



**UNIVERSIDADE ESTADUAL PAULISTA
“JÚLIO DE MESQUITA FILHO”
FACULDADE DE MEDICINA**

Welder Zamoner

**Comparação quanto à eficácia e segurança de
diferentes esquemas de administração de
vancomicina em pacientes com injúria renal
aguda em hemodiálise: um ensaio clínico
randomizado**

Tese apresentada à Faculdade
de Medicina, Universidade
Estadual Paulista “Júlio de
Mesquita Filho”, Campus de
Botucatu, para obtenção do
título de Doutor em
Fisiopatologia em Clínica
Médica

Orientadora: Profa. Dra. Daniela Ponce
Coorientador: Prof. Dr. Ricardo de Souza Cavalcante

**Botucatu
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Palavras-chave: Diálise; IRA; Injúria renal aguda; Seps; Vancomicina.

*"A tarefa não é tanto ver aquilo que ninguém viu, mas pensar o que
ninguém ainda pensou sobre aquilo que todo mundo vê."*

Arthur Schopenhauer

Dedicatória

À mulher da minha vida, Soraya

Minha esposa, companheira e amiga, pelo apoio incondicional e sonhos compartilhados. Por ser minha parceira e confidente, pela compreensão e estímulo em todas as escolhas e decisões. Sem a qual nenhuma conquista valeria a pena.

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Capítulo I: Artigo expandido

Comparação quanto à eficácia e segurança de diferentes esquemas de administração de vancomicina em pacientes com injúria renal aguda em hemodiálise: um ensaio clínico randomizado

RESUMO

Introdução: Sepsé é a principal causa de Injúria Renal Aguda (IRA) com necessidade dialítica em pacientes críticos, sendo a vancomicina amplamente utilizada. Sua farmacocinética e farmacodinâmica (PK/PD) sofrem alterações durante a hemodiálise (HD), aumentando o risco de concentrações subterapêuticas. **Objetivo:** Comparar diferentes protocolos de administração de vancomicina a fim de avaliar as concentrações séricas e razão área sob a curva/concentração inibitória mínima (ASC/CIM) a partir da PK/PD. **Metodologia:** Ensaio clínico randomizado, não-cego, incluindo pacientes críticos adultos, com diagnóstico de IRA séptica em HD convencional (4 horas) e prolongada (6 e 10 horas) e em uso de vancomicina há pelo menos 72 horas de maio/2019 a maio/2021. Foram analisadas sessões de pacientes randomizados em 3 grupos (G): G controle (C, dose de 15mg/kg após a sessão de HD), G intervenção (I) 2 horas (dose de 7,5mg/kg na segunda hora da HD e 7,5mg/kg após a sessão) e GI infusão contínua (dose de 30mg/kg em bomba de infusão contínua, em 24 horas). Foram excluídos pacientes em diálise crônica, gestantes e com sessão interrompida por razões clínicas ou técnicas. **Resultados:** Dos 316 pacientes recrutados, 87 foram randomizados e 174 sessões de HD monitorizadas. Houve predomínio do sexo masculino (69,5%), idade 61 ± 11 anos, APACHE II 31 ± 6 , ATN-ISS $0,79 \pm 0,14$. Para a análise, 28 sessões pertenciam ao GC, 47 sessões ao GI 2 horas e 31 sessões ao GI infusão contínua. Os grupos foram semelhantes quanto à idade, peso, comorbidades, escores de gravidade, uso de diurético e drogas nefrotóxicas, diurese, albumina, PCR, hematócrito, modalidade de HD, recuperação de função renal e óbito. Ao serem analisadas as sessões de HD, não houve diferença entre os grupos quanto a Kt/V, ultrafiltração, coagulação de sistema ou hipotensão. O GC apresentou maior frequência de concentração sérica subterapêutica ao término da HD em comparação com o GI 2 horas e infusão contínua (86,7% vs. 42,2% vs. 3,2%, $p < 0,0001$), maior *clearance* dialítico ($p = 0,04$) e menor ASC/CIM ($p < 0,0001$). O GI infusão contínua apresentou maior frequência de concentrações supratrapêuticas (71%). Regressão logística identificou a variável concentração inicial (OR 1,16, $p = 0,001$) como fator de risco para uma concentração não terapêutica (ASC/CIM menor que 400 mg·h/L ou maior que 600 mg·h/L) de vancomicina, enquanto que o grupo intervenção 2 horas foi identificado como fator de proteção (OR 0,24, $p = 0,04$). **Conclusão:** Nossos resultados sugerem que administrar vancomicina durante a diálise resultou em menor proporção de concentrações supratrapêuticas ou subterapêuticas quando comparada à administração em infusão contínua ou após o término da sessão, respectivamente. Novos estudos são necessários para sugerir doses mais adequadas e avaliar o impacto desses achados nos desfechos clínicos.

Palavras-chave: sepsé, injúria renal aguda, IRA, diálise, vancomicina, farmacocinética, farmacodinâmica.

ABSTRACT

Introduction: Sepsis is the main cause of Acute Kidney Injury (AKI), requiring dialysis in critically ill patients, with vancomycin being widely used. Its pharmacokinetics and pharmacodynamics (PK/PD) change during hemodialysis (HD), increasing the risk of subtherapeutic concentrations. **Objective:** To compare different vancomycin administration protocols to assess serum concentrations and area under the curve/minimum inhibitory concentration (AUC/MIC) ratio from PK/PD. **Methodology:** Randomized, non-blind clinical trial, including critically ill adults diagnosed with septic AKI on conventional (4 hours) and prolonged HD (6 and 10 hours) and using vancomycin for at least 72 hours from May/2019 to May /2021. Sessions of patients were analyzed and randomized into three groups (G): G control (C, dose of 15mg/kg after HD session), G intervention (I) 2 hours (dose of 7.5mg/kg in the second hour of HD and 7.5mg/kg after the session) and IG continuous infusion (dose of 30mg/kg in continuous infusion pump, in 24 hours). Patients on chronic dialysis, pregnant women, and those whose session was interrupted for clinical or technical reasons were excluded. **Results:** Of the 316 patients recruited, 87 were randomized, and 174 HD sessions were monitored. There was a predominance of males (69.5%), age 61 ± 11 years, APACHE II 31 ± 6 , ATN-ISS 0.79 ± 0.14 . For the analysis, 28 sessions belonged to the CG, 47 sessions to the 2-hour IG, and 31 to the continuous infusion IG. The groups were similar in age, weight, comorbidities, severity scores, use of diuretics and nephrotoxic drugs, urine output, albumin, CRP, hematocrit, HD modality, recovery of renal function, and death. When HD sessions were analyzed, there was no difference between the groups regarding Kt/V, ultrafiltration, system coagulation, or hypotension. The CG had a higher frequency of subtherapeutic serum levels at the end of HD compared to the 2-hour IG and continuous infusion (86.7% vs. 42.2% vs. 3.2%, $p < 0.0001$), higher clearance dialysis ($p = 0.04$) and lower AUC/MIC ($p < 0.0001$). The IG continuous infusion had a higher frequency of supratherapeutic concentrations (71%). Logistic regression identified the initial concentration variable as a risk factor (OR 1.16, $p = 0.001$) for a non-therapeutic concentration (AUC/MIC less than 400 mg·h/L or greater than 600 mg·h/L) of vancomycin. In contrast, the 2-hour intervention group was identified as a protective factor (OR 0.24, $p = 0.04$). **Conclusion:** Our results suggest that administering vancomycin during dialysis resulted in a lower proportion of supratherapeutic or subtherapeutic concentrations compared to administration in continuous infusion or after the end of the session, respectively. New studies are needed to suggest more appropriate doses and assess these findings' impact on clinical outcomes.

Keywords: sepsis, acute kidney injury, AKI, dialysis, vancomycin, pharmacokinetics, pharmacodynamics.

1. INTRODUÇÃO

A sepse, grande problema de saúde pública, é definida como uma disfunção orgânica que ameaça a vida, causada por resposta exacerbada a uma infecção ^[1,2]. Está implicada em falência de vários órgãos, dentre eles os rins, sendo a principal etiologia de injúria renal aguda (IRA) em ambiente de terapia intensiva, com elevada mortalidade ^[3,4,5]. Assim, justifica-se a adoção de medidas que cursem com diminuição de mortalidade e redução de custos ligados a tratamento e internação, como a administração precoce de antimicrobianos, cuja escolha deve ser baseada na história do paciente, no uso recente de antibióticos e na origem dos patógenos (comunitários ou hospitalares) ^[6].

Tendo destaque nessa população as infecções por germes Gram positivos, o uso de vancomicina como antimicrobiano de escolha é frequente e estratégico ^[6,7].

1.1. Vancomicina

Trata-se de um antimicrobiano da classe dos glicopeptídeos, com peso molecular de 1450 Da, ação bactericida, agindo por inibição da síntese da parede celular. A vancomicina foi introduzida na prática clínica em meados de 1950 para o tratamento de infecções bacterianas por germes Gram-positivos, sendo considerado pela *Infectious Disease Society of America* (IDSA) como primeira linha de tratamento para infecções por *Staphylococcus aureus* resistente a meticilina (MRSA) ^[8,9]. No entanto, também apresenta ação contra *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus bovis*, *Streptococcus viridans*, *Enterococcus*, espécies de *Clostridium*, *Difteróides*, *Listeria monocitogenes*, *Actinomíceos* e espécies de *Lactobacillus* ^[10].

Sua farmacocinética é descrita pelo modelo de dois compartimentos com tempo de meia vida de eliminação bifásica (figura 1). A distribuição da droga ocorre rapidamente em indivíduos saudáveis, com volume de distribuição (V_d) de 0,4 a 1 L/kg. Pacientes críticos apresentam V_d alterado, podendo chegar a duas ou três vezes o valor habitual. Sua ligação com proteínas varia de 10 a 50% e é dependente da concentração total de proteínas séricas. A droga não é metabolizada e sua excreção é 80-90% renal, com tempo de meia vida de eliminação altamente dependente da função renal [11,12,13,14,15]. Em indivíduos com depuração de creatinina normal, a vancomicina tem uma fase de distribuição de 30 minutos a 1 hora e uma eliminação com meia vida de 6 a 12 horas [14,16,17].

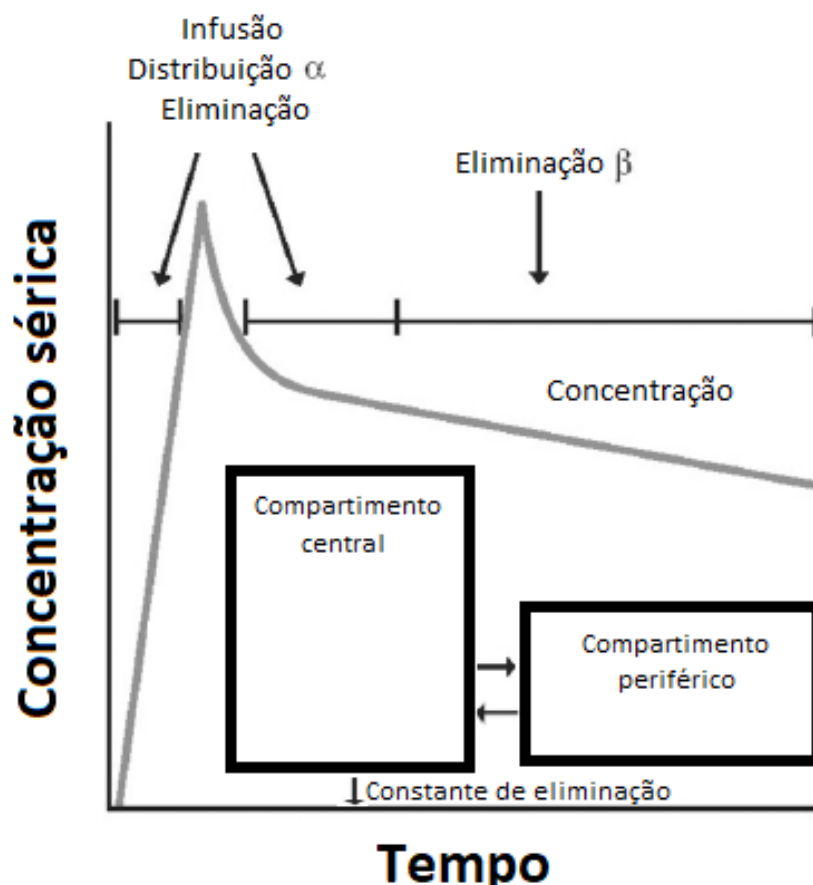


Figura 1. Representação esquemática do modelo farmacocinético de 2 compartimentos. Adaptado de Rybak MJ [14]

Segundo o consenso mais atual de monitorização terapêutica de vancomicina para infecções por MRSA ^[17], ao ser realizada a administração intermitente deste antimicrobiano, poderia ser realizada uma dose de ataque entre 20 a 35mg/kg (baseada no peso atual e não excedendo 3000mg) a fim de ser atingida mais rapidamente a concentração terapêutica em pacientes criticamente doentes ou naqueles em terapia dialítica, seguido de doses de manutenção entre 15 e 20mg/kg administradas a cada 8 a 12 horas para indivíduos com função renal normal quando assumida a concentração inibitória mínima (CIM) de 1mg/L.

Para os pacientes com função renal alterada, recomenda-se ajuste posológico baseado na estimativa de filtração glomerular ^[18]. Para depurações entre 20 e 50mL/min/1,73m² recomenda-se a dose de 15-20mg/kg a cada 24horas, e se abaixo de 20mL/min/1,73m², 15-20mg/kg a cada 48horas.

A administração de vancomicina através de infusão contínua parece uma opção atrativa na população crítica por conta da variabilidade no volume de distribuição, e *clearance* da droga. Poderia ser realizada uma dose de ataque entre 15 e 20mg/kg, seguida por uma manutenção em infusão contínua de 30 a 40mg/kg. ^[17,19].

Revisão realizada por DiMondi *et al* ^[19] englobou 14 estudos: 2 prospectivos, 11 retrospectivos e 1 metanálise, comparando infusão contínua e intermitente de vancomicina. Não houve diferença de eficácia nos tratamentos. Os estudos prospectivos não identificaram taxas diferentes quanto à nefrotoxicidade, e os estudos retrospectivos foram heterogêneos em seus resultados, sem que houvesse determinação de quais subgrupos poderiam se beneficiar da infusão contínua. Somam-se ainda questionamentos sobre compatibilidade, segurança e eficácia com esta forma de administração, sendo necessários mais estudos.

