Serum concentration of vancomycin is a diagnostic predictor of nephrotoxic acute kidney injury in critically ill patients

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Background

There have been few studies to evaluate the monitoring of plasmatic concentrations of vancomycin in septic patients and their association with acute kidney injury (AKI) and death. This study aimed to evaluate the prevalence of adequate, subtherapeutic, and toxic serum concentrations of vancomycin in hospitalized septic patients and to associate the adequacy of therapeutic monitoring with clinical outcomes.

Methods

This was a prospective observational cohort study of adult patients diagnosed with sepsis defined using the quick SOFA and admitted to intensive care units (ICU) of Clinics Hospital of Botucatu Medical School during August 2016 to July 2017. Vancomycin was used according to the institution's protocols: loading dose of 25 mg/kg and maintenance of 15 mg/kg, with dosing intervals of 12/12-96/96 hours, depending on the serum concentration of the anti-microbial.

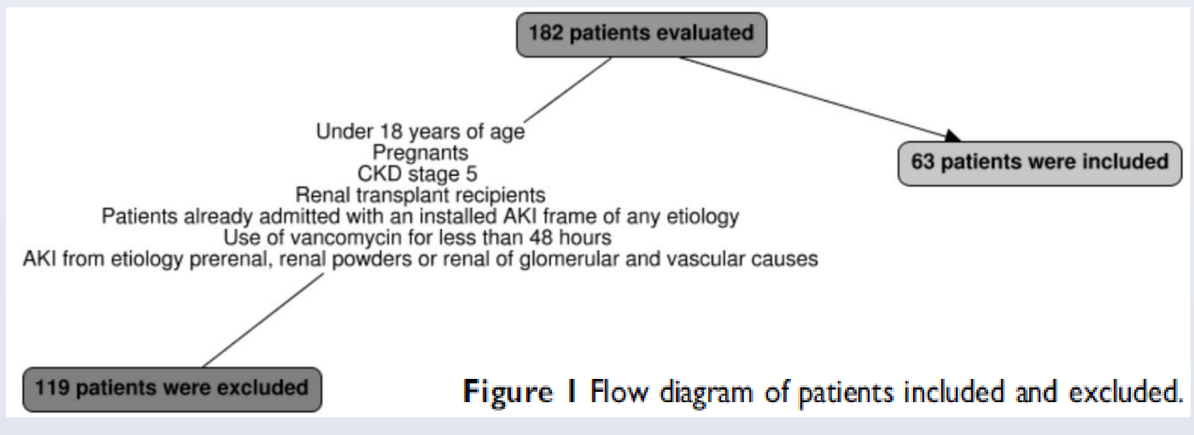

Figure 1 Flow diagram of patients included and excluded.

The study was approved by the local research ethics committee and registered in the Brazilian Registry of Clinical Trials (ReBEC) under number RBR-4zrwtz.

Results

We included 63 patients, aged 54.67 ± 18.7 years, male predominance (66.7%), BMI 26.1 ± 6.8 and mean time of use of vancomycin 11.4 ± 7.33 days. The vast majority of patients (92%) had performed the serum vancomycin measurement, and 53.96% were in a concentrations considered toxic (greater than 20mg/L). The prevalence of AKI was 44.4%, with the stage KDIGO 3 being most common (46.4%), and 46% died.

Table 3. Cox regression of the associated variables presence of AKI in patients using vancomycin admitted to the ICU

Variables	HR	Confidence interval	P-Value
Albumin (g/dL)	0.49	0.12-1.91	0.3
Estimated GFR (mL/min)	0.99	0.97-1.017	0.74
Vasoactive drug	0.59	0.16-2.2	0.43
Diuretic	1.004	0.27-3.71	0.99
Serum concentration T2-T4 (mg/L)	**1.086**	**1.02-1.15**	**0.009**

GFR: glomerular filtration rate (CKD-EPI); T2-T4: Serum concentration between the second and fourth day of use of vancomycin (48-96hours)

In Cox regression analysis, it can be observed that the parameter of between 48 and 96 hours (T2-4) (HR = 1,086, p = 0.009) was the only one identified as a risk factor for AKI. The ROC curve analysis showed that between the 2nd and 4th day, a value of sérum concentration of vancomycin above 17.53 was a predictor of AKI with a sensitivity of 79.7%, 83.3% specificity, area under the curve of 0.806 (IC 95% 0.624-0.987, p=0.011) and preceded the diagnosis of AKI by at least 2 days (AKI occurred on average on the 6th day using of vancomycin).

When constructing the free time curve for AKI, based on the values of cutoff obtained by the ROC curve at the moment 2 to 4 days, it was observed that in the group with serum concentration > 20 mg/L the free time for the development of AKI was lower when compared to the group that had serum concentration between 17.5 and 20mg/L, which also presented shorter free time compared to the group with serum concentration < 17.5 mg/L, log rank <0.001

