non-questioning by the nursing team was interpreted as an administration error regarding the respective parameter. Administrations in which at least three of these parameters were considered adequate.

Adequate vancocinemia samples were performed one hour before the next dose of vancomycin and their adjustment was appropriate when performed immediately, i.e., when the vancocinemia result was awaited for the administration of the dose immediately following the collection.

The levels of vancocinemia obtained from the medical records were subdivided into low (< 10 µg/dL), adequate (10 and 20 µg/dL) and high (> 20 µg/dL).

AKI was determined using the KDIGO 2012 criteria, using only creatinine as a parameter. Thus, AKI was defined as an increase in creatinine equal to or greater than 0.3 mg/dL in 48 hours or an increase greater than or equal to 1.5 times the baseline creatinine in an interval of up to seven days (KDIGO, 2012).

RESULTS

Six visits were made to the Internal Medicine, Neurology and Orthopedics wards and five visits to the Vascular Surgery and to Wards 1 and 2 of the Intensive Care Service, so that 67 patients were included in the study, distributed throughout the hospital as follows: 12 in the Internal Medicine ward, 11 in Neurology, 12 in Orthopedics, 9 in Vascular Surgery, 12 in SETI 1 and 11 in SETI 2.

Table 1 shows the characteristics of the patients evaluated hospitalized in the different wards and in the SETIs.

Table 1 – Profile of hospitalized patients using intravenous vancomycin by hospitalization sector, HC-FMB, Botucatu-SP, 2018

	Internal Medicine (n=12)	Neurol. (n=11)	Ortop. (n=12)	Vascular Surgery (n=9)	SETI 1 (n=12)	SETI 2 (n=11)	p
Age Years	57,7 ± 18,7ab	40.6 ± 17.7b	47,9 ± 17,1ab	65.1 ± 8.0a	58,7 ± 17,2ab	49,2 ± 17,6ab	0,031
Sexo masks. (%)	7(58,3)	8(72,7)	9(75,0)	7(77,8)	7(58,3)	9(81,8)	0,74
Gretinina Basel MG/DL	0,6 (0,5–2,2)	0,7 (0,5–0,8)	0,7 (0,7–1,0)	0,8 (0,7–1,2)	0,9 (0,7–1,2)	0,9 (0,7–1,0)	0,10
Day of hospitalization	13,0 (8,7–42,2)	8,0 (7,0–28,0)	14,0 (7,0–32,7)	18,0 (10,5–21,0)	13,0 (9,0– 24,5)	12,0 (8,0 – 18,0)	0,91
Vancomycin Day	8,0 (2,5–15,0)	8,0 (4,0–18,0)	4,0 (2,2– 8,7)	4,0 (1,5– 7,5)	3,0 (1,2–17,2)	4,0 (2,0 – 17,0)	0,62

Data expressed as mean ± standard deviation or median and quartiles
Distinct superscript letters represent a statistical difference, being a>b.
Neurol.: neurology; Orthopedics: orthopedics; SETI: intensive care service.

The patients' ages ranged from 17 to 87 years, with an overall mean of 52.9 ± 17.9 years. Among the sectors studied, the mean age was lower in Neurology (40.6 ± 17.7 years) and higher in Vascular Surgery (65.1 ± 8.0 years).

Similar general characteristics were observed throughout the study population, with a predominance of males, creatinine levels of 0.8mg/dL (0.7 – 1.0), 14.0 (8.0 – 21.0) days of hospitalization and 4.0 (2.0 – 9.0) days of antibiotic therapy with vancomycin.

Similarly, there was no significant difference in weight between the sectors with a median of 66.4 kg (59.8 – 75.0) in the entire population. However, of the 67 patients evaluated, only 58 had weight records in electronic medical records, 50 of them found in the nutrition notes, with Orthopedics being the sector with the fewest weight records. The characteristics of patient weights per hospitalization unit are detailed in Table 2.

Table 2 – Weight in the sectors studied, HC-FMB, Botucatu-SP, 2018

	Internal Medicine (n=12)	Neurology (n=9)	Orthopedics (n=8)	Vascular Surgery (n=7)	SETI 1 (n=11)	SETI 2 (n=11)	p
Weight – Kg*	60,9 (56,5-73,5)	62,0 (58,2-75,3)	68,0 (56,8-87,0)	64,3 (59,8-68,7)	70,0 (63,0-77,8)	68,0 (60,5-76,5)	0,75

*Data expressed as median and quartiles
SETI: intensive care service.

In all, 57 attacks were prescribed, and 1 patient used vancomycin at two different times, with 2 attack prescriptions. There was a wide prescription for attacks in SETI 2, Internal Medicine, and Orthopedics, with no statistically significant differences, as shown in Table 3. There was also no difference in the frequency of attack prescription between wards and SETIs (p 0.73).

Table 3 – Frequency of prescription for vancomycin attacks, according to the hospitalization unit of the HC-FMB, Botucatu-SP, 2018

	Internal Medicine (n=12)	Neurol. (n=11)	Ortop. (n=12)	Cx.Vasc (n=9)	SETI 1 (n=13)	SETI 2 (n=11)	p
No. of loading doses prescribed (%)	11 (91,7)	7 (63,6)	11 (91,7)	7 (77,8)	10 (76,9)	11 (100,0)	0,20

Neurol.: neurology; Orthopedics: orthopedics; Cx. Vasc.: vascular surgery; SETI: intensive care service.