Um ensaio clínico randomizado e cinco estudos de coorte foram incluídos em metanálise desenvolvida por Ye *et al* [20] que mostrou estar a monitorização terapêutica da droga associada a maiores taxas de eficácia clínica (OR 2,62, $p=0,005$) e menores taxas de nefrotoxicidade (OR 0,25, $p<0,0001$). Não houve diferença na duração do tratamento com vancomicina ou tempo de internação hospitalar.

A atividade bactericida da vancomicina é considerada concentração-tempo-dependente [11,15]. Por sua farmacodinâmica, recomenda-se uma razão de área sob a curva pela concentração inibitória mínima (ASC/CIM) entre 400 e 600 mg·h/L para MRSA com CIM 1 mg/L [17].

Devido a dificuldade logística em determinar essa área na prática clínica, identificou-se que esse valor é atingido quando concentrações séricas de vancomicina no “vale” estão entre 10 e 20mg/L [14,21]. Para infecções mais graves (bacteremia, endocardite, osteomielite, meningite e pneumonia nosocomial) recomenda-se uma concentração entre 15 e 20mg/L. Foram estudadas concentrações maiores, porém sem evidência de melhores desfechos terapêuticos [22].

Até 2009 acreditava-se que concentrações no vale acima de 10mg/L garantiam uma ASC/CIM acima de 400 mg·h/L. Entretanto, alguns estudos apontaram que até 50% dos pacientes com razão maior que 400 mg·h/L apresentavam concentração sérica inferior a 15mg/L [17,21]. E muitos pacientes com concentração terapêutica não atingiam essa razão mínima. Assim, a atual recomendação de monitorização terapêutica de vancomicina para infecções por MRSA, baseada em simulações de Monte Carlo, é com modelos guiados pela ASC, seja com coleta de duas concentrações (pico e vale) e utilização de equações para estimativa da ASC, ou através do uso de programas de software Bayesiano [17].

Os principais pontos polêmicos sobre a vancomicina dizem respeito à sua eficácia e segurança [5,6,7,8]. Quanto à eficácia, a preocupação no paciente crítico é a alteração da sua farmacocinética (Figura 2), geralmente relacionada à distribuição, metabolismo e eliminação da droga [6,8], o que pode levar a concentrações subterapêuticas e seleção de mutantes resistentes. Em relação à segurança, ênfase tem sido dada ao principal efeito colateral da medicação: a nefrotoxicidade, a qual pode agravar o quadro clínico e contribuir para o desfecho desfavorável.

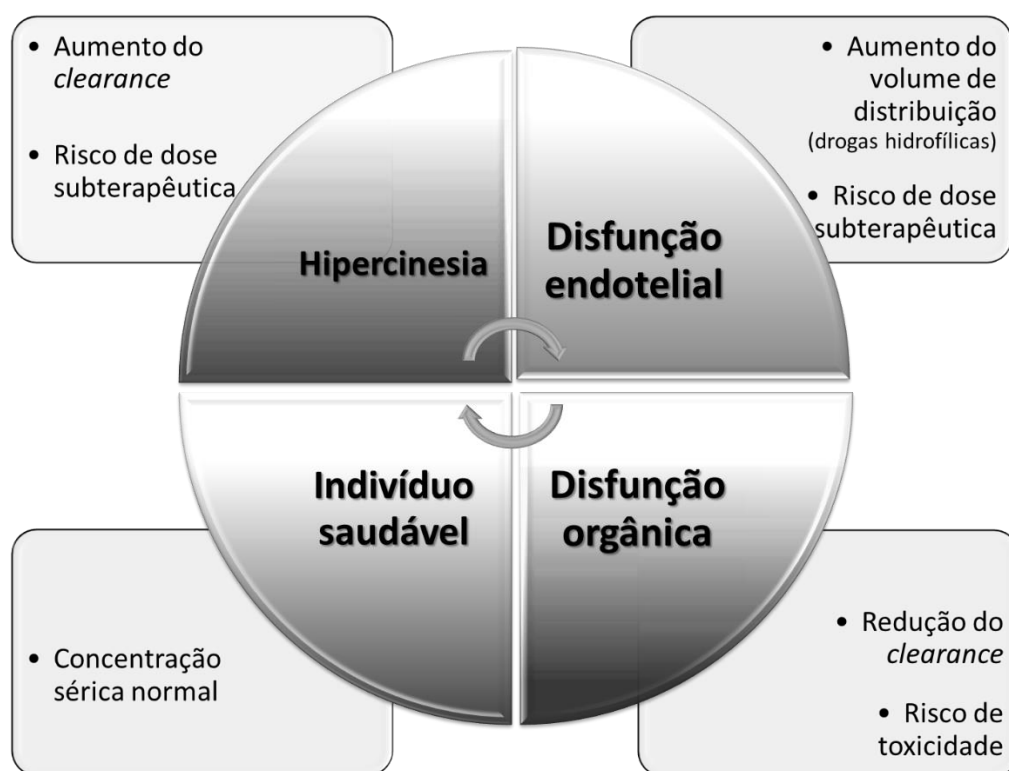


Figura 2. Influência do estado clínico do paciente na farmacocinética antimicrobiana. Adaptado de Roberts J.A e Lipman, J. 2009 [12]

Essa situação pode ainda ser agravada quando o paciente necessita de suporte renal agudo, o qual pode remover parcial ou totalmente as drogas que já estão com sua cinética alterada.

1.2. Suporte renal agudo (SRA)

Como cerca de 50% dos pacientes críticos com IRA associada à sepse necessitam de SRA [3,23,24], torna-se importante o estudo de remoção de drogas nessa população. De um modo geral, as drogas que são primariamente eliminadas pelos rins, com pequeno peso molecular, pequeno volume de distribuição e pouco ligadas a proteínas, podem ser removidas pela diálise. Nos pacientes críticos, como há diminuição da ligação de drogas a proteínas, apesar do aumento do volume de distribuição, há maior eliminação delas, visto que há maior fração livre para ser removida. Outro fator que interfere nessa remoção é a técnica de diálise, que pode ser baseada no transporte de difusão ou convecção, ambos eficientes na remoção de solutos de baixo peso molecular, sendo, porém, a terapia convectiva mais efetiva na eliminação de drogas com maior peso molecular.

São opções de SRA em pacientes críticos, a diálise peritoneal (DP) e a hemodiálise (HD), que pode ser classificada de acordo com sua duração e fluxos de sangue e dialisato, em intermitente convencional (HDI), prolongada (HDP) e contínua (HDC) [25,26,27]. Cada uma das terapias tem suas vantagens e desvantagens, devendo, portanto, a escolha da modalidade ser primariamente baseada na disponibilidade no serviço, experiência da equipe e estado clínico do paciente no momento da indicação [28].

A HDI caracteriza-se por fluxos de sangue e de dialisato altos, entre 300-400 mL/min e 500 mL/min, respectivamente, duração de 4 a 5 horas e custo acessível por utilizar máquinas e filtros semelhantes aos utilizados na diálise crônica [29,30]. A HDI está indicada em pacientes com IRA que se apresentem hemodinamicamente estáveis e pode ser feita em dias alternados ou diariamente, de acordo com as condições clínicas e laboratoriais dos pacientes, a fim de manter o balanço hídrico e controlar a geração de ureia.

Alguns autores têm sugerido que os pacientes críticos com IRA e sepse, por serem hemodinamicamente instáveis, em uso drogas vasoativas e hipercatabólicos, devem ser tratados por métodos contínuos [31]. A HDC é definida como um tratamento longo e contínuo, com duração de 24 horas e que utiliza fluxos de sangue e de dialisato menores que o convencional, entre 100-150 mL/min e 1000-1500 mL/hora, respectivamente [30]. Trata-se de método eficiente por proporcionar adequado controle metabólico e volêmico sem prejudicar a estabilidade hemodinâmica do paciente. Porém, apresenta algumas desvantagens como o custo elevado, tanto em relação ao material utilizado como aos recursos humanos, a necessidade de anticoagulação contínua e a utilização de máquina específica para essa terapia [31,32]. Considerando estas dificuldades, buscou-se um método intermediário entre a HDI e HDC, que proporcionasse estabilidade hemodinâmica e controle metabólico adequado do paciente, com custo acessível e menor duração, surgindo a hemodiálise prolongada (HDP), com duração entre 6 e 12 horas e fluxo de sangue e dialisato intermediários.

A remoção de antimicrobianos pela HD depende das características da membrana dialisadora, como a área de superfície (eficiência) e tamanho de seus poros (fluxo/permeabilidade) [6,7], e de particularidades do fármaco como a hidrossolubilidade, o peso molecular e a extensão de ligação às proteínas, bem como tipo de ligante. Há ainda impacto do fluxo sanguíneo utilizado, do tempo de terapia e do tipo de transporte utilizado (difusão e/ou convecção) [21].

HDI e HDP podem ser realizadas com capilares de baixo ou alto fluxo e eficiência, ou seja, com maior ou menor capacidade de remoção de moléculas médias, de acordo com seus coeficientes de ultrafiltração e desempenho (K_{uf} e K_{oA} , respectivamente) e com duração da terapia e fluxo sanguíneo adotados variáveis. As HDC são realizadas por meio de hemofiltros, ou seja, capilares com grande capacidade de remoção de

moléculas maiores e utilizam fluxos sanguíneos baixos [33].

No paciente séptico com IRA a prevenção de novos insultos renais, como a nefrotoxicidade, é fundamental. Assim, a correção da dose dos antimicrobianos deve ser realizada. Naqueles em que há indicação de SRA, estudos sobre dose de antimicrobianos são escassos, com recomendações extrapoladas de trabalhos realizados em pacientes não críticos com função renal em estado estável ou com doença renal crônica em estágio final recebendo terapia renal substitutiva crônica [24,34].

As doses de vancomicina a serem administradas de acordo com a terapia dialítica são: de 7,5 a 15mg/kg devem ser administrados após o término da diálise (ou na última hora de terapia) para a HD convencional e prolongada [17,18]; 7,5mg/kg-10mg/kg a cada 12 horas nas terapias venovenosas contínuas (com volume de efluente entre 20 e 25mL/kg/h) [17,18]; 7,5mg/kg a cada 48-96 horas para diálise peritoneal ambulatorial contínua (CAPD) [18]; 18mg/kg a cada 48-72 horas para a diálise peritoneal de alto volume (DPAV) [35].

Nas terapias hemodialíticas, a vancomicina não é significativamente removida quando se utiliza um capilar de baixo fluxo, como cuprofano [36,37]. Entretanto, quando se utiliza um capilar de alto fluxo, a vancomicina é dialisada significativamente, com taxas variando entre 30 e 46% [37,38,39,40,41], sendo evidenciado efeito rebote de 16 a 36% [37] ao final da sessão, com duração entre 3 e 6 horas, resultado de recirculação da droga proveniente de locais de ligação de proteínas (fase de redistribuição), conforme esboçado na figura 3. Assim, a recomendação de monitorização do nível sérico nesses pacientes é de que a coleta da amostra de sangue ocorra antes da sessão de hemodiálise [37].

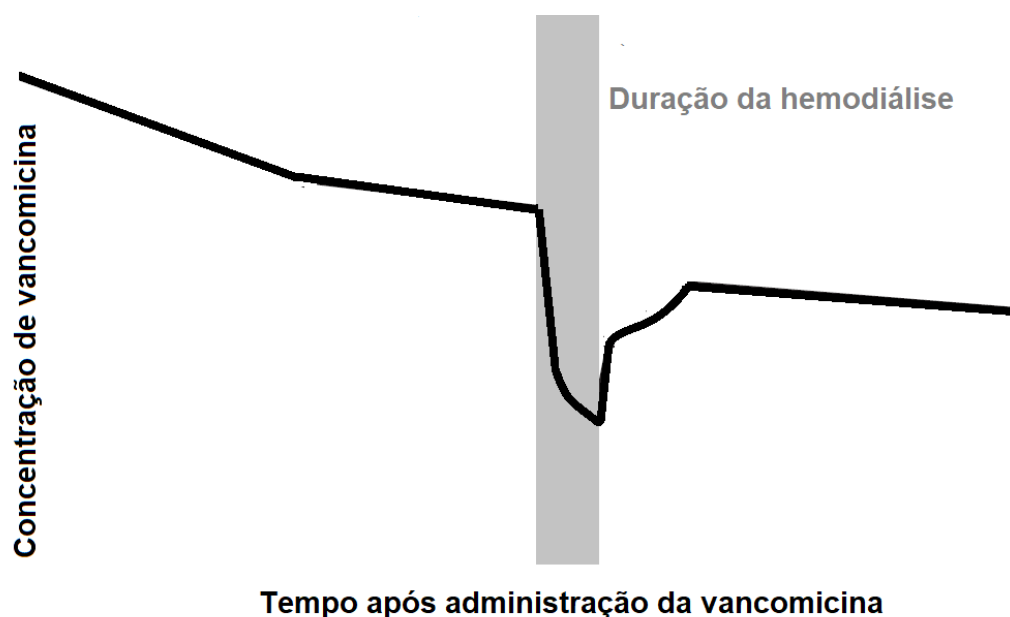


Figura 3. Representação esquemática do modelo farmacocinético da vancomicina durante hemodiálise em esquema crônico. Adaptado de Welage et al ^[37]

Quando a vancomicina é administrada durante a última hora de diálise, tem sido reportada eliminação de 13 a 50% da dose. Estudo prospectivo unicêntrico conduzido por Ghouti-terki *et al* ^[42] avaliou 20 pacientes, em 280 sessões de diálise, que receberam dose de vancomicina durante a última hora da sessão de diálise, mostrando taxa de sucesso terapêutico de 85%, com médias de concentração pré-diálise de 10,2 a 24,4mg/L.

Um estudo randomizado e com crossover de 3 vias desenvolvido por Mason *et al* ^[43] comparou, em 9 pacientes recebendo hemodiálise aguda, a infusão de 15mg/kg de vancomicina após a diálise, a mesma dose durante a última hora da terapia, e 30mg/kg durante as últimas 2 horas da diálise. A vancomicina foi significativamente removida durante a 3ª para a 4ª hora da sessão (33,4 a 39,5%) e a administração de 30mg/kg nas últimas duas horas da diálise rendeu concentrações séricas

semelhantes à dosagem convencional de 15mg/kg após a diálise. Entretanto, a administração de 15mg/kg na última hora resultou em concentração pré-diálise subsequente muito menor.