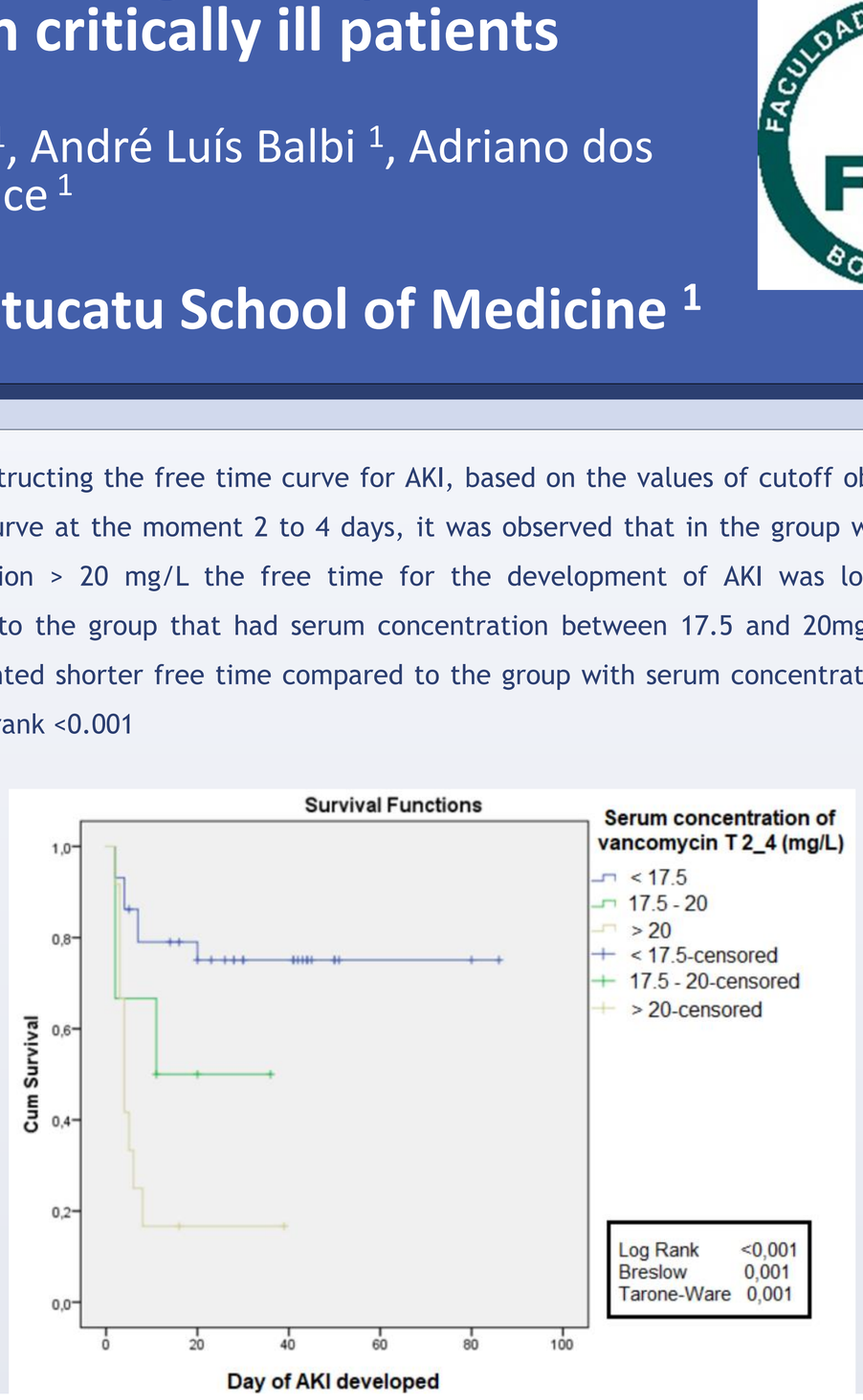

Figure 3. Free time for the outcome of death according to values of serum concentration between T2-4 days (48-96hours) of vancomycin use in ICU patients

In Cox regression, it was observed that the variables age (HR = 1.13, p= 0.018), glomerular filtration rate estimated by CKD-EPI (HR 1.23, p=0.015), levels of serum concentration at the moment 2 to 4 days (HR = 1.60, p=0.021) and mean PCR value (HR 1.26, p=0.011) were identified as risk factors for death.

Table 6. Cox regression of the associated variables to death in patients using vancomycin admitted to the ICU

Variables	HR	Confidence interval	P-Value
Age (years)	**1.13**	**1.02-1.26**	**0.018**
Estimated GFR (mL/min)	**1.23**	**1.04-1.45**	**0.015**
Number of settings	3.21	0.94-10.9	0.06
Vasoactive drug	30.68	0.37-2502.8	0.127
Vancomycin T2-T4 (mg/L)	**1.60**	**1.07-2.4**	**0.021**
Diuretic	0.153	0.005-4.25	0.26
PCR (mg/dL)	**1.26**	**1.05-1.51**	**0.011**

PCR: Protein C Reactive GFR: glomerular filtration rate estimated by CKD-EPI T2-T4: Serum concentration between the second and fourth day of use of vancomycin (48-96hours)

Categorization was performed serum concentrations of vancomycin in the period from the 2nd to the 4th days of use evaluating, through the Cox regression model, the free time for the outcome with adjustment of the variable serum concentration for the variables that also showed statistical significance (age, PCR and glomerular filtration rate), being found as the only predictor for the death was the age (HR 1.06, p=0.012)

Conclusion

Serum concentration of vancomycin was na excelente predictor of AKI in critical patients, preceding the diagnosis of AKI in at least 48hours. Although guidelines recommend therapeutic concentrations between 15 and 20mg/L for patients in ICU, the results of this study suggest the the target of monitoring should be between 15 and 17.5mg/L.