Of these 57 attack prescriptions evaluated, only 50 had their dose calculated in mg/kg, since 7 of the patients did not have weight records in their medical records. The overall median loading dose was 25.0 mg/kg (24.0 – 25.0), equivalent to that of most units individually, as shown in Table 4.

Table 4 – Vancomycin loading dose, HC-FMB, Botucatu-SP, 2018

	Internal Medicine (n=11)	Neurol. (n=5)	Ortop. (n=7)	Cx. Vasc (n=6)	SETI 1 (n=10)	SETI 2 (n=11)	p
Loading dose mg/Kg*	25,0 (25,0– 29,0)	25,0 (22,0– 28,5)	25,0 (22,0–25,0)	23,0 (21,7–25,0)	24,0 (23,2–25,2)	25,0 (24,0–25,0)	0,37

*Data expressed as median and quartiles

Neurol.: neurology; Orthopedics: orthopedics; Cx. Vasc.: vascular surgery; SETI: intensive care service.

Such patients without weight recording had their loading doses classified as inadequate, since it was not possible to calculate the dose per kg of weight. A total of 33 loading doses were adequate (57.9%) and 24 were inadequate (42.1%), with similar distribution among the subgroups (Table 5).

As also shown in Table 5, the evaluation of the loading prescriptions as a whole, considering not only the dose, but also the dilution and infusion speed prescribed, indicated that no loading prescription met the adequacy criteria.

Table 5 – Adequacy of the vancomycin attack, HC-FMB, Botucatu-SP, 2018

	Internal Medicine (n=11)	Neurol. (n=7)	Ortop. (n=11)	Cx. Vasc (n=7)	SETI 1 (n=10)	SETI 2 (n=11)	p
Adequate prescribed loading doses (%)	7 (63,6)	3 (42,8)	4 (36,4)	2 (28,6)	8 (80,0)	9 (81,8)	0,08
Appropriate attack prescriptions (%)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	>0.05

*Data expressed as median and quartiles

Neurol.: neurology; Orthopedics: orthopedics; Cx. Vasc.: vascular surgery; SETI: intensive care service.

The rates of adequacy of the loading dose were higher in the SETIs, with a statistically significant difference in relation to the wards (p 0.02).

In addition to the maintenance prescriptions for each patient, one more was included, referring to the second vancomycin regimen received by one of the patients, totaling 68 maintenance

prescriptions. The lack of weight records of 9 patients also led to a reduction in the number of maintenance doses evaluated, so that the median of the 59 maintenance doses was 15.0mg/kg (14.0 – 16.0), close to that of each sector, as shown in Table 6.

Table 6 – Vancomycin maintenance dose, HC-FMB, Botucatu-SP, 2018

	Internal Medicine (n=12)	**Neurol. (n=9)**	**Ortop. (n=8)**	**Cx. Vasc (n=7)**	**SETI 1 (n=12)**	**SETI 2 (n=11)**	**p**
Maintenance dose mg/Kg*	15,0 (11,0–16,0)	16,0 (14,0–17,5)	15,0 (14,0–15,7)	15,0 (13,0–15,0)	14,5 (13,2–15,7)	15,0 (14,0–16,0)	0,74

*Data expressed as median and quartiles
Neurol.: neurology; Orthopedics: orthopedics; Cx. Vasc.: vascular surgery; SETI: intensive care service.

Analogous to the loading dose, the maintenance doses of the 9 patients whose weight was unknown were considered inadequate, as were another 20 doses, resulting in an inadequate rate of 42.6%. SETI 2 and Internal Medicine were the hospital units with the best rates of adequacy of the maintenance dose and, together with Vascular Surgery, also adequacy of the maintenance prescription, advantages that were not statistically significant (Table 7).

In the comparison between the wards and the SETIs, there were no significant differences regarding the rates of adequacy of dose (p 0.37) and maintenance prescription (p 1.00).

Table 7 – Adequacy of vancomycin maintenance, HC-FMB, Botucatu-SP, 2018

	Internal Medicine (n=12)	**Neurol. (n=11)**	**Ortop. (n=12)**	**Cx. Vasc (n=9)**	**SETI 1 (n=13)**	**SETI 2 (n=11)**	**p**
Adequate prescribed maintenance doses (%)	9 (75,0)	4 (36,4)	6 (50,0)	4 (44,4)	7 (53,8)	9 (81,8)	0,21
Appropriate maintenance requirements (%)	3 (25,0)	0 (0,0)	0 (0,0)	2 (22,2)	0 (0,0)	2 (18,2)	0,11

*Data expressed as median and quartiles
Neurol.: neurology; Orthopedics: orthopedics; Cx. Vasc.: vascular surgery; SETI: intensive care service.

Dilution and infusion time were prescribed, respectively, in 768 (77.6%) and 212 (21.4%) of the 989 prescriptions evaluated.

Leading the way in terms of prescribed dilution frequency, Neurology (97.8%) was statistically superior to the other sectors. On a second level, SETI 2 (87.6%) and Internal Medicine (84.9%) are similar to each other, although there is a statistically significant difference between SETI 2 and SETI 1 (77.2%), but non-existent between Internal Medicine and SETI 1. Following SETI 1,

the Vascular Surgery (57.9%) and Orthopedics (46.5%) wards are statistically inferior to the other units, as shown in Table 8.

Table 8 also shows that the infusion time was prescribed more frequently in SETI 2 (51.1%) when compared to the other units. In order of frequency, there are followed by Internal Medicine (33.3%) and Vascular Surgery (31.6%), which are similar to each other, but statistically different from the others. In SETI 1, the infusion time was prescribed in 14.6% of prescriptions, similar to that prescribed in the Orthopedics ward (13.5%). The Neurology ward was notably the one with the shortest prescribed infusion time, since none of its prescriptions included the infusion time.