Ahem *et al* ^[44] estudaram a farmacocinética da vancomicina em pacientes recebendo HD prolongada e encontraram tempo de meia vida de $43,1 \pm 21,6$ horas, para administrações a cada 24-72 horas. Os autores sugeriram, em sua conclusão, a administração de 15mg/kg como dose inicial e, dada a grande variabilidade da meia vida do antimicrobiano durante a terapia, monitorização sérica após 24 horas da dose inicial e ajustes de acordo com os resultados obtidos. Kanji *et al* ^[45] encontraram *clearance* de vancomicina durante e fora da sessão de HDP de $5,97 \pm 4,04$ e $2,4 \pm 1,46$ L/h, respectivamente.

Estudo conduzido por Freitas *et al* ^[46] avaliou a remoção da vancomicina por diferentes métodos de diálise com membranas de alto fluxo ($K_{uf} > 20 \text{ mL/mmHg}$) em pacientes críticos com IRA associada à sepse. A redução ao final da sessão foi de $45,78 \pm 12,79\%$, maior no grupo HDP 10 horas (57,7%), e predominantemente nas primeiras 2 horas das terapias. A partir da modelagem farmacocinética-farmacodinâmica (PK/PD), 46,34% dos pacientes apresentavam ASC/CIM menor que 400 (considerando CIM de 1mg/L), sendo 84,2% dos pacientes em HDP e 15,8% em HDI. Na regressão logística, HDP foi um fator de risco para ASC/CIM menor que 400mg·h/L (OR=11,59, p=0,033).

Manter a concentração de vancomicina pré-diálise entre 15 e 20 mg/L parece ser razoável para atingir a meta da ASC/CIM entre 400 e 600mg·h/L, ainda que baseado em dados escassos da literatura ^[17].

Nas terapias venovenosas contínuas, não há efeito rebote na concentração sérica, podendo ser realizada a qualquer momento a determinação da concentração sérica ^[37]. A infusão contínua parece ter mais sucesso em alcançar as necessidades farmacocinéticas e

farmacodinâmicas nessa população, porém com estudos escassos [47]. DelDot *et al* [48] estudaram 10 pacientes críticos com IRA recebendo hemodiafiltração, evidenciando remoção de 50% em um período de 12 horas e sugerindo esquema posológico de 750mg a cada 12 horas.

Em diálise peritoneal, sabe-se desde 1956, por estudo de Geraci *et al* [49], que a vancomicina se difunde para o dialisato, atingindo concentração de 51% (23-75%) de concentração sérica simultânea, tendo sido as coletas realizadas de 1 a 2 horas após a administração endovenosa de 500mg do antimicrobiano. Estudo de Ponce *et al* [35] avaliou 10 pacientes em DP de alto volume e uso de vancomicina, com dose administrada de $18 \pm 2,95\text{mg/kg}$ e remoção de $21,7 \pm 2,2\%$, com *clearance* peritoneal de $8,1 \pm 2,2\text{mL/min}$, meia-vida sérica de vancomicina de $71,2 \pm 24,7\text{horas}$ e ASC/CIM maior que 400 mg·h/L em todos os pacientes.

Diante de muitos serem os determinantes envolvidos na concentração sérica dos antimicrobianos em pacientes críticos com IRA em terapia dialítica, e considerando que a manutenção de concentrações terapêuticas é necessária nessa população para reduzir a mortalidade, justifica-se a realização de novos estudos para estabelecer protocolos específicos de administração de antimicrobianos a partir da correlação *in vivo* - *in vitro* fornecida pela modelagem PK/PD.

2. OBJETIVOS

Comparar diferentes protocolos de administração de vancomicina em pacientes sépticos com IRA em SRA a fim de avaliar as concentrações séricas terapêuticas, subterapêuticas e tóxicas, e ASC/CIM antes, durante e após as sessões de HD a partir da abordagem farmacocinética e modelagem farmacocinética-farmacodinâmica.

3. METODOLOGIA

3.1. Características do estudo

Foi conduzido um estudo do tipo ensaio clínico randomizado não-cego, em que foram comparadas formas diferentes de administrar o antimicrobiano vancomicina em pacientes críticos com injúria renal aguda (IRA) em terapia hemodialítica. Este estudo foi submetido à Comissão de Ética em Pesquisa (CEP) local e foi aprovado em março/2019, sob número do parecer: 3.198.161 e CAAE: 04729118.4.0000.5411. Em abril/2019 o protocolo do estudo foi registrado e aprovado no Registro Brasileiro de Ensaios Clínicos (ReBEC) sob identificador RBR-5rcknr.

O termo de consentimento livre esclarecido (TCLE) foi assinado por cada paciente (ou responsável) incluído antes do início dos procedimentos previstos no estudo, sendo a partir de então alocados em ordem numérica crescente e identificados pela numeração, com manutenção da confidencialidade dos pacientes incluídos no protocolo de estudo.

3.2. População do estudo

Foram incluídos pacientes adultos (maiores de 18anos), internados nas unidades de terapia intensiva (UTI) do Hospital das Clínicas da Faculdade de Medicina de Botucatu – HC UNESP entre maio/2019 e maio/2021, com critérios de sepse identificados pelo escore SOFA[#] [2], em uso de vancomicina por pelo menos 72horas, com diagnóstico de IRA de acordo com o KDIGO^{\$} [5] e em suporte renal agudo, modalidades de hemodiálise intermitente (convencional e prolongada). Foram excluídos pacientes em diálise crônica, transplantados renais,

gestantes e aqueles cujas sessões de diálise tenham sido interrompidas por razões clínicas ou técnicas.

A prescrição de antimicrobianos aos pacientes obedeceu a um protocolo instituído pela Comissão de Controle das Infecções Relacionadas à Assistência à Saúde (CCIRAS) da instituição, a saber: dose de ataque de 25mg/kg, seguido de manutenção de 15mg/kg com intervalo posológico de 24/24h até 96/96h a depender do nível sérico dosado em vale (antes da sessão de diálise). As concentrações consideradas terapêuticas compreendem dosagem no vale/pré-diálise entre 15 e 20mg/dL ^[17].

3.3. Protocolo do Estudo

Após o diagnóstico da IRA associada à sepse e indicação de SRA, foi implantado o cateter venoso central para início do tratamento. A indicação de SRA foi realizada pela equipe da Nefrologia-IRA para pacientes com indicações de urgência dialítica ou que apresentavam desbalanço entre a demanda e a capacidade renal ^[28]. Os pacientes foram selecionados para entrar no estudo a partir da segunda sessão de diálise e após pelo menos três dias de calendário com uso da vancomicina visando seu estado estável.

Sepse: definida como disfunção de órgãos ameaçadora a vida, causada pela resposta desregulada a uma infecção. Pode ser identificada como uma pontuação ≥ 2 no escore SOFA (*"Avaliação sequencial de falência de órgãos"*) é um escore de gravidade para pacientes críticos, realizado quando da admissão na UTI que mede a falência de 6 órgãos (respiratório, hepático, renal, neurológico, hematológico e cardíaco). Cada órgão é graduado com score de 0 a 4, proporcionando uma contagem de 0 a 24 pontos.

\$ **IRA**: elevação da creatinina sérica maior ou igual a 0,3mg/dl em 48 horas; ou maior que 50% em relação ao basal em até 7 dias; ou redução do débito urinário para menos de 0,5mL/kg/hora em 6 horas.

Todas as sessões de HD foram realizadas por técnicos de enfermagem da equipe, sob responsabilidade de enfermeira e médico do serviço. De acordo com o grau de instabilidade hemodinâmica, os pacientes tiveram sua modalidade de HD definida:

- **Doses de norepinefrina abaixo de 0,3mcg/kg/min:** HD intermitente convencional (HDI)
- **Doses de norepinefrina entre 0,3 e 0,6mcg/kg/min:** HD intermitente prolongada 6 horas (HDP 6h)
- **Doses de norepinefrina acima de 0,6mcg/kg/min:** HD intermitente prolongada 10 horas (HDP 10h)

Na realização das sessões de HD foram utilizadas máquinas de proporção (Fresenius 4008) e dialisadores de alto fluxo (FX 60, FX 80 ou FX 100), com áreas de superfície 1,6; 1,8 e 2,0m², respectivamente. A sessão de HDI foi realizada com fluxo de sangue de 300 mL/min e fluxo de dialisato de 500 mL/min e capilar, com duração de 4 horas. A sessão de HDP foi realizada com fluxo de sangue de 200 mL/min, fluxo de dialisato de 300 mL/min com duração de 6 horas ou 10 horas.

Durante as sessões, os pacientes foram anticoagulados com 50 a 100 UI/Kg de heparina em bolus, e 500 a 1000 UI/hora nas demais horas. Na presença de contraindicação para anticoagulação, o sistema foi lavado com 50 a 100 mL de cloreto de sódio a 0,9% a cada 30 minutos durante o procedimento. Concentrações de bicarbonato (26-36 mEq/L), potássio 1-4 mEq/L, sódio (135-145 mEq/L) e cálcio (2,5-3,5 mEq/L) do banho de diálise foram ajustados conforme a necessidade individual e exames laboratoriais dos pacientes. A taxa de ultrafiltração (UF) não excedeu 5 ± 3 mL/kg/hora ^[50].

Foram utilizados dados coletados durante a rotina de atendimento, extraídos de prontuários eletrônicos. O tempo de seguimento foi durante todo o período de internação até o desfecho clínico e sempre pela mesma

equipe. Essas informações incluíram dados demográficos, peso, altura, cálculo do índice de massa corpórea [$\text{Peso}/(\text{altura})^2$] ^[51], comorbidades, motivo da internação, foco infeccioso, escore de gravidade APACHE II ^[52], escore prognóstico de IRA (ATN-ISS) ^[53], diurese, uso de droga vasoativa, uso de diurético de alça, uso de drogas nefrotóxicas ou que apresentam sinergismo de toxicidade (piperacilina-tazobactam, aminoglicosídeos, anfotericina B), dados laboratoriais [ureia sérica pré e pós diálise, albumina sérica, hematócrito sérico, proteína C reativa sérica, resultados de culturas, concentração inibitória mínima para vancomicina (foi atribuído valor de 1mg/L para os resultados não conhecidos) ^[17], concentração sérica de vancomicina antes do início da sessão], dados dialíticos [tempo da sessão, ultrafiltração, Kt/V recebido ^[54], uso de heparina, intercorrências durante a sessão (como coagulação do sistema ou hipotensão)].

Foi realizada coleta seriada de amostras sanguíneas (2mL cada) através do cateter venoso central e de efluente da diálise (2mL cada) pela equipe de enfermagem da diálise para a determinação das concentrações séricas e do efluente de vancomicina antes de iniciar a diálise (T0), após 2 horas (T2) e ao seu término (Tfinal). Esse procedimento foi realizado duas vezes por paciente, em duas sessões de hemodiálise consecutivas.

O material coletado foi transferido para tubos de coleta a vácuo (10 mL) contendo gel da Benton Dickinson (BD) e mantido em isopor com placa ou em geladeira até a última coleta do dia, quando foram encaminhados ao Laboratório para separação e armazenamento.

Os tubos de coleta com o material foram devidamente identificados com o número de alocação do paciente, e na ordem sequencial das coletas realizadas para cada paciente investigado. Finalizada a última coleta do dia ao término do procedimento de diálise, os tubos contendo o material coletado foram encaminhados à Unidade de Pesquisa Experimental da Faculdade de Medicina de Botucatu – UNESP (UNIPEX)

para separação e armazenamento das matrizes até o transporte para a unidade analítica. Na UNIPLEX foi realizada a separação do soro em centrífuga (3000g, 20 minutos), transferência do soro para tubos de Eppendorf (2mL), devidamente identificados e reservados para conter a matriz biológica/soro. O acondicionamento das matrizes foi efetuado em caixas de papelão fornecidas pelo Laboratório Analítico, e o armazenamento realizado em congelador (-80° C) com controle de temperatura em prateleira reservada para o protocolo de estudo.

3.4. Randomização

Os pacientes foram submetidos a um processo de randomização em blocos (*block randomization*) através do *web site Randomization.com* (<http://www.randomization.com>) e alocados em 3 grupos, de acordo com a dose de manutenção.

- **Grupo Controle:** administração de vancomicina após o término da sessão de hemodiálise, em dose única de 15mg/kg
- **Grupo Intervenção 2horas:** administração de 7,5mg/kg de vancomicina na 2ª hora da sessão de hemodiálise, com outros 7,5mg/kg administrados ao término do procedimento
- **Grupo Intervenção infusão contínua:** administração de 30mg/kg de vancomicina em bomba de infusão contínua, por 24horas.

3.5. Etapa Analítica

A quantificação dos antimicrobianos na matriz biológica foi realizada através de Imunoensaio enzimático homogêneo (*Enzyme Multiplied Immunoassay Technique* - EMIT) [55]. A partir desses resultados,

a concentração sérica de vancomicina nos diferentes momentos da diálise foi utilizada para o cálculo de dados de farmacocinética, conforme mostra a tabela 1.

Tabela 1. Fórmulas utilizadas para cálculos de farmacocinética da Vancomicina [40,56,57]

FARMACOCINÉTICA	FÓRMULA
VOLUME DE DISTRIBUIÇÃO (L)	$VD = \text{dose de vancomicina (mg)} / \text{concentração vancomicina (mg/L)}$
CLEARANCE DIALÍTICO DA VANCOMICINA (L/H)	$CI \text{ vanco} = (\text{Concentração inicial} - \text{final}) / \text{concentração inicial} \times QD / t$
TEMPO DE MEIA VIDA	$T_{1/2} \text{ vida} = 0,693 \times VD / CI$
% REDUÇÃO DA VANCOMICINA	$\% \text{ red} = (C \text{ pré HD} - C \text{ final HD}) / C \text{ pré HD} \times 100$

VD: volume de distribuição; CI vanco: *Clearance* dialítico da vancomicina; QD: fluxo de dialisado (L/h); t: tempo em horas); T½ vida: tempo de meia vida; C pré HD: concentração de vancomicina pré hemodiálise; C final HD: concentração de vancomicina no final da hemodiálise.

A ASC foi determinada utilizando o método trapezoidal até ao último ponto temporal diferente de zero [58]. A ASC do último ponto temporal não nulo foi determinada pelo método farmacocinético, concentração/k, em que k é a constante da taxa de eliminação determinada a partir da regressão log-linear da fase terminal do perfil concentração-tempo. Um modelo monoexponencial foi usado para todos os cálculos farmacocinéticos. Foram utilizadas as seguintes equações: A constante de velocidade de eliminação do soro (k el) para os períodos de repouso foi obtida pela regressão das concentrações séricas ao longo do tempo entre o início do tempo de permanência e o final do tempo de permanência. A fórmula usada para determinar a concentração sérica aproximada foi $C = C_0 * e^{-k t}$, onde C = concentração, C 0 = concentração original, -k = taxa de eliminação constante, e t = tempo

entre os pontos de amostragem. A ASC do soro durante as primeiras 24 horas foi calculada pela soma da ASC de cada pausa, utilizando a regra do trapézio, e de 24 horas até o infinito por extrapolação da concentração sérica a 24 h / k el último.

3.6 Desfechos

Para as sessões de diálise monitorizadas, foram avaliados os desfechos relacionados à monitorização terapêutica da vancomicina. Foram consideradas concentrações terapêuticas aquelas entre 15 e 20mg/L, e/ou com ASC/CIM entre 400 e 600 mg·h/L; subterapêuticas quando abaixo de 15mg/L e/ou com ASC/CIM menor que 400 mg·h/L e supraterapêuticas acima de 20mg/L e/ou com ASC/CIM maior que 600 mg·h/L.

Para os pacientes foram considerados os desfechos clínicos recuperação de função renal, como saída de hemodiálise, e óbito por todas as causas.

3.7 Análise Estatística

Foi realizado o cálculo do tamanho amostral utilizando *software* GPower 3.1. Estudo piloto identificou que a intervenção implicaria em 50% menos concentrações subterapêuticas quando comparado com o grupo controle. Assim, considerando amostras não independentes, seriam necessárias 27 sessões para cada grupo (81 sessões). Pelo protocolo do estudo, cada paciente faria 2 sessões monitorizadas, sendo, portanto, necessários pelo menos 14 pacientes por grupo (42 pacientes), considerando erro alfa de 0,05 e poder de estudo de 80%.

A partir do protocolo de estudo, os dados foram digitados em planilha eletrônica e verificados possíveis erros de digitação, e sua análise foi feita com auxílio de programa estatístico IBM SPSS 20 ou *sigma stat* 3.5.

Na estatística descritiva, os dados foram expressos através de médias, desvio padrão, mediana e interquartil. Os dados foram analisados inicialmente quanto à distribuição (Teste W de normalidade de Shapiro-Wilk). Para as variáveis contínuas foram usadas as medidas de tendência central, média e desvio padrão para aquelas com distribuição normal e mediana e interquartil para aquelas de distribuição não normal. Para as variáveis categóricas foram utilizadas as medidas de frequência.

As sessões de HD e posteriormente os pacientes foram comparados entre as modalidades de diálise (HD convencional e HD prolongada 6 e 10 horas), entre os grupos controle e intervenções (2horas e infusão contínua) e posteriormente em relação à ASC/CIM em concentração terapêutica ou não. Para as variáveis contínuas paramétricas foi utilizado teste-T de Student e ANOVA, e para as não-paramétricas foi utilizado teste de Mann-Whitney e Kruskal-Wallis, com pós-teste de Tuckey utilizado. O Teste do Qui-Quadrado foi utilizado para comparação de variáveis categóricas entre os grupos.

Foram construídas as curvas de sobrevida e de tempo para a recuperação de função renal entre os grupos controle e intervenções (2 horas e infusão contínua) utilizando-se modelo de Kaplan Meier e comparação por Log rank.

3. RESULTADOS

De maio/2019 a maio/2021 foram recrutados 316 pacientes que preencheram os critérios de elegibilidade. Destes pacientes, 87 foram randomizados para os três grupos: controle (n=28, 56 sessões de HD a

serem analisadas), intervenção 2 horas (n=30, 60 sessões de HD a serem analisadas), e intervenção infusão contínua (n=29, 58 sessões de HD a serem analisadas), conforme mostra a figura 4. Durante o seguimento, 28 pacientes foram considerados inelegíveis e 12 sessões de diálise foram retiradas da análise por interrupção técnica.

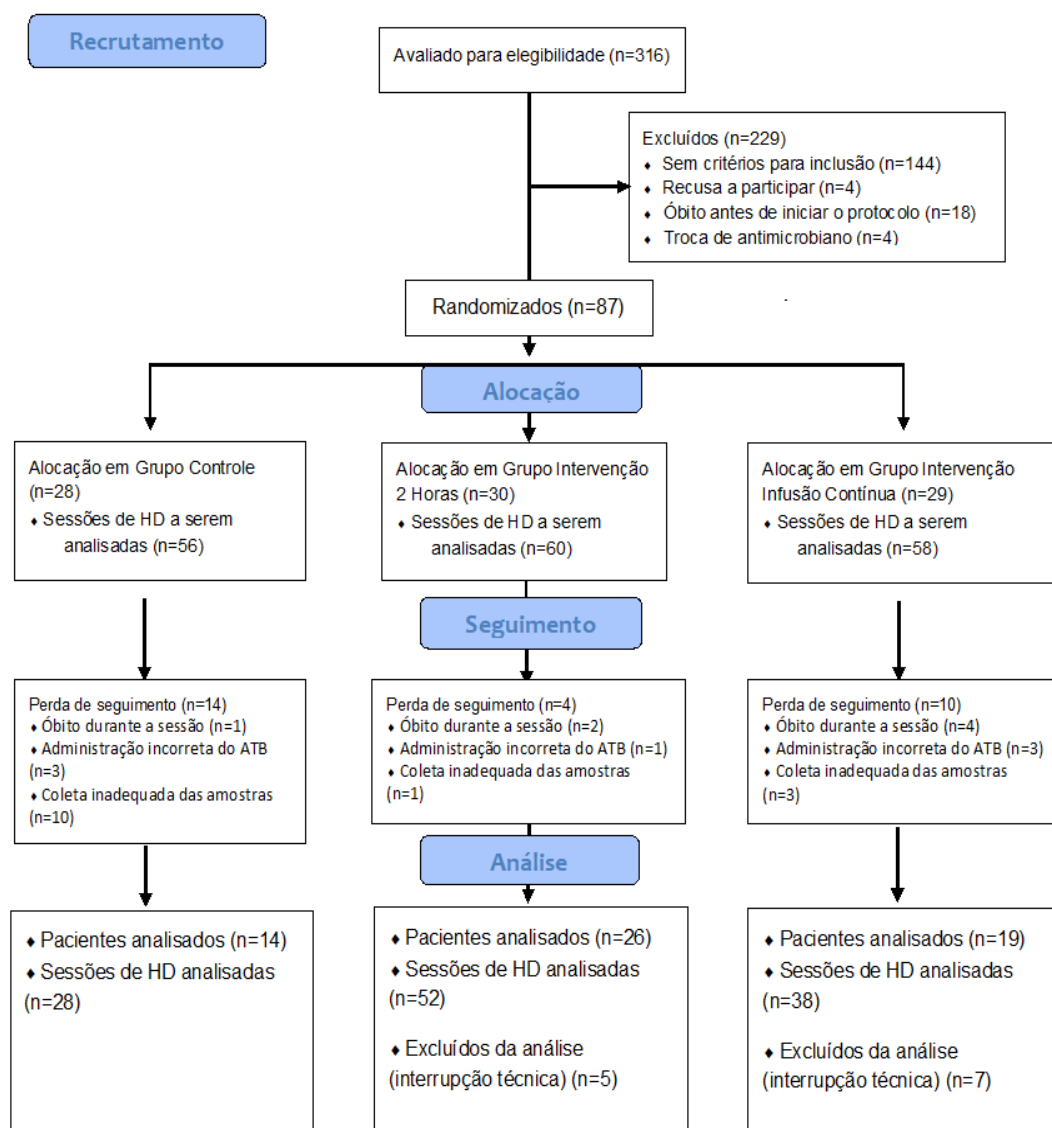


Figura 4. Fluxograma de recrutamento dos pacientes. Adaptado de CONSORT 2010 Flow Diagram, disponível em <http://www.consort-statement.org/>

4.1. Sessões de hemodiálise

Foram analisadas 106 sessões de HD, 61 (57,5%) HD convencional e 45 (42,5%) HD prolongada, sendo 34 HDP 6 horas (32,1%) e 11 (10,4%) HDP 10 horas. Os grupos foram semelhantes quanto a intercorrências intradialíticas (hipotensão e coagulação), Kt/V recebido, ultrafiltração, volume de distribuição da droga e concentrações plasmáticas de vancomicina inicial e final. O *clearance* dialítico, avaliado em L/h, foi menor nos grupos de HDP em comparação com HD convencional ($p<0,001$). Já a ASC/CIM durante a análise, o tempo de meia vida e as concentrações do dialisato nos tempos T0, T2 e Tfinal foram menores no grupo que realizou a sessão de HD convencional ($p=0,006$, $p=0,001$, $p=0,001$, $p<0,001$ e $p=0,009$, respectivamente), conforme mostram as tabelas 2 e 3.

Tabela 2. Características dialíticas na população geral e nos grupos de acordo com a modalidade de HD realizada.

VARIÁVEL	TODAS AS SESSÕES (N=106)	HD CONVENCIONAL (N=61)	HDP 6 HORAS (N=34)	HDP 10 HORAS (N=11)	VALOR P
COAGULAÇÃO DO SISTEMA (%)	20 (18,9)	10 (16,4)	9 (26,5)	1 (9,1)	0,43
HIPOTENSÃO (%)	34 (32,1)	17 (27,9)	12 (35,3)	5 (45,5)	0,43
DIURÉTICO (%)	37 (34,9)	19 (31,1)	15 (44,1)	3 (27,3)	0,39
ULTRAFILTRAÇÃO (ML)	2500 (1500- 2800)	2000 (1500- 2500)	2500 (2000- 3000)	3000 (1200- 3500)	0,17
KT/V RECEBIDO	0,91 ± 0,3	0,95 ± 0,31	0,81 ± 0,26	0,97 ± 0,32	0,1

HD: Hemodiálise; HDP: Hemodiálise Prolongada

Tabela 3. Características farmacocinéticas e farmacodinâmicas da vancomicina na população geral e nos grupos de acordo com a modalidade de HD realizada.

VARIÁVEL	TODAS AS SESSÕES (N=106)	HD CONVENCIONAL (N=61)	HDP 6 HORAS (N=34)	HDP 10 HORAS (N=11)	VALOR P
CONCENTRAÇÃO PRÉVIA DE VANCOMICINA (MG/L)	23,42 (18,73-27,6)	24,1 (18,73-27,6)	22,27 (18,75-25,62)	22,23 (17,4-30,1)	0,76
DOSE DIÁRIA DE VANCOMICINA (MG)	1200 (1000-1500)	1160 (1000-1500)	1200 (900-1350)	1275 (1140-2400)	0,07
VOLUME DE DISTRIBUIÇÃO (L/KG)	0,74 ± 0,37	0,78 ± 0,41	0,62 ± 0,31	0,82 ± 0,24	0,09
CONCENTRAÇÃO T0 (MG/L)	26,21 ± 9,33	25,53 ± 9,17	27,99 ± 10,34	24,47 ± 6,23	0,32
CONCENTRAÇÃO T2 (MG/L)	20,84 ± 7,62	20,14 ± 7,95	22,11 ± 7,24	20,79 ± 6,98	0,48
CONCENTRAÇÃO TF (MG/L)	16,91 (12,41-21,9)	18,17 (11,14-22,68)	17,76 (13,27-20,67)	14,76 (10,08-21,2)	0,68
CONCENTRAÇÃO SUBTERAPÊUTICA AO FINAL DA HD (%)	46 (43,4)	26 (42,6)	14 (41,2)	6 (54,5)	0,74
CONCENTRAÇÃO SUPRATERAPÊUTICA AO FINAL DA HD (%)	32 (30,2)	22 (36,1)	7 (20,6)	3 (27,3)	0,31
CONCENTRAÇÃO TERAPÊUTICA AO FINAL DA HD (%)	28 (26,4)	13 (21,3)	13 (38,2)	2 (18,2)	0,18
CLEARANCE DIALÍTICO (L/H)	1,78 ± 1,15	2,35 ± 1,13^a	1,12 ± 0,58^b	0,66 ± 0,31^b	<0,001
REDUÇÃO EM 2 HORAS (%)	19,6 ± 13	20,84 ± 12,97	18,53 ± 13,78	15,97 ± 10,56	0,44
REDUÇÃO TOTAL (%)	33,04 ± 14,72	31,29 ± 15,13	35,06 ± 13,05	36,54 ± 17,18	0,34
TEMPO DE MEIA VIDA (H)	52,52 ± 39,3	56,31 ± 30,01^b	38,4 ± 30,93^b	93,65 ± 54,79^a	0,001
ASC/CIM DURANTE A ANÁLISE (MG·H/L)	80,13 (61,31-107,89)	68,81 (59,98-94,42)^a	92,57 (67,99-124,3)^b	88,85 (75-113,05)^b	0,006
ASC/CIM 24 HORAS (MG·H/L)	290,88 (231,61-396,47)	291,68 (247,01-389,27)	304,27 (23,61-423,56)	250 (215,97-312,06)	0,29

a: significativamente diferente de b

HD: Hemodiálise; HDP: Hemodiálise Prolongada; ASC/CIM: área sob a curva/concentração inibitória mínima; T0: tempo inicial; T2: segunda hora; TF: término da sessão

Das 106 sessões de HD, 28 pertenciam ao grupo controle, 47 sessões ao grupo intervenção 2 horas e 31 sessões ao grupo intervenção

infusão contínua. Não houve diferença entre os grupos quanto à modalidade de HD, Kt/V, ultrafiltração, intercorrências intradialíticas (coagulação de sistema ou hipotensão) ou uso de diurético. O grupo intervenção infusão contínua recebeu maior dose diária de vancomicina em comparação com os demais grupos ($p<0,0001$) e maior concentração sérica nos tempos T0, T2 e Tfinal ($p<0,0001$). O grupo controle apresentou maior frequência de concentração sérica subterapêutica ao término da HD, maior *clearance* dialítico ($p=0,04$) e menor ASC/CIM ($p<0,0001$), conforme descrito nas tabelas 4 e 5.