Both rates of dilution prescription frequency and infusion time were higher in SETIs compared to wards (p 0.04 and p <0.001, respectively).

Table 8 – Frequency of dilution prescription and vancomycin infusion time, according to the hospitalization unit of the HC-FMB, Botucatu-SP, 2018

	Internal Medicine (n=192)	**Neurol. (n=224)**	**Ortop. (n=170)**	**Cx.Vasc (n=95)**	**SETI 1 (n=171)**	**SETI 2b (n=137)**	**p**
No. of prescribed dilutions (%)	163 (84.9)^{bc}	219 (97.8)^{a}	79 (46,5)^{d}	55 (57,9)^{d}	132 (77,2)^{c}	120 (87,6)^{b}	<0.051
No. of prescribed infusion time (%)	64 (33,3)^{b}	0 (0,0)^{d}	23 (13.5)^{c}	30 (31,6)^{b}	25 (14.6)^{c}	70 (51.1)^{a}	<0.052

Distinct superscript letters represent a statistical difference, being a>b>c>d.
Neurol.: neurology; Orthopedics: orthopedics; Cx. Vasc.: vascular surgery; SETI: intensive care service.

Of the total of 768 dilutions prescribed in the 6 units studied, 433 (56.4%) were adequate.

Evaluating the sectors, Internal Medicine (82.8%) is at the top, with the highest rates of dilution adequacy. The second level is composed of Vascular Surgery (74.5%), SETI 2 (69.2%) and Orthopedics (59.5%), all of which are similar to each other and, with the exception of Vascular Surgery, statistically inferior to Internal Medicine. Finally, there is SETI 1 (36.4%) and Neurology (36.1%), as can be seen in Table 9. SETIs and wards were similar in terms of dilution adequacy (p 0.10).

Table 9 – Adequacy of the prescribed vancomycin dilutions, according to the hospitalization unit of the HC-FMB, Botucatu-SP, 2018

	Internal Medicine (n=163)	Neurol. (n=219)	Ortop. (n=79)	Cx.Vasc (n=55)	SETI 1 (n=132)	SETI 2 (n=120)	P
No. adequate prescribed dilutions (%)	135 (82.8)[a]	79 (36.1)[c]	47 (59,5)[b]	41 (74.5)[ab]	48 (36.4)[c]	83 (69,2)[b]	<0.051

Distinct superscript letters represent a statistical difference, being a>b>c.
Neurol.: neurology; Orthopedics: orthopedics; Cx. Vasc.: vascular surgery; SETI: intensive care service.

Prescribed only 212 times, the infusion time was correct in 169 (79.7%) records. Table 10 shows the frequency of adequate prescription of the infusion time, according to the hospitalization units of the HC-FMB, through which it is possible to observe that it was not prescribed once in Neurology, while in Orthopedics, although prescribed in 23 evaluations, it was not adequate in any of them. In the other sectors studied, the infusion time, when prescribed, was mostly adequate, with no significant differences between them. There was also a discrepant trend between SETI Wards 1 and 2 (p 0.058).

In the analysis of SETIs *versus* wards, there were higher rates of adequacy of the prescribed infusion time in SETIs (p 0.003).

Table 10 – Adequacy of the prescribed vancomycin infusion times, according to the hospitalization unit of the HC-FMB, Botucatu-SP, 2018

	Internal Medicine (n=64)	Neurol. (n=0)	Ortop. (n=23)	Cx. Vasc (n=30)	SETI 1 (n=25)	SETI 2 (n=70)	P
No. of adequate prescribed infusion time (%)	55 (85.9)[a]	0 (0,0)[b]	0 (0,0)[b]	29 (96.7)[a]	25 (100.0)[a]	60 (85.7)[a]	<0.051

Distinct superscript letters represent a statistical difference, being a>b.
Neurol.: neurology; Orthopedics: orthopedics; Cx. Vasc.: vascular surgery; SETI: intensive care service.

Among the 67 patients, 9 cases of cutaneous reaction to vancomycin were recorded, of which 7 presented as *a rash* and 2 as pruritus. In 7 of the 9 cases, antihistamines were prescribed after the skin reaction, with discontinuation of antibiotic therapy in only one refractory case. There was no statistically significant difference between the units (Table 11), between the two SETI wards (p 0.49) or between the SETI and the wards (p 0.15).