Tabela 4. Características dialíticas na população geral e nos grupos controle e intervenção (2 horas e infusão contínua)

VARIÁVEL	TODAS AS SESSÕES (N=106)	GRUPO CONTROLE (N=28)	GRUPO INTERVENÇÃO 2 HORAS (N=47)	GRUPO INTERVENÇÃO INFUSÃO CONTÍNUA (N=31)	VALOR P
MODALIDADES DE HD					0,06
HD CONVENCIONAL (%)	61 (57,5)	17 (56,7)	23 (51,5)	21 (67,7)	
HDP 6 HORAS (%)	34 (32,1)	9 (30)	20 (44,4)	5 (16,1)	
HDP 10 HORAS (%)	11 (10,4)	4 (13,3)	2 (4,4)	5 (16,1)	
COAGULAÇÃO DO SISTEMA (%)	20 (18,9)	8 (26,7)	7 (15,6)	5 (16,1)	0,43
HIPOTENSÃO (%)	34 (32,1)	11 (36,7)	15 (33,3)	8 (25,8)	0,64
DIURÉTICO (%)	37 (34,9)	15 (50)	12 (26,7)	10 (32,3)	0,1
ULTRAFILTRAÇÃO (ML)	2500 (1500- 2800)	2500 (2000- 3000)	2500 (0-2800)	2000 (1700- 2500)	0,17
KT/V RECEBIDO	0,91 ± 0,3	0,9 ± 0,25	0,9 ± 0,31	0,93 ± 0,33	0,89

HD: Hemodiálise; HDP: Hemodiálise Prolongada

Tabela 5. Características farmacocinéticas e farmacodinâmicas da vancomicina na população geral e nos grupos controle e intervenção (2 horas e infusão contínua)

VARIÁVEL	TODAS AS SESSÕES (N=106)	GRUPO CONTROLE (N=28)	GRUPO INTERVENÇÃO 2 HORAS (N=47)	GRUPO INTERVENÇÃO INFUSÃO CONTÍNUA (N=31)	VALOR P
CONCENTRAÇÃO SÉRICA DE VANCOMICINA ANTES DA HD (MG/L)	23,42 (18,73- 27,6)	23,01 (18,06- 26,13) ^b	22,2 (17,4-25,3) ^b	26,74 (20,69- 36,9) ^a	0,007
VOLUME DE DISTRIBUIÇÃO (L/KG)	0,74 ± 0,37	0,83 ± 0,4 ^b	0,6 ± 0,32 ^a	0,85 ± 0,37 ^b	0,006
DOSE DIÁRIA DE VANCOMICINA (MG)	1200 (1000- 1500)	1050 (900- 1250) ^b	1110 (900- 1260) ^b	1800 (1350- 2300) ^a	<0,0001
CONCENTRAÇÃO T0 (MG/L)	26,21 ± 9,33	19,51 ± 5,41 ^c	27,08 ± 9,84 ^b	31,43 ± 7,75 ^a	<0,0001
CONCENTRAÇÃO T2 (MG/L)	20,84 ± 7,62	14,22 ± 4,05 ^c	21,36 ± 6,52 ^b	26,49 ± 6,91 ^a	<0,0001
CONCENTRAÇÃO TF (MG/L)	16,91 (12,41- 21,9)	11,14 (8,9- 13,59) ^c	16,26 (13,71- 20,5) ^b	23,37 (20,67- 25,36) ^a	<0,0001
CONCENTRAÇÃO SUBTERAPÊUTICA AO FINAL DA HD (%)	46 (43,4)	26 (86,7) ^a	19 (42,2)	1 (3,2) ^b	<0,0001
CONCENTRAÇÃO SUPRATERAPÊUTICA AO FINAL DA HD (%)	32 (30,2)	0 (0) ^b	10 (22,2)	22 (71) ^a	<0,0001
CONCENTRAÇÃO TERAPÊUTICA AO FINAL DA HD (%)	28 (26,4)	4 (13,3)	16 (35,6)	8 (25,8)	0,10
CLEARANCE DIALÍTICO (L/H)	1,78 ± 1,15	2,09 ± 1,4 ^b	1,84 ± 1,05 ^b	1,38 ± 0,91 ^a	0,04
REDUÇÃO EM 2HORAS (%)	19,6 ± 13	25,35 ± 13,43 ^a	18,58 ± 13,95 ^b	15,5 ± 8,94 ^b	0,009
REDUÇÃO TOTAL (%)	33,04 ± 14,72	39,9 ± 15,65 ^b	35,1 ± 13,61 ^b	23,42 ± 10,06 ^a	<0,0001
TEMPO DE MEIA VIDA (H)	52,52 ± 39,3	32 ± 27,4 ^b	27,08 ± 25,64 ^b	82,29 ± 66,21 ^a	0,002
ASC/CIM DURANTE A ANÁLISE (MG·H/L)	80,13 (61,31- 107,89)	65,85 (50,35- 76,93) ^a	85,07 (61,97- 109,77) ^b	98,16 (76,94- 118,16) ^b	<0,0001
ASC/CIM 24HORAS (MG·H/L)	290,88 (231,61- 396,47)	253,37 (195,36- 288,55) ^a	306,94 (246,25- 432,34) ^b	373,62 (268,93- 426,42) ^b	<0,0001

a: significativamente diferente de b; c: significativamente diferente de a e b; ab: semelhante a e b

HD: Hemodiálise; HDP: Hemodiálise Prolongada; ASC/CIM: área sob a curva/concentração inibitória mínima;
T0: tempo inicial; T2: segunda hora; TF: término da sessão

O grupo controle apresentou 86,7% das sessões finalizadas com concentrações subterapêuticas ($p<0,0001$). O grupo intervenção infusão contínua foi o que apresentou maior frequência de concentração sérica supraterapêutica (71%) ao final da sessão, em comparação com os demais grupos ($p<0,0001$). A figura 5 apresenta as porcentagens da monitorização terapêutica da vancomicina ao término das sessões de HD de acordo com o grupo.

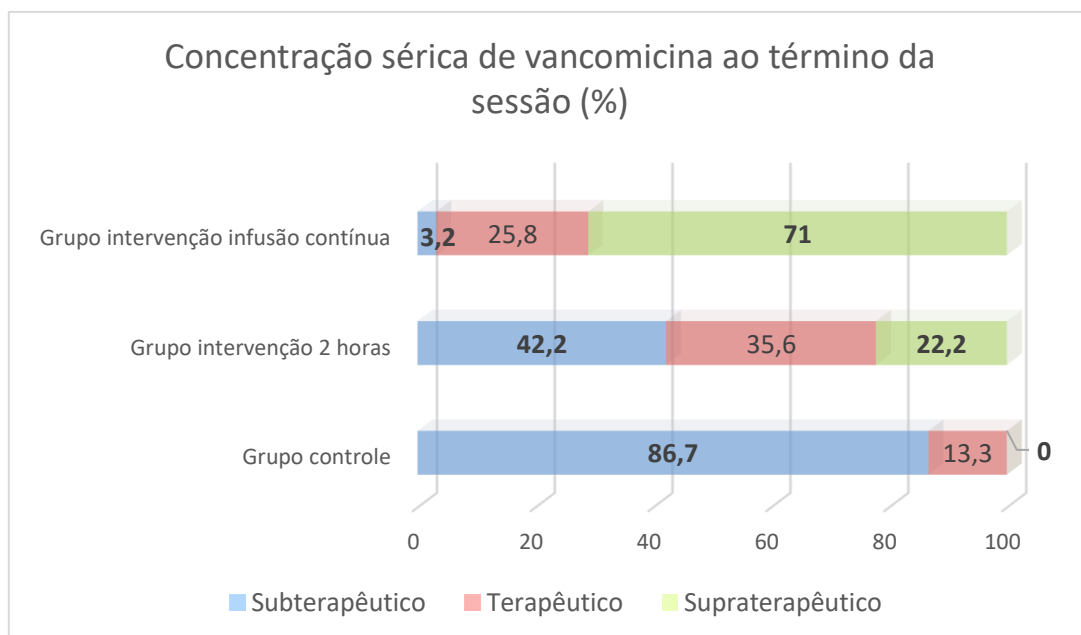


Figura 5. Representação gráfica da porcentagem de concentrações subterapêutica, terapêutica ou supraterapêutica ao final da sessão de hemodiálise de acordo com o grupo

Os grupos de intervenção apresentaram maiores ASC/CIM em 24 horas em comparação com o grupo controle [306,94 (246,25-432,34) mg·h/L e 373,62 (268,93-426,42) mg·h/L versus 253,37 (195,36-288,55) mg·h/L, com $p<0,0001$], conforme figura 6.

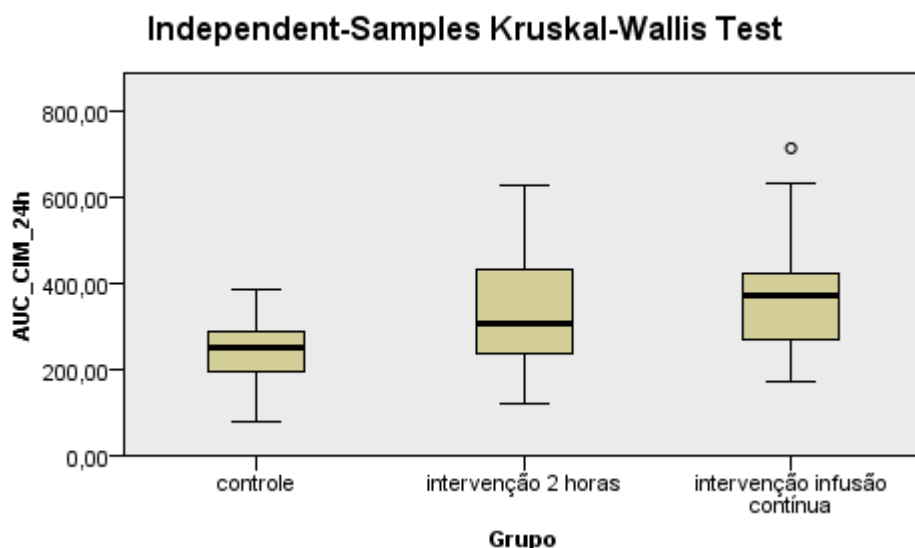


Figura 6. Box plot da área sob a curva/concentração inibitória mínima de vancomicina de acordo com o grupo

A tabela 6 apresenta os fatores relacionados às concentrações terapêutica e não terapêutica da vancomicina (razão ASC/CIM entre 400 e 600 mg·h/L, e abaixo de 400 mg·h/L ou acima de 600 mg·h/L, respectivamente). Os grupos de intervenção mostraram maior frequência de concentração terapêutica em relação ao grupo controle ($p < 0,002$). Menor volume de distribuição, maior dose diária de vancomicina e maiores concentrações séricas de vancomicina no T0, T2horas e Tfinal associaram-se a ASC/CIM em concentração terapêutica ($p < 0,0001$, $p = 0,001$, $p < 0,0001$, $p < 0,0001$ e $p < 0,0001$, respectivamente). Não houve diferença entre os grupos quanto à modalidade de HD, Kt/V, ultrafiltração, intercorrências intradialíticas (coagulação de sistema ou hipotensão), uso de diurético ou concentração sérica colhida antes do início da sessão de HD.

Tabela 6. Características associadas à prescrição da vancomicina e sua farmacodinâmica e farmacocinética na população geral em relação à concentração terapêutica (ASC/CIM entre 400 e 600 mg·h/L) e não terapêutica (ASC/CIM menor que 400 mg·h/L ou maior que 600 mg·h/L) do antimicrobiano

VARIÁVEL	TODAS AS SESSÕES (N=106)	ASC/CIM EM CONCENTRAÇÃO NÃO TERAPÊUTICA (N=82)	ASC/CIM EM CONCENTRAÇÃO TERAPÊUTICA (N=24)	VALOR P
MODALIDADES DE HD				0,4
HD CONVENCIONAL (%)	61 (57,5)	48 (58,5)	13 (54,2)	
HDP 6 HORAS (%)	34 (32,1)	24 (29,3)	10 (41,7)	
HDP 10 HORAS (%)	11 (10,4)	10 (12,2)	1 (4,2)	
GRUPO				0,002
CONTROLE (%)	28 (26,5)	30 (36,6)	0 (0) ^a	
INTERVENÇÃO 2 HORAS (%)	47 (44,3)	31 (37,8)	14 (58,3) ^b	
INTERVENÇÃO INFUSÃO CONTÍNUA (%)	31 (29,2)	21 (25,6)	10 (41,7) ^b	
COAGULAÇÃO DO SISTEMA (%)	20 (18,9)	18 (22)	2 (8,3)	0,23
HIPOTENSÃO (%)	34 (32,1)	27 (32,9)	7 (29,2)	0,72
DIURÉTICO (%)	37 (34,9)	30 (36,6)	7 (29,2)	0,5
CONCENTRAÇÃO SÉRICA DE VANCOMICINA ANTES DA HD (MG/L)	23,42 (18,73-27,6)	23,01 (17,6-26,19)	25,6 (21,92-29,9)	0,11
ULTRAFILTRAÇÃO (ML)	2500 (1500- 2800)	2500 (1500-3000)	2250 (1000-2500)	0,62
KT/V	0,91 ± 0,3	0,9 ± 0,31	0,93 ± 0,25	0,66
VOLUME DE DISTRIBUIÇÃO (L/KG)	0,74 ± 0,37	0,81 ± 0,38	0,5 ± 0,21	<0,0001
DOSE DIÁRIA DE VANCOMICINA (MG)	1200 (1000- 1500)	1150 (900-1275)	1500 (1200-1800)	0,001
CONCENTRAÇÃO T0 (MG/L)	26,21 ± 9,33	23,29 ± 8,16	36,15 ± 5,37	<0,0001
CONCENTRAÇÃO T2 (MG/L)	20,84 ± 7,62	18,98 ± 7,36	27,19 ± 4,41	<0,0001
CONCENTRAÇÃO TF (MG/L)	16,91 (12,41-21,9)	14,36 (10,83-20,28)	23,35 (20,17- 24,98)	<0,0001
CONCENTRAÇÃO SUBTERAPÊUTICA AO FINAL DA HD (%)	46 (43,4)	45 (54,9)	1 (4,2)	<0,0001
CONCENTRAÇÃO SUPRATERAPÊUTICA AO FINAL DA HD (%)	32 (30,2)	16 (19,5)	16 (66,7)	<0,0001
CONCENTRAÇÃO TERAPÊUTICA AO FINAL DA HD (%)	28 (26,4)	21 (25,6)	7 (29,1)	0,72
CLEARANCE DIALÍTICO (L/H)	1,78 ± 1,15	1,77 ± 1,21	1,8 ± 0,91	0,89
REDUÇÃO 2HORAS (%)	19,6 ± 13	18,45 ± 12,32	25,53 ± 14,69	0,09
REDUÇÃO TOTAL (%)	33,04 ± 14,72	32,38 ± 14,69	35,3 ± 14,92	0,39
TEMPO DE MEIA VIDA (H)	52,52 ± 39,3	56,76 ± 43,15	31,8 ± 26,16	0,16

a: significativamente diferente de b

HD: Hemodiálise; HDP: Hemodiálise Prolongada; ASC/CIM: área sob a curva/concentração inibitória mínima; T0: tempo inicial; T2: segunda hora; TF: término da sessão

Ao serem analisados os dois grupos por meio de regressão logística binária, identificou-se a variável concentração inicial como um fator de risco para uma concentração não terapêutica (ASC/CIM menor que 400 mg·h/L ou maior que 600 mg·h/L) de vancomicina (OR 1,16, p=0,001), enquanto o grupo intervenção 2 horas foi identificado como um fator de proteção (OR 0,24, p=0,04), conforme a tabela 7.

Tabela 7. Regressão logística binária das variáveis associadas à concentração não terapêutica (ASC/CIM menor que 400 mg·h/L ou maior que 600 mg·h/L) de vancomicina

VARIÁVEIS	OR	INTERVALO DE CONFIANÇA	VALOR P
DOSE DIÁRIA DE VANCOMICINA	1,001	1,000-1,002	0,12
CONCENTRAÇÃO SUBTERAPÊUTICA AO FINAL DA HD	5,734	0,563-58,391	0,14
CONCENTRAÇÃO T0	1,163	1,061-1,275	0,001
GRUPO INTERVENÇÃO 2 HORAS	0,239	0,058-0,978	0,04

HD: Hemodiálise; ASC/CIM: área sob a curva/concentração inibitória mínima; T0: tempo inicial

4.2. Pacientes

Entre os 59 pacientes analisados, houve predomínio do sexo masculino (69,5%), com idade 61±11 anos e IMC 26,23 (23,53 – 31,89). As principais comorbidades foram tabagismo (49%), hipertensão arterial sistêmica (44,1%) e doença cardiovascular (27,1%). A gravidade dos pacientes estudados foi avaliada pelo escore prognóstico APACHE II, com média de 31 ± 6, e o prognóstico da IRA pelo escore ATN-ISS, com média de 0,79 ± 0,14.

As internações foram predominantemente devido a quadro

infeccioso (64,4%), seguido por internação cirúrgica (20,3%) e cardiovascular (18,6%). O principal foco de infecção em tratamento foi o pulmonar (72,9%), sendo que 64,4% dos pacientes tinham cultura positiva. Destas, 23,7% detectaram um microrganismo Gram-positivo (14% com *Staphylococcus aureus*, 86% com *Staphylococcus coagulase negativo*).

Durante o seguimento, 28 pacientes evoluíram a óbito (47,5%) e 20 pacientes recuperaram sua função renal (33,9%).

Os pacientes que não necessitavam de droga vasoativa (DVA) ou estavam com dose de norepinefrina abaixo de 0,3mcg/kg/min realizaram HD convencional (4horas, n=32). Aqueles que necessitavam de DVA em doses entre 0,3 e 0,6mcg/kg/min ou acima de 0,6mcg/kg/min realizaram HD prolongada (HDP) por 6 e 10 horas, respectivamente (n=20 e n=7, respectivamente). Os grupos foram semelhantes quanto às características clínicas e laboratoriais, e escores de gravidade, exceto pela dose de DVA ($p<0,001$) e mortalidade ($p=0,002$), maiores no grupo HDP 10 horas, e pela taxa de recuperação de função renal ($p=0,028$), menor no grupo HDP 10 horas, conforme evidenciado na tabela 8.

Tabela 8. Características clínicas e laboratoriais da população geral e nos grupos de acordo com a modalidade de HD realizada.

VARIÁVEL	POPULAÇÃO GERAL (N=59)	HD CONVENCIONAL (N=32)	HDP 6 HORAS (N=20)	HDP 10 HORAS (N=7)	VALOR P
SEXO MASCULINO (%)	41 (69,5)	21 (65,6)	15 (75)	5 (71,4)	0,84
IDADE (ANOS)	61 ± 11	61 ± 12	62 ± 9	60 ± 13	0,87
IMC (KG/M²)	26,23 (23,53-31,89)	26,13 (23,01-31,55)	26,3 (24,11-31,55)	26,73 (24,82-33,42)	0,77
COMORBIDADES					
HAS (%)	26 (44,1)	14 (43,8)	9 (45)	3 (42,9)	1,00
DM2 (%)	14 (23,7)	10 (31,2)	2 (10)	2 (28,6)	0,16
DCV (%)	16 (27,1)	12 (37,5)	4 (20)	0 (0)	0,10
DRC (%)	7 (11,9)	6 (18,8)	1 (5)	0 (0)	0,30
TABAGISMO (%)	29 (49,2)	17 (53,1)	9 (45)	3 (42,9)	0,81
NEOPLASIA (%)	8 (13,6)	5 (15,6)	2 (10)	1 (14,3)	0,87
APACHE-II	31 ± 6	32 ± 7	30 ± 6	31 ± 8	0,58
ATN-ISS	0,79 ± 0,14	0,78 ± 0,15	0,81 ± 0,12	0,79 ± 0,13	0,72
DVA (MCG/KG/MIN)	0,21 (0,02-0,36)	0,04 (0-0,19) ^a	0,36 (0,3-0,48) ^b	1,03 (0,9-1,08) ^c	<0,001
DIURESE (ML/24HORAS)	150 (50-500)	100 (35-300)	425 (70-750)	100 (0-400)	0,28
DROGAS NEFROTÓXICAS (%)	4 (6,8)	3 (9,4)	1 (5)	0 (0)	1,00
DIURÉTICO (%)	16 (27,1)	7 (21,9)	7 (35)	2 (28,6)	0,54
HEMATÓCRITO (%)	26,63 ± 3,98	26,31 ± 3,9	26,14 ± 3,65	29,51 ± 4,66	0,12
PCR (MG/DL)	17 (5,3-23,3)	16,4 (5,15-20,4)	17,4 (5,2-23,6)	22,5 (16,7-26,9)	0,33
ALBUMINA (G/DL)	2,36 ± 0,48	2,31 ± 0,56	2,41 ± 0,36	2,46 ± 0,28	0,67
RECUPERAÇÃO DE FUNÇÃO RENAL (%)	20 (33,9)	15 (46,9) ^a	5 (25) ^b	0 (0) ^c	0,028
ÓBITO (%)	28 (47,5)	9 (28,1) ^c	13 (65) ^b	6 (85,7) ^a	0,002

a: significativamente diferente de b; c: significativamente diferente de a e b

HD: Hemodiálise; HDP: Hemodiálise Prolongada; IMC: Índice de Massa Corpórea; HAS: Hipertensão Arterial Sistêmica; DM2: Diabetes Melito tipo 2; DCV: Doença Cardiovascular; DRC: Doença Renal Crônica; DVA: Droga Vasoativa; PCR: Proteína C-Reativa

Dos 59 pacientes analisados, 14 foram alocados no grupo controle e 45 nos grupos de intervenção (26 no protocolo 2 horas; 19 no protocolo infusão contínua). A mediana de dias de uso da vancomicina foi de 6 dias (5-10). Não houve diferença significativa entre os grupos para as características clínicas (idade, IMC, comorbidades, diurese, uso de diurético ou outras drogas nefrotóxicas) e laboratoriais (albumina, hematócrito, PCR), escores de gravidade (APACHE II e ATN-ISS) ou desfecho clínico (, exceto pela frequência de pacientes do sexo masculino ($p=0,033$) e dose diária de vancomicina recebida ($p<0,0001$), maiores no grupo intervenção infusão contínua, conforme apresentado na tabela 9 e figura 7.

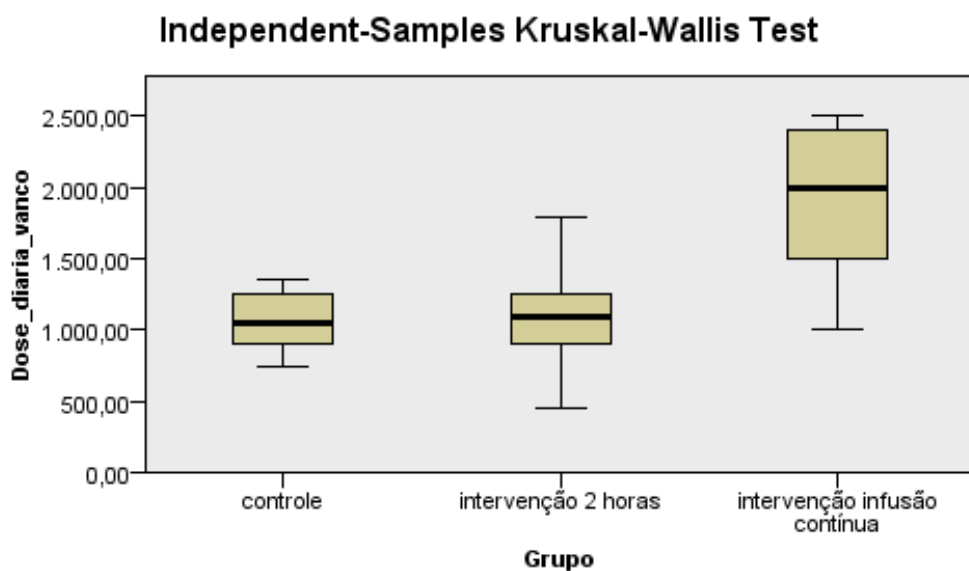


Figura 7. Box plot da dose diária de vancomicina de acordo com o grupo

Tabela 9. Características clínicas e laboratoriais da população geral e nos grupos controle e intervenção (2 horas e infusão contínua)

VARIÁVEL	POPULAÇÃO GERAL (N=59)	GRUPO CONTROLE (N=14)	GRUPO INTERVENÇÃO 2 HORAS (N=26)	GRUPO INTERVENÇÃO INFUSÃO CONTÍNUA (N=19)	VALOR P
MODALIDADES DE HD					0,46
HD CONVENCIONAL	32 (54,2)	8 (57,1)	12 (46,2)	12 (63,2)	
HDP 6 HORAS	20 (33,9)	4 (28,6)	12 (46,2)	4 (21,1)	
HDP 10 HORAS	7 (11,9)	2 (14,3)	2 (7,7)	3 (15,8)	
SEXO MASCULINO (%)	41 (69,5)	7 (50)^b	17 (65,4)^b	17 (89,5)^a	0,033
IDADE (ANOS)	61 ± 11	57 ± 14	62 ± 10	64 ± 11	0,24
IMC (KG/M²)	26,23 (23,53-31,89)	26,29 (24,97-35,25)	25,47 (23,14-31,89)	26,64 (23,53-31,22)	0,69
COMORBIDADES					
HAS (%)	26 (44,1)	6 (42,9)	10 (38,5)	10 (52,6)	0,63
DM2 (%)	14 (23,7)	4 (28,6)	4 (15,40)	6 (31,6)	0,38
DCV (%)	16 (27,1)	4 (28,6)	6 (23,1)	6 (31,6)	0,81
DRC (%)	7 (11,9)	1 (7,1)	2 (7,7)	4 (21,1)	0,40
TABAGISMO (%)	29 (49,2)	6 (42,9)	12 (46,2)	11 (57,9)	0,64
NEOPLASIA (%)	8 (13,6)	2 (14,3)	2 (7,7)	4 (21,1)	0,49
APACHE-II	31 ± 6	30 ± 6	31 ± 7	31 ± 7	0,68
ATN-ISS	0,79 ± 0,14	0,75 ± 0,13	0,8 ± 0,14	0,82 ± 0,14	0,32
DVA (MCG/KG/MIN)	0,21 (0,02-0,36)	0,19 (0-0,6)	0,24 (0,05-0,32)	0,21 (0-0,43)	0,98
DIURESE (ML/24HORAS)	150 (50-500)	375 (50-700)	163 (20-500)	100 (60-300)	0,56
DROGAS NEFROTÓXICAS (%)	4 (6,8)	1 (7,1)	3 (11,5)	0 (0)	0,34
DIURÉTICO (%)	16 (27,1)	5 (35,7)	7(26,9)	4 (21,1)	0,65
HEMATÓCRITO (%)	26,63 ± 3,98	26,08 ± 3,82	26,7 ± 4,37	26,95 ± 3,71	0,82
PCR (MG/DL)	17 (5,3-23,3)	17 (5,3-25,8)	16,55 (5-20)	18,55 (6,9-25,3)	0,36
ALBUMINA (G/DL)	2,36 ± 0,48	2,36 ± 0,33	2,23 ± 0,55	2,52 ± 0,45	0,15
DIAS DE USO DE VANCOMICINA	6 (5-10)	9 (6-12)	6 (5-9)	5 (4-8)	0,15
DOSE DIÁRIA DE VACOMICINA (MG)	1250 (1000-1800)	1050 (900-1250)^b	1095 (900-1260)^b	2000 (1500-2400)^a	<0,0001
RECUPERAÇÃO DE FUNÇÃO RENAL (%)	20 (33,9)	4 (28,6)	9 (34,6)	7 (36,8)	0,94
ÓBITO (%)	28 (47,5)	6 (42,9)	15 (57,70)	7 (36,8)	0,36

a: significativamente diferente de b

HD: Hemodiálise; HDP: Hemodiálise Prolongada; IMC: Índice de Massa Corpórea; HAS: Hipertensão Arterial Sistêmica; DM2: Diabetes Melito tipo 2; DCV: Doença Cardiovascular; DRC: Doença Renal Crônica; DVA: Droga Vasoativa; PCR: Proteína C-Reativa

Foram construídas as curvas de Kaplan-Meier para ambos os desfechos, recuperação de função renal e óbito (figuras 8 e 9), e não houve diferença entre os grupos (Log rank 0,72 e 0,9, respectivamente).