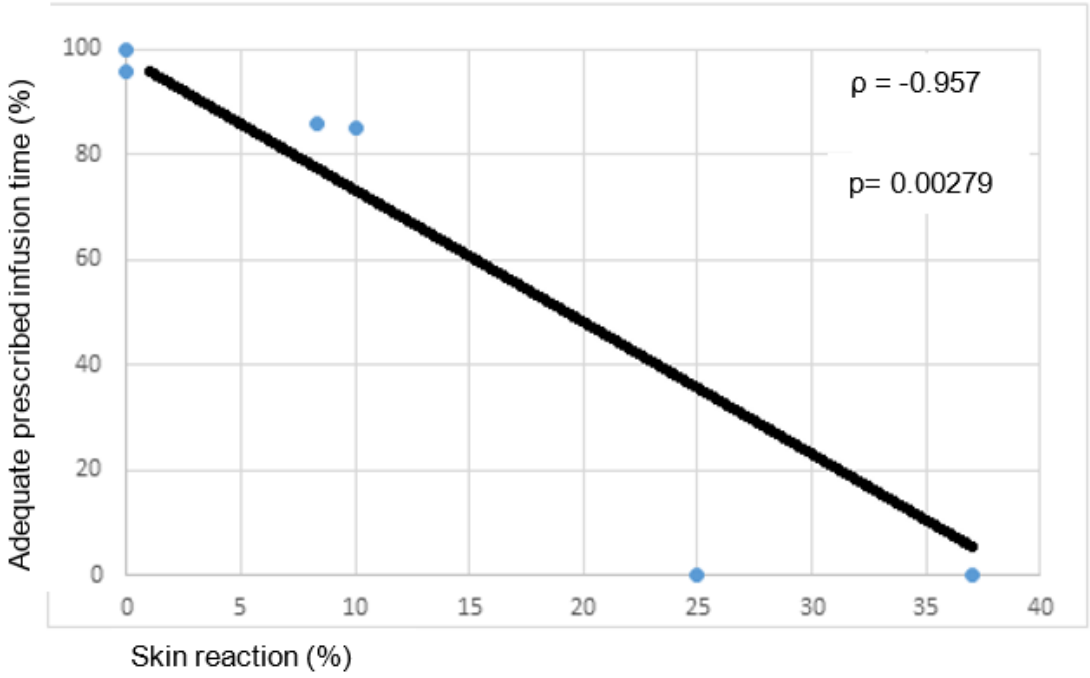
Table 11 – Skin reaction in patients using intravenous vancomycin by hospitalization sector, HC-FMB, Botucatu-SP, 2018

	Internal Medicine (n=12)	Neurology (n=11)	Orthopedics (n=12)	Vascular Surgery (n=9)	SETI 1 (n=12)	SETI 2 (n=11)	p
Skin reaction (%)	1 (8,3)	4 (36,4)	3 (25,0)	0 (0,0)	0 (0,0)	1 (9,1)	0,074

SETI: intensive care service.

Figure 1 shows the inverse relationship between the appropriate prescription of the infusion time and the presentation of an adverse skin reaction. Thus, it can be seen that in the sectors in which, although the infusion time was not frequently prescribed, it was proportionally prescribed more appropriately, there was no development of skin reaction, as in SETI 1, in which the infusion time was only prescribed in 14.6% of the cases, but always adequately (100% of the infusion prescriptions). No cases of adverse skin reaction observed.

Figure 1 – Correlation between skin reaction and prescription of adequate infusion time in the inpatient units of HC-FMB, Botucatu-SP, 2018



Comparing what was prescribed and what was done, 56 administrations were observed, of which 32 (57.1%) were in disagreement with what was prescribed (Table 12).

During the direct observation of the administrations, 8 discrepancies were observed regarding the administered and prescribed dose, of which 4 resulted from conflicting information in the medical records, with different dose records between the proper field for dose insertion and the one intended for placing prescription-related observations in the MV-PEP system.

Of the 15 errors related to dilution, 11 (73.3%) were classified as such due to the non-prescription of dilution without questioning it by the nursing team.

Failures related to infusion time were the most frequent in all units, with 50 cases (89.3%) identified, of which 10 (20%) were attributed solely to non-prescription by the nursing team without a request for clarification, 5 (10%) were due only to infusion by macrodrops without counting the drip, 34 (68%) by the association of both and only 1 (2%) by inserting a different time than the prescribed time in the infusion pump.

The use of a continuous infusion pump in the administration of vancomycin was only observed in one third of the administrations attended in the Medical Clinic, in half of those in SETI 1 and in all those of SETI 2, so that the administration errors related to the infusion time were due to the non-prescription in the latter only due to the non-prescription without requesting clarification.

There were delays in 15 administrations, 7 (46.7%) of which were from 31 minutes to 1 hour and 8 (53.3%) were longer than 1 hour.

In an analysis, by sector, of the factors related to administration, there were statistically higher rates of dilution adequacy in Internal Medicine compared to Orthopedics, Vascular Surgery and SETI 1 and infusion time in SETI 2 compared to Orthopedics, as shown in Table 12.

No significant differences were identified regarding the adequacy of administration in comparison between wards and SETIs (p 0.21).

Table 12 – Adequacy of Vancomycin administration in the sectors evaluated, HC-FMB, Botucatu-SP, 2018

	Internal Medicine (n=12)	**Neurol. (n=9)**	**Ortop. (n=13)**	**Cx. Vasc (n=7)**	**SET 1 (n=8)**	**SET 2 (n=7)**	**p**
Administration dose (%)	9 (75,0)	7 (77,8)	10 (76,9)	7 (100,0)	8 (100,0)	7 (100,0)	0,30
Administration dilution (%)	12 (100.0)[a]	8 (88,9)[ab]	6 (46,1)[b]	4 (57,1)[b]	5 (62,5)[b]	6 (85,7)[ab]	<0,05
Administration infusion time (%)	3 (25,0)[ab]	0 (0,0)[ab]	0 (0,0)[b]	0 (0,0)[ab]	0 (0,0)[ab]	3 (42.9)[a]	0,03
Time of administration (%)	8 (66,7)	7 (77,8)	9 (69,2)	5 (71,4)	6 (75,0)	6 (85,7)	0,96
Adequate administrations (%)	5 (41,7)	6 (66,7)	2 (15,4)	2 (28,6)	4 (50,0)	5 (71,4)	0,10

Distinct superscript letters represent a statistical difference, being a>b.
Neurol.: neurology; Orthopedics: orthopedics; Cx. Vasc.: vascular surgery; SETI: intensive care service.

Of the 59 patients using the first vancomycin regimen during hospitalization for two or more days, 52 (88.1%) had at least one vancocinemia collected.

It was observed that, in the entire population, the collection of the first vancokineemia was mostly performed on the second day of antibiotic therapy (median of 2.0, 2 – 2.7), which is similar among the hospital sectors.

Due to logistical difficulties, only 15 vancocinemia samples were followed, and none of them could be followed up in Neurology. Of the 9 adequate collections, 6 were carried out in SETI 1, with a 100% adequacy rate in this sector.

Adjustment of the vancomycin dose, according to its serum result, was also observed in 15 patients, with 8 (53.3%) adjustments made immediately after the release of the test and thus considered adequate. Although the request for vancocinemia was observed in the Vascular Surgery ward, because it was not collected, it was not possible to follow the adjustment of the antibiotic dose.

No comparative analyses were performed between the units regarding the collection of vancocinemia and dose adjustment due to the reduced number of observations, and no significant differences were identified in a comparative analysis between wards and SETIs (p 0.12 and p 0.20, respectively).

A total of 265 vanchokinemias were evaluated, with a median of 17.5mg/L (13.0 – 23.4), of which 34 (12.8%) were considered low, 132 (49.8%) adequate, and 99 (37.4%) were high. According to Table 13, Internal Medicine and Vascular Surgery had the highest levels of vancokineemia, similar to each other and significantly higher than the others, with the exception of SETI 2, which did not show a significant difference to the other sectors.

Table 13 – Levels of vancocinemia in the sectors studied, HC-FMB, Botucatu-SP, 2018

	Internal Medicine (n=63)	**Neurol. (n=41)**	**Ortop. (n=16)**	**Cx.Vasc (n=25)**	**SET 1 (n=70)**	**SETI 2 (n=50)**	**p**
Vancocinemia mg/L*	22,0 (15.4–33.0)[a]	14,9 (11,2– 17,9)[b]	13,4 (9,5– 16,2)[b]	22,8 (16.3–29.8)[a]	17,2 (12,7–20,6)[b]	16,7 (12.9–21.9)[ab]	<0.051

*Data expressed as median and quartiles.
Distinct superscript letters represent a statistical difference, being a>b.
Neurol.: neurology; Orthopedics: orthopedics; Cx. Vasc.: vascular surgery; SETI: intensive care service.

The development of AKI during the use of vancomycin was evaluated in 41 patients, since of the 67 individuals included in the study, 4 only had creatinine levels prior to the start of vancomycin therapy, 18 had the last creatinine level up to the second day of antibiotic therapy, 3 patients were on chronic dialysis and 1 was on dialysis at the beginning of hospitalization.

In all, 13 patients (31.7%) developed AKI, according to the KDIGO 2012 criteria, considering only the creatinine parameter.

Table 14 shows the development of AKI by hospitalization sector.

Table 14 – Acute kidney injury from the 3rd day of vancomycin use, according to the hospitalization unit of the HC-FMB, Botucatu-SP, 2018

	Internal Medicine (n=8)	Neurol. (n=8)	Ortop. (n=7)	Cx. Vasc. (n=4)	SETI 1 (n=7)	SETI 2 (n=7)	p
Acute kidney injury (%)	1 (12.5)^{BC}	0 (0)^{c}	0 (0)^{bc}	2 (50)^{AC}	6 (85.7)^{a}	4(57,1)^{ab}	<0.051

Distinct superscript letters represent a statistical difference, being a>b>c.
Neurol.: neurology; Orthopedics: orthopedics; Cx. Vasc.: vascular surgery; SETI: intensive care service; AKI: acute kidney injury.

The highest frequency of AKI recorded was in SETI 1, in which 85.7% of the patients included in the analysis had altered renal function. However, despite being superior to SETI 2 and the Vascular Surgery ward, these differences were not statistically significant. The Internal Medicine, Neurology and Orthopedics wards were the ones with the lowest AKI rates, statistically lower than those of SETI 1, and Neurology was also significantly lower than SETI 2.

Comparing the data from wards and SETIs, higher rates of AKI were observed in SETIs (p<0.001), but with no significant difference regarding the day of vancomycin use at the time of the last creatinine measurement (p 0.95).

Among the patients evaluated for the outcome of AKI, we compared the day of antibiotic therapy with vancomycin, in which each patient was at the time of the last creatinine measurement, with a median of 16.0 (5.5 – 27.0) days among those who had AKI and a median of 7.0 (4.1 – 12.7) days, in those who maintained stable renal function, a clinically significant difference. although not statistically significant (p 0.06).

Of the 41 individuals evaluated for the development of AKI, 1 patient did not have any dosage of vankokineemia, so that among the remaining 40 individuals, it was found that the values of the first vankocinemia were statistically higher among those who developed AKI, with a median of 21.0 (12.8 – 30.7) mg/L, while that of those who maintained stable renal function was 10.3 (7.1 – 14.0) mg/L (p=0.002).

DISCUSSION

The group of patients evaluated presented homogeneous general characteristics, with a predominance of older patients in the Vascular Surgery ward and patients with a lower mean age in Neurology, however, despite the similar general characteristics, it is not possible to state that the population was really homogeneous, since the causes of admission and severity scores that would allow the comparison of outcomes such as the development of AKI were not accurately evaluated.