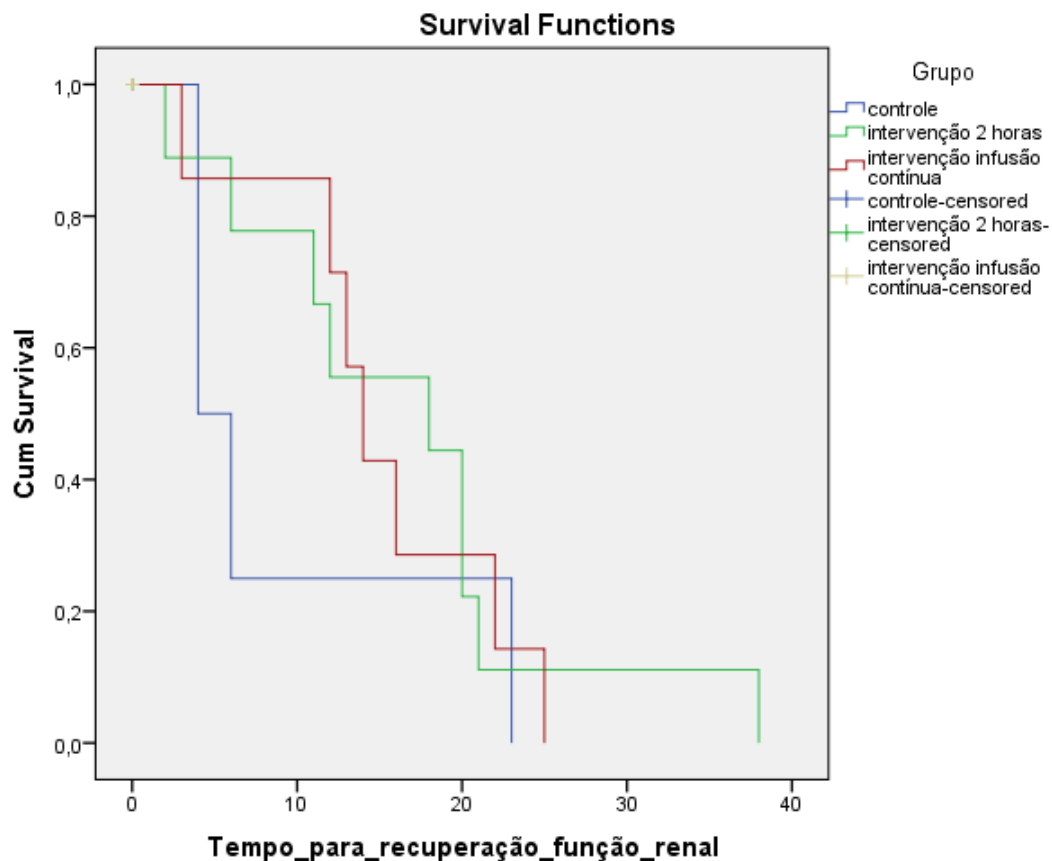


Figura 8. Tempo para a recuperação de função renal entre os grupos controle e intervenções (2horas e infusão contínua). Log rank 0,72

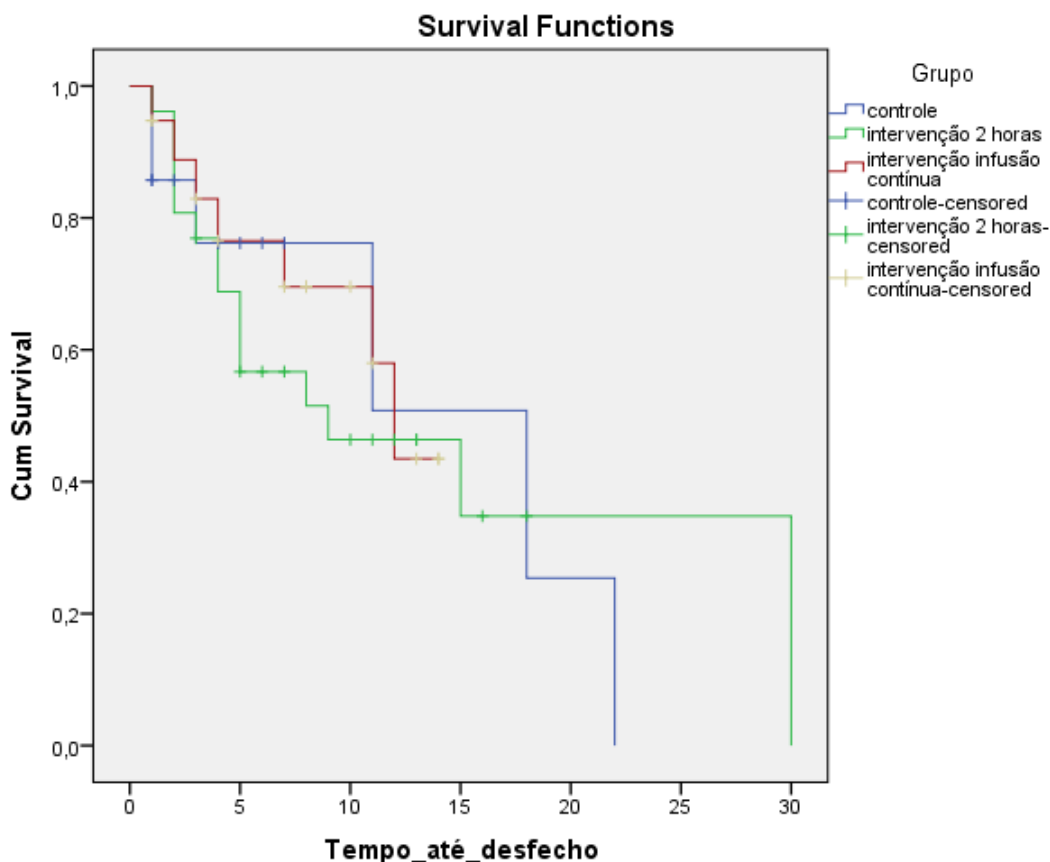


Figura 9. Sobrevida entre os grupos controle e intervenções (2horas e infusão contínua).

Log rank 0,9

5. DISCUSSÃO

Considerando que os pacientes críticos com sepse que apresentam IRA e necessidade de SRA podem apresentar mortalidade de até 60% [3,4,5], faz-se necessária a adoção de medidas que possam reduzir esse desfecho, recebendo destaque a administração precoce e apropriada de antimicrobianos. E dentre os principais pontos polêmicos sobre a antibioticoterapia nessa população está a alteração da sua farmacocinética, relacionada à distribuição, metabolismo, eliminação e remoção da droga [6,8], o que pode levar a concentrações subterapêuticas,

cursando com seleção de mutantes resistentes e maior mortalidade. Em relação à segurança, ênfase tem sido dada ao papel da nefrotoxicidade, a qual pode agravar o quadro clínico e contribuir para o desfecho desfavorável.

As infecções por germes Gram positivos correspondem a aproximadamente um quarto das infecções hospitalares, e dentre os patógenos com perfil de resistência isolados, o MRSA ainda é o predominante, tornando o uso da vancomicina frequente e estratégico [59,60,61].

Este ensaio clínico randomizado não-cego teve por objetivo comparar diferentes protocolos de administração de vancomicina a fim de avaliar as concentrações séricas e ASC/CIM a partir da PK/PD durante sessões de hemodiálise. Foram analisadas 106 sessões (57,5% de HD convencional e 42,5% de HD prolongada), sendo os grupos semelhantes. O *clearance* dialítico, avaliado em L/h, foi menor nos grupos de HD prolongada em comparação com HD convencional, provavelmente relacionado à maior duração da sessão de diálise. O volume de distribuição foi semelhante entre os grupos, e está relacionado à capacidade da droga de distribuir-se entre os compartimentos do organismo.

Já o tempo de meia vida foi menor no grupo que realizou a sessão de HD convencional. O tempo de meia vida é diretamente proporcional ao volume de distribuição e inversamente proporcional ao *clearance* dialítico, justificando-se o menor valor encontrado nesta modalidade.

Das 106 sessões de HD, 28 pertenciam ao grupo controle, 47 sessões ao grupo intervenção 2 horas e 31 sessões ao grupo intervenção infusão contínua. O grupo intervenção infusão contínua recebeu maior dose diária de vancomicina em comparação com os demais grupos e maior concentração sérica nos tempos T0, T2 e Tfinal, justificado pelo

protocolo clínico de administração da vancomicina em doses mais elevadas.

O grupo controle apresentou maior frequência de concentração sérica subterapêutica ao término da HD (86,7% das sessões). Estudo de Freitas *et al* ^[46], avaliando a remoção da vancomicina por diferentes métodos de diálise com membranas de alto fluxo a partir da modelagem farmacocinética-farmacodinâmica (*PK/PD*), identificou que 46,34% dos pacientes apresentavam ASC/CIM menor que 400, sendo 84,2% dos pacientes em HDP e 15,8% em HDI.

De acordo com o *guideline* mais atual sobre o uso da vancomicina ^[17], manter a concentração pré-diálise entre 15 e 20 mg/L parece ser razoável para atingir a meta da ASC/CIM entre 400 e 600mg·h/L, já que os dados que confirmam essa associação para pacientes em hemodiálise são escassos na literatura, sendo as informações extrapoladas da população não dialítica ^[62]. A maioria dos estudos sobre dose de antimicrobianos em pacientes criticamente doentes em terapia dialítica tem sido realizada na população tratada por terapia contínua ^[63,64,65].

Por outro lado, a HDI ainda é o principal método dialítico utilizado em países em desenvolvimento. A maioria dos estudos sobre uso de antimicrobianos em HDI foi realizada em pacientes com doença renal crônica (DRC) recebendo esquema de HD três vezes por semana. A HDP consiste em método híbrido, com características da HDI e HD contínua. Os estudos que abordam dosagem de antimicrobianos são ainda mais escassos nesta modalidade de HD ^[66,67], muitas vezes com posologia inadequada acarretando concentrações subterapêuticas ^[68,69].

No nosso estudo, ambos os grupos de intervenção, 2 horas e infusão contínua, apresentaram maiores ASC/CIM em 24 horas em comparação com o grupo controle. No entanto, o grupo intervenção infusão contínua foi o que apresentou maior frequência de concentração

sérica supratrapêutica ao final da sessão, em comparação com os demais grupos. A nefrotoxicidade está associada a maiores tempo de hospitalização, custos e mortalidade ^[71], sendo uma grande preocupação para as equipes assistenciais.

Ao serem avaliadas as variáveis relacionadas às concentrações terapêutica (razão ASC/CIM entre 400 e 600 mg·h/L) e não terapêutica da vancomicina (abaixo de 400 mg·h/L ou acima de 600 mg·h/L), os grupos de intervenção mostraram maior frequência de concentração terapêutica em relação ao grupo controle. Menor volume de distribuição, maior dose diária de vancomicina e maiores concentrações séricas de vancomicina tanto no início quanto o final da sessão associaram-se a ASC/CIM em nível terapêutico. Em regressão logística, a variável concentração inicial foi identificada como um fator de risco para uma concentração não terapêutica (ASC/CIM menor que 400 mg·h/L ou maior que 600 mg·h/L) de vancomicina (OR 1,16, p=0,001), enquanto o grupo intervenção 2 horas foi identificado como um fator de proteção (OR 0,24, p=0,04).

Entre os 59 pacientes analisados, houve predomínio do sexo masculino, com idade 61±11 anos e IMC 26,23 (23,53 – 31,89). As principais comorbidades foram tabagismo (49%), hipertensão arterial sistêmica (44,1%) e doença cardiovascular (27,1%). As internações foram predominantemente devido a quadro infeccioso (64,4%), sendo o principal foco de infecção o pulmonar (72,9%), com 64,4% dos pacientes apresentando cultura positiva (23,7% delas isolando microrganismo Gram-positivo). Esses dados são compatíveis com a literatura. Sales Jr *et al* ^[72], em estudo sobre a epidemiologia da sepse no Brasil, identificou média de idade de 61,7 anos, com mortalidade global de 46,6%, e insuficiência cardíaca e diabetes melito como comorbidades principais. Outro estudo brasileiro, multicêntrico, conduzido por Santos *et al* ^[73], identificou mortalidade de 44,5% em pacientes de UTI, além de elevada prevalência de doenças cardiovasculares e HAS (30,8%). Ou *et al* ^[74]

avaliaram 4488 pacientes críticos, com predomínio do sexo masculino (63,9%), IMC médio de 24,4 kg/m², admissão na UTI por sepse em 57,6% (predomínio do foco pulmonar), sendo que 52,6% tinham cultura positiva.

A gravidade dos pacientes estudados foi avaliada pelo escore prognóstico APACHE II, com média de 31 ± 6 , e o prognóstico da IRA pelo escore ATN-ISS, com média de $0,79 \pm 0,14$. Durante o seguimento, 28 pacientes evoluíram a óbito (47,5%) e 20 pacientes recuperaram sua função renal (33,9%). Esses dados são compatíveis com a literatura, com mortalidade variando entre 46% [75] até 60,3% [76]. Estudo de Fernandes *et al* [77], avaliando pacientes críticos com IRA, identificaram escore APACHE II 25.5 ± 7.2 e ATN-ISS 0.811 ± 0.195 , e recuperação de função renal em 29% dos pacientes.

De acordo com a modalidade de diálise realizada, os grupos foram semelhantes quanto às características clínicas e laboratoriais, e escores de gravidade, exceto pela dose de DVA e mortalidade, maiores no grupo HDP 10 horas, e pela taxa de recuperação de função renal, menor no grupo HDP 10 horas. Apesar dos escores APACHE II e ATN-ISS serem semelhantes entre os grupos, a necessidade de maiores doses de drogas vasoativas aumenta a mortalidade, devido a alterações na microcirculação e alterações na oferta/consumo de oxigênio [76,78]. Recente estudo de Song *et al* [79] avaliou um índice VIS (*Vasoactive-Inotropic Score*), calculado com as doses máximas de vasopressores e inotrópicos durante as primeiras 6 horas da admissão na UTI [VIS máx = dose de dopamina (µg/kg/min) + dose de dobutamina (µg/kg/min) + 100 × dose de epinefrina (µg/kg/min) + 10 × dose de milrinona (µg/kg/min) + 10.000 × dose de vasopressina (unidades/kg/min) + 100 × dose de norepinefrina (µg/kg/min)], e mostrou que quanto mais elevado o índice, menor a sobrevida em pacientes sépticos.

Este estudo tem algumas limitações. A análise de dados em um único centro acadêmico limita sua generalização. Os médicos assistentes,

equipe de Enfermagem e pacientes e/ou familiares estavam cientes de qual esquema de administração da vancomicina havia sido randomizado, impossibilitando o cegamento. Os desfechos clínicos recuperação de função renal e mortalidade de todas as causas não foram diferentes entre os grupos controle e intervenções, porém o tamanho amostral foi insuficiente para essa conclusão. A bactéria predominante foi *Staphylococcus* coagulase negativo, o que também pode ter influenciado nos desfechos.