Diffuse medical knowledge was observed regarding the indications for vancomycin attack, however, with levels of adequacy of loading and maintenance doses in the entire population still of approximately 57%, with no significant differences between sectors. However, an important

difference was found regarding the adequacy of the loading dose of the wards and SETIs, which is not justified only by the lower number of weight records in the wards, and this would also reflect a discrepancy in the adequacy of the maintenance doses between wards and SETIs, which was not found. Thus, it is inferred that SETI physicians have a greater knowledge of the recommended attack dose.

The prescription of dilution was shown to be frequent, with lower rates in the Orthopedics and Vascular Surgery wards, but with still low levels of adequacy in almost all sectors, especially Neurology, whose frequency of dilution prescription was the highest, standing out to the other units, although with the lowest adequacy index.

The infusion time, although hardly prescribed, even in SETIs, showed high levels of adequacy, with the exception of Orthopedics, which stands out for all its prescribed infusion times being inadequate. This evidences a devaluation of the prescription of the infusion time by the medical team, which, despite showing knowledge of the recommendations, does not seem to understand the importance of its prescription.

A significant difference was found regarding the frequency and adequacy of the prescribed infusion time between wards and SETIs, however, this discrepancy appears to be due to the rates of prescription and adequacy of Orthopedic Neurology notoriously lower than the others, increasing the inequality between wards and SETIs.

The high rates of non-prescription or inadequacy of dilution and infusion time have repercussions on reduced rates of adequacy of attack and maintenance prescriptions.

With a very variable incidence in the literature, ranging from 4 to 50%, in infected patients treated with parenteral therapy, the occurrence of vancomycin-related skin reaction was 13.4% in HC-FMB (MARTEL; WHITTEN, 2018).

An inversely proportional relationship between the occurrence of adverse skin reaction and adequate prescription of the infusion time was identified, but not between such effect and the frequency of prescription of the infusion time. This reflects that the non-prescription of the infusion time does not necessarily represent an administration at an infusion speed related to a higher risk of skin reaction, i.e., even without medical guidance, the nursing team has some knowledge about the need for slow infusion of vancomycin.

It is also inferred that, when prescribed, the infusion time is usually administered in a manner similar to that prescribed, since the development of skin reaction was inversely proportional to the adequate prescription of the infusion time. Administration observation data reinforce this induction, since among the 12 administrations observed, whose infusion times were prescribed, 6 were fully in accordance with the prescribed, whether the prescription was adequate or not, 5 were not adequately executed, since the drip count was not performed in any of them, so that the infusion speed could or

could not be adequate. and in 1 of the administrations, despite being prescribed and administered by means of BIC, the infusion time inserted was different from that prescribed. This relationship reinforces the direct association between infusion time and skin reaction already established in the literature (SÍLVA JÚNIOR, 2015; HOEFEL et al., 2008; MATSUMOTO et al. 2013; DRISYAMOL; MAHESH, 2016).

It was observed that the sector that best meets the criteria of an adequate prescription (loading dose, maintenance dose, concentration and infusion speed) is SETI 2, followed by Internal Medicine, but both still have points that can be improved.

Also in the global evaluation, regarding all items related to prescription, discrepancies between the two SETI wings stand out, with significantly higher dilution prescription frequencies and infusion time in SETI 2, while the adequacy rate of the prescribed infusion time was statistically higher in SETI 1, data that show the non-uniformity of prescription among the medical team of both sectors.

A study developed by Cassiani, Freire and Gimenes (2003) analyzed 1,351 electronic medical prescriptions from a university hospital and interviewed 84 medical professionals from the nursing team and the administrative sector about the advantages and disadvantages of this prescription system. In the evaluation of the prescriptions, erasures, manually suspended medications, information susceptible to doubts, and manual prescription of medications were found. The advantages of the electronic prescription system were: ease of reading data, speed of prescription release, reduction of prescription errors, greater organization and practicality, agility with the pharmacy, data archiving, antimicrobial form included, standardization of medications and the presence of the prescriber's name. Users complained, especially, about the repetition of prescriptions from previous days without review, incorrect typing of information, dependence on the electronic system, manual changes of prescriptions, confusing prescriptions, and loss of dynamism in emergency situations. The interviewees also addressed the small number of computers available.

A similar reality is experienced at the HC-FMB, in which the electronic medical record solved many problems regarding medical prescription, integration of information and closer communication between professionals. However, in the course of this study, changes in prescriptions and suspensions of manual medications were also identified, devaluing the electronic medical record as a source of data for research, in addition to erasures and repetition of previous prescriptions without review of prescription and, mainly, observation data, leading to the generation of prescriptions with the recording of the same observations that, Frequently, they advise a dose that differs from the prescribed one or wait for medical clearance for administration after the result of vancocinemia on occasions when it was not even requested.

Other difficulties related to the MV-PEP electronic medical record system were observed, such as the automatic scheduling of vancomycin every 6 hours, which must be changed by the prescriber, the permission to insert the dose in the form of the number of vials or in milligrams, being an important cause of administration errors related to the dose, in which the dose, in milligrams, oriented in the field of observation, differs from that prescribed in number of vials.

There were 2 scheduling trends among the hospital units: one followed in the Medical Clinic and in the SETIs, in which the prescribed dose of vancomycin is scheduled according to the previous dose administered and another in force in the Neurology, Vascular Surgery and Orthopedics wards, in which the medications to be administered every 12 hours, The most common frequency of vancomycin prescriptions is scheduled for 10 a.m. and 10 p.m., regardless of the time of previous administration. Both models have positives and negatives. The former allows for a more correct administration, in theory, with immediate administration of the loading dose and fixed administration intervals, while the latter leads in some situations to delayed initiation of therapy and variable intervals between the loading dose and the first maintenance dose. On the other hand, the first model, if not performed by a prepared team, can generate confusion and administration errors because they do not fit into the standard schedules of the ward, which would be avoided with the second.

In the sectors in which the scheduling is performed according to the previous dose, it was observed that there was no use or lack of knowledge of the functionality of changing the standard scheduling of the MV-PEP system, causing the frequent need to prescribe scheduled doses for now, in order to allow the release of the medication by the pharmacy without this actually representing the administration at that moment.

Another obstacle to scheduling, according to the previous administration, is the non-standardization of the transfer of those patients with prescriptions already made and medications already dispensed by the pharmacy, between sectors or coming from the Municipal Hospital, also under the administration of UNESP, leading to the need for a new prescription, with several schedules for now and the professional's displacement to receive the medications at the pharmacy. Which, in addition to hindering the correct scheduling and delaying administrations, also makes it difficult to refund medications to the pharmacy, generating higher costs to the service.

As important as the prescription itself is its execution, since both play an inseparable role in the final result, which can alter clinical outcomes (adverse reactions, toxicities and therapeutic response) and lead to the emergence of vancomycin-resistant strains of bacteria. In Brazil, this effector function is performed by the nursing team, so that the administration of intravenous antibiotic therapy is performed by nursing technicians, under the supervision of the nurse (HOEFEL et al., 2008).

The administration failures reflected the medical prescription errors, in the expressive majority, since the main administration errors, with regard to the dose, resulted from conflicting information in the medical records, those related to dilution and infusion time related to the non-prescription of the doctor, and the practice of not counting drips was also of great importance to the latter. Thus, the nursing team sinned with regard to the administration by not requesting clarification regarding doubtful information and non-prescribed data, the habit of not counting the drip, even starting the infusion at a certain speed with an increase in it when close to the end of the prescribed infusion period, in addition to delays, which should be better evaluated, in order to clarify the factors involved and analyze the possibility of team overload.

Vancomycin monitoring is recommended by most authors only for a population at risk for the development of vancomycin-induced nephropathy or in situations in which serum levels are considered unpredictable (MATSUMOTO et al., 2013; DOMBROSKI; SILVA; SILVEIRA, 2015; YE et al. 2016).

In the population studied, although the causes of admission, comorbidities, and severity scores were not evaluated, only the indications for monitoring in the elderly, in patients using vancomycin for more than 3 days and hospitalized in the ICU, would justify this practice in the vast majority of individuals. Thus, the extent of the risk population and the duration of treatment regimens with vancomycin support the recommendation of routine monitoring at HC-FMB, which should be done one hour before the next dose to be administered, according to the recommendations in the literature (MATSUMOTO et al., 2013; DOMBROSKI; SILVA; SILVEIRA, 2015; YE et al. 2016). It was found that such guidelines are generally followed appropriately.

This collection is carried out in the wards, from Monday to Friday, from 7 a.m. to 4 p.m., by an employee exclusively for the collection of tests and the blood transported to the laboratory, along with the other laboratory tests in the sector, by an employee in charge at regular intervals of 1 hour. During the night, weekends and holidays, the collection from the wards is done by the technician responsible for patient care and sent to the laboratory as soon as possible. In SETIs, vancocinemia is collected by the nurse in the sector, and the patient is taken to the laboratory soon after.

Despite the reduced number of collection observations and vancocinemia adjustment due to logistical issues, SETI 1 stood out for the follow-up of a considerable number of collections with a collection adequacy rate of 100%, leading to high reliability of vancocinemia results collected in this sector.

Regarding the annotation of the times of collection of vancocinemia and administration of vancomycin, it was found that, for practical reasons, the nursing technicians confirm at a single moment the collection of the tests to be collected in the sector in the next few hours, not representing the reliable time of collection. The verification of the administration of the medications in the printed

prescription is often recorded as if proceeded at the time scheduled in the prescription, without annotation of the actual time of administration, even in cases of delays due to waiting for the result of the vancokineemia.

On weekends and at night, when the sectors work on an on-call basis, it is easier to adjust the vancomycin of patients hospitalized in SETIs and to the care of the Medical Clinic, most of whom are hospitalized in the ward of the specialty itself, since these units have exclusive on-call staff for the sector, unlike surgical specialties. Neurology and Orthopedics, which has a small number of on-call physicians in charge, not only of its wards, but also of the emergency sector.

In all, 265 vancocinemia were evaluated. However, this analysis, as it considers all samples from each sector, may be biased, since it does not consider the possibility of a larger number of samples from the same patient who may have had high initial levels.

Reports of AKI range from 0 to 5% in monotherapy, with a significantly higher frequency when in combination with aminoglycosides or piperacillin-tazobactam, of 35% and 42%, respectively (ALMEIDA, 2011; MIN et al., 2011). In the HC-FMB, 31.7% of the individuals evaluated developed AKI. Despite the relatively high incidence, because other prescription data, such as the use of risk drug combinations, are not evaluated, it is not possible to establish a parallel with the data in the literature.

The development of AKI was significantly higher in SETIs and was not related to vancocinemia levels or prolonged therapy, since the sectors with the highest serum vancomycin levels were the Internal Medicine and Vascular Surgery wards and no significant discrepancies were found regarding the duration of antibiotic therapy between SETIs and wards. Thus, although no causes of admission or severity scores were evaluated, it is inferred that the development of AKI is related to the greater severity of individuals hospitalized in SETIs.