Entretanto, este foi o primeiro estudo clínico com desenho randomizado que avaliou a razão ASC/CIM durante sessões de hemodiálise tanto convencional como prolongada em pacientes sépticos com IRA sob diferentes esquemas de administração da vancomicina.

6. CONCLUSÃO

Nossos resultados sugerem que administrar vancomicina durante a diálise resultou em menor proporção de concentrações supratherapêuticas ou subterapêuticas quando comparada à administração em infusão contínua ou após o término da sessão, respectivamente. Novos estudos são necessários para sugerir doses mais adequadas e avaliar o impacto desses achados nos desfechos clínicos.

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8. ANEXOS

8.1. Cronograma

2018	Jan	Fev	Mar	Abr	Mai	Jun	Jul	Ago	Set	Out	Nov	Dez
Atualização bibliográfica												
Elaboração do projeto												

2019	Jan	Fev	Mar	Abr	Mai	Jun	Jul	Ago	Set	Out	Nov	Dez
Etapa clínica												
Etapa Analítica												

2020	Jan	Fev	Mar	Abr	Mai	Jun	Jul	Ago	Set	Out	Nov	Dez
Etapa clínica												
Etapa Analítica												

2021	Jan	Fev	Mar	Abr	Mai	Jun	Jul	Ago	Set	Out	Nov	Dez
Etapa clínica												
Etapa Analítica												
Etapa estatística												

2022	Jan	Fev	Mar	Abr	Mai	Jun	Jul	Ago	Set	Out	Nov	Dez
Etapa Analítica												
Etapa estatística												
Redação												
Exame Geral de Qualificação												
Congresso												
Publicação												

8.2. Termo de Consentimento Livre e Esclarecido (TCLE)



UNIVERSIDADE ESTADUAL PAULISTA
"JÚLIO DE MESQUITA FILHO"
Campus de Botucatu



TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO (TCLE)

RESOLUÇÃO 466/2012

(Participante maior de 18 anos)

CONVIDO, o Senhor (a) para participar do Projeto de Pesquisa intitulado ***"Comparação de diferentes esquemas de administração de vancomicina em pacientes com lesão renal aguda em terapia hemodialítica de suporte renal agudo: um ensaio clínico"***, que será desenvolvido por mim, Dr Welder Zamoner, médico nefrologista, com orientação da médica Prof Dra Daniela Ponce da Faculdade de Medicina de Botucatu –UNESP.

Estou estudando diferentes maneiras de administrar um antibiótico utilizado para tratar infecções graves causadas por bactérias, durante a realização de hemodiálise (método de limpeza do sangue por meio de uma máquina) em pacientes que apresentam lesão renal aguda (incapacidade temporária dos rins executarem suas funções). Sabemos que durante a sessão de hemodiálise há a retirada de considerável quantidade desse antibiótico o que pode comprometer o tratamento. Assim, ao iniciar a participação neste projeto de pesquisa, o(a) senhor(a) será sorteado para 1 dos 3 grupos propostos: um que já é feito normalmente (grupo controle), e outros dois propostos (grupo 2 horas e grupo infusão contínua).

Dessa forma, solicito o seu consentimento para consultar seu prontuário médico e coletar outras informações lá contidas como idade, peso, presença de outras doenças como hipertensão arterial, diabetes melito entre outras, diagnóstico da internação, sinais vitais, avaliação de função renal, hemograma e outros exames laboratoriais, data do início e tempo de uso da vancomicina, referentes a consultas feitas anteriormente pelo(a) senhor(a). Serão colhidas de três a quatro amostras de sangue de 2 ml cada uma, totalizando 6 a 8 ml de sangue, durante a terapia de diálise, sem necessidade de uso de agulhas em sua pele, o que não implicará em qualquer risco para o seu tratamento. Este procedimento será repetido por duas sessões de hemodiálise. Essas amostras serão encaminhadas para o laboratório e será analisada a concentração do antibiótico no seu sangue em diferentes momentos da hemodiálise.

O conhecimento dessas características permitirá diversos benefícios para a ciência/sociedade, pois possibilitará o conhecimento sobre o impacto de administrar

antibióticos durante a diálise na evolução da infecção, de modo a garantir a eficácia do tratamento e evitar a toxicidade da droga, possibilitando a redução da mortalidade. Não há qualquer risco adicional ao paciente que for sorteado para os grupos de intervenção, tendo em vista que são doses descritas na literatura como seguras. A hipótese testada é de que nos grupos onde haverá a intervenção a concentração do antibiótico no sangue durante a sessão de hemodiálise permaneça dentro do que é recomendado para garantir sucesso no tratamento, o que não ocorre com a forma atual de administração.

Fique ciente de que sua participação neste estudo é voluntária e que mesmo após ter dado seu consentimento para participar da pesquisa, você poderá retirá-lo a qualquer momento sem qualquer prejuízo na continuidade do seu tratamento.

Este Termo de Consentimento Livre e Esclarecido será elaborado em 2 vias de igual teor, sendo uma via entregue ao Senhor (a) devidamente rubricada, e a outra via será arquivada e mantida pelos pesquisadores por um período de 5 anos após o término da pesquisa.

Qualquer dúvida adicional você poderá entrar em contato com o Comitê de Ética em Pesquisa através dos telefones (14) 3880-1608 ou 3880-1609 que funciona de 2ª a 6ª feira das 8.00 às 11.30 e das 14.00 às 17horas, na Chácara Butignolli s/nº em Rubião Júnior – Botucatu - São Paulo. Os dados de localização dos pesquisadores estão abaixo descritos:

Após terem sido sanadas todas minhas dúvidas a respeito deste estudo, CONCORDO EM PARTICIPAR de forma voluntária, estando ciente que todos os meus dados estarão resguardados através do sigilo que os pesquisadores se comprometeram. Estou ciente que os resultados desse estudo poderão ser publicados em revistas científicas, sem que minha identidade seja revelada.

Botucatu, ____/____/____

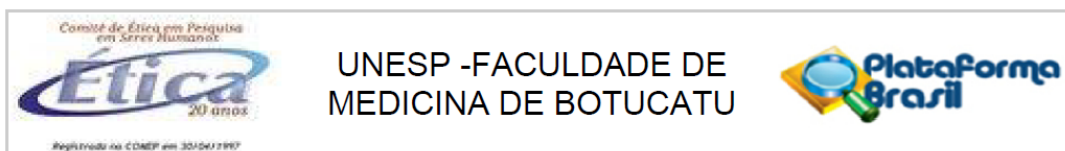
Pesquisador

Participante da Pesquisa(ou responsável)

Nome: Welder Zamoner
Endereço: Rua Damião Pinheiro Machado, 751, apto 64, CEP 18603-560, Centro, Botucatu-SP
Telefone: (14) 98217-2334
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Nome: Profª Dra Daniela Ponce
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Telefone: (14) 99762-4351
E-mail: dponce@fmb.unesp.br

8.3. Parecer Consubstanciado do CEP



PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Comparação de diferentes esquemas de administração de vancomicina em pacientes com lesão renal aguda em terapia hemodialítica quanto à vancocinemia: um ensaio clínico

Pesquisador: WELDER ZAMONER

Área Temática:

Versão: 2

CAAE: 04729118.4.0000.5411

Instituição Proponente: Departamento de Clínica Médica

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.198.161

Apresentação do Projeto:

As informações descritas nos campos "Apresentação do Projeto", "Objetivo da Pesquisa" e "Avaliação dos Riscos e Benefícios" foram retiradas dos documentos e arquivo - Informações Básicas da Pesquisa.

A sepse está implicada em falência de vários órgãos, dentre eles os rins, sendo a principal etiologia de lesão renal aguda (LRA) em ambiente de terapia intensiva, com elevada mortalidade e necessidade de suporte renal agudo (SRA). O controle da infecção frequentemente inclui o uso da vancomicina para combater patógenos hospitalares Gram positivos, ocorrendo grandes alterações em sua farmacocinética e remoção parcial ou total por métodos dialíticos, o que aumenta o risco de concentrações subterapêuticas durante a terapia e, conseqüentemente, aumenta a mortalidade.

Hipótese: Esquema com administração de vancomicina intradialítica garante concentrações terapêuticas durante todo o procedimento e pode diminuir mortalidade, sem impactar no desfecho renal.

Metodologia: Será realizado estudo tipo ensaio clínico randomizado. Os pacientes serão selecionados para entrar no estudo a partir da segunda sessão de diálise e após pelo menos três dias de calendário com uso da vancomicina visando seu estado estável. O tempo de seguimento será durante todo o período de internação. Os pacientes serão randomizados por meio de um processo de randomização em blocos (block randomization) por meio da web site Randomization.

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Bairro: Rubião Junior

UF: SP

Município: BOTUCATU

CEP: 18.618-970

Telefone: (14)3880-1609

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UNESP -FACULDADE DE MEDICINA DE BOTUCATU



Continuação do Parecer: 3.198.161

com <http://www.randomization.com> e alocados em 3 grupos: 1. Grupo Controle: administração de vancomicina após o término da sessão de hemodiálise, 15 mg/Kg; 2. Grupo 2h: administração de vancomicina na 2ª hora da sessão de hemodiálise, 7,5mg/kg, com outros 7,5mg/kg administrados ao término do procedimento; 3. Grupo infusão contínua: administração de vancomicina em bomba de infusão em 24horas. dose de ataque de 15-20mg/kg em 30-60minutos e, em seguida, 30mg/kg em 24horas.

Os participantes serão alocados em 3 grupos:- Grupo Controle: administração de vancomicina após o término da sessão de hemodiálise - Grupo 2h: administração de vancomicina na 2ª hora da sessão de hemodiálise- Grupo infusão contínua: administração de vancomicina em bomba de infusão em 24horasSerão realizadas coletas seriadas de sangue (2mL/cada) nos tempos zero (antes do início do procedimento), durante o procedimento na 2ª hora e ao término da terapia.Serão realizadas análises parciais a cada inclusão de 10 pacientes no protocolo do estudo e, caso seja identificado benefício em um dos grupos, o estudo será interrompido e a intervenção que mostrar-se superior será realizada para todos os pacientes. O protocolo de estudo compreenderá coleta de informações em prontuário, referentes a dados clínicos gerais, dados laboratoriais; dados dialíticos; dados de avaliação da farmacocinética e farmacodinâmica da Vancomicina.Será realizada coleta seriada de amostras sanguíneas (2 mL cada) através do cateter venoso central pela equipe de enfermagem da diálise para a determinação das concentrações séricas de vancomicina antes de iniciar a diálise, após 2horas e ao seu término. Esse procedimento será realizado duas vezes por paciente, em duas sessões de hemodiálise consecutivas, para fins de estudo nesse protocolo.

Critério de Inclusão: Serão incluídos pacientes sépticos internados no setor de terapia intensiva (SETI) do HC FMB UNESP, maiores de 18 anos, com LRA e apresentação clínica sugestiva de Necrose Tubular Aguda (NTA) associada à sepse, em terapia de suporte renal agudo convencional ou prolongada e em uso de vancomicina.

Critério de Exclusão: Serão excluídos do estudo: gestantes, pacientes que apresentarem LRA de outras etiologias, pacientes que se encontrarem em terapia renal substitutiva crônica (diálise ou transplante renal), pacientes que tiverem sua sessão dialítica interrompida por razões clínicas ou técnicas, e pacientes com níveis séricos pré diálise de vancomicina superiores a 25 mg/dL.

Tamanho amostral: 72 participantes, sendo 24 em cada grupo.

Haverá retenção de amostra, apresentado o regulamento de Biorrepositório.

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Continuação do Parecer: 3.198.161

Objetivo da Pesquisa:

Objetivo primário: - Avaliar os níveis séricos e ASC/CIM antes, durante e após as sessões de hemodiálise a partir da abordagem farmacocinética e modelagem farmacocinética-farmacodinâmica;

Objetivo secundário: - Analisar o impacto dos diferentes protocolos nos desfechos: recuperação de função renal e mortalidade

Avaliação dos Riscos e Benefícios:

Riscos: Aumento na concentração sérica do antimicrobiano.

Benefícios: Impacto em redução de tempo de internação hospitalar, diminuição de mortalidade e recuperação mais rápida de função renal.

Comentários e Considerações sobre a Pesquisa:

Trata-se de projeto de pesquisa relevante com metodologia adequada. O custo será de R\$50,00 (informado pelo pesquisador).

Considerações sobre os Termos de apresentação obrigatória:

Todos os termos obrigatórios foram apresentados. Os pesquisadores apresentaram novo TCLE, que se encontra adequado conforme a Resolução n. 466/2012.

Recomendações:

Não há.

Conclusões ou Pendências e Lista de Inadequações:

Após análise em REUNIÃO ORDINÁRIA, o Colegiado deliberou APROVADO o projeto de pesquisa apresentado.

Considerações Finais a critério do CEP:

Conforme deliberação do Colegiado em REUNIÃO ORDINÁRIA do Comitê de Ética em Pesquisa da FMB/UNESP, realizada em 11 de MARÇO de 2019, o projeto analisado está APROVADO para ser iniciado, sem necessidade de envio à CONEP.

No entanto, ao final da execução do projeto de pesquisa, é necessário enviar o "Relatório Final de Atividades", na forma de "NOTIFICAÇÃO", via sistema Plataforma Brasil.

Atenciosamente,

Comitê de Ética em Pesquisa da Faculdade de Medicina de Botucatu – UNESP

Endereço: Chácara Butignolli, s/n

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Continuação do Parecer: 3.198.161

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1259741.pdf	14/02/2019 21:54:02		Aceito
Outros	CartaCEP_pendencias.pdf	14/02/2019 21:53:19	WELDER ZAMONER	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLEcorrigido.pdf	14/02/2019 21:52:49	WELDER ZAMONER	Aceito
Declaração de Instituição e Infraestrutura	TermoDeAnuencialInstitucional.pdf	06/02/2019 23:35:22	WELDER ZAMONER	Aceito
Declaração de Instituição e Infraestrutura	Anuencia_HCFMB.pdf	06/02/2019 23:34:57	WELDER ZAMONER	Aceito
Folha de Rosto	FolhaDeRostoAssinada.pdf	06/02/2019 23:34:19	WELDER ZAMONER	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_completo.pdf	04/12/2018 00:19:54	WELDER ZAMONER	Aceito
Declaração de Manuseio Material Biológico / Biorepositório / Biobanco	Biorrepositorio.pdf	18/11/2018 16:48:05	WELDER ZAMONER	Aceito
Cronograma	