Among the individuals who developed AKI, it was observed that the duration of antibiotic therapy with clinically superior vancomycin was observed, as well as higher levels of the 1st vancokineemia. These findings corroborate the data described in the literature that vancomycin-induced nephropathy is dose-dependent and that individuals undergoing long-term therapy are at greater risk of developing it, reinforcing the need for correct monitoring and dose adjustment (NORTON et al., 2013; AZEVEDO, 2015). In addition, it suggests that the value of the 1st vancokineemia could be a predictor of the appearance of AKI during treatment, and for confirmation, a study should be carried out that evaluates together and in a more detailed way the adjustment of the dose according to serum levels, in order to exclude the possibility that such association is due to the incorrect adjustment of vancomycin, with the perpetuation of high levels of vancocinemia.

The management of vancomycin is very fine, interfered with by several factors and involves a multidisciplinary team, so that the entire team should have general knowledge about the complete

process and training in what concerns it, allowing the team itself to identify failures and assist in its inspection (RYBAK, 2009; MATSUMOTO et al., 2013; PHILLIPS; GORDON, 2015; OLIVEIRA, 2016; YE et al., 2016). Thus, it is suggested that an institutional protocol be standardized and developed through the MV-PEP system that addresses prescription guidelines, vancocinemia collection, and dose adjustment, both in patients with normal renal function and in those with dysfunction and in renal replacement therapy.

Some studies attempt to assess the impact of educational interventions on vancomycin monitoring. Swartling et al. (2012) developed a short manual for the administration and monitoring of vancomycin for physicians and pharmacists and an instrument with guidance on the collection of vancocinemia for nurses, in addition to distributing cards containing doses of antimicrobials and recommendations for monitoring vancomycin for physicians and pharmacists, and found a significant increase in the adequacy rates of the initial dose of vancomycin prescribed and collection of vancocinemia after the intervention.

Coleman and Wilson (2015), on the other hand, carried out an intervention aimed only at nurses, through voluntary educational lectures, observing an improvement in the collection rates of adequate vancocinemia, although not significant, and an important increase in nursing knowledge regarding vancomycin monitoring, accessed through a questionnaire ($p<0.001$).

Another study conducted by Melanson et al. (2013) sought solutions based on information technology with the implementation of an electronic alert to nurses, advising that vancocinemia should be collected 60 minutes before the next dose to be administered. They identified a gradual decline in the frequency of collection errors, however, since before the intervention, with no significant reduction after the measurements. They also found a higher incidence of collection errors between 4 and 10 a.m. ($p<0.0001$), when the previous dose was administered late ($p<0.0001$) and when performed by nursing technicians ($p<0.0001$), and a reduction in errors when there was a specification at the time of requesting the date and time of collection.

Although significant increases in the number of adequate vancocinemia collections were only observed in the study by Swartling et al. (2012), in which the target audience of the measures was physicians and nurses, both in the study by Coleman and Wilson (2015) and in that of Melanson et al. (2013), a low participation of nurses was considered due to the scheduled time for lectures and the need to accept participation in the electronic system. respectively, which may have resulted in less significant results. This hypothesis is reinforced by the results of the pre- and post-intervention tests applied by Coleman and Wilson (2015), which showed a significant improvement in nursing knowledge after the lectures ($p<0.0001$).

It is also necessary to emphasize that, in the service in which the study by Melanson et al. (2013) was conducted, the same intervention had already been previously implemented, targeting

physicians, which explains the reduction in vancokinemic collection errors, since before the intervention carried out with nurses, and suggests that such intervention with the team of prescribing physicians is effective and could have attenuated the effect of the intervention with nurses.

Another important point to be considered is the duration of the effects achieved with the intervention, which were only observed for short periods in the studies by Swartling et al. (2012) and Coleman and Wilson (2015), for 1 and two months, respectively, while the study by Melanson et al. (2013) performed follow-up for 1 year after the intervention.

Considering that the HC-FMB is a university hospital, the nucleus of several medical residency programs, with frequent rotation of the prescribing medical team and with differences between the sectors regarding the support of the faculty, it is proposed to carry out intervention measures focused mainly on the nursing team, responsible for carrying out the actions of administration and collection of vancocinemia. It is important to emphasize the need to standardize the time of administration of vancomycin and the collection of vancocinemia in situations of delay of the previous dose of the antibiotic and the need or not to wait for the result of vancocinemia, according to the reality of each sector.

It is also suggested that it is mandatory to change prescriptions via the MV-PEP system and standardize the transfer of the patient between the sectors, accompanied by their prescription and the medications already dispensed by the pharmacy, with verification of them upon receipt of the patient in the destination sector, in order to facilitate the understanding of the electronic medical record and the reversal of medications to the pharmacy. reducing service costs.

CONCLUSION

There are failures in the prescription, administration and monitoring of vancomycin in all sectors of this UH. SETI 2 and Internal Medicine were the sectors that best met the criteria for adequate prescribing. There is a need to implement measures for the qualification and training of medical and nursing professionals, as well as inspection actions regarding the rigor of prescription and administration.

The data from medical records were not completely reliable to what was done in practice, however, the study was not able to reduce the importance of medical records as a data collection tool. It is suggested that further studies be carried out to monitor the process of administration, collection of vancocinemia and dose adjustment with a larger population.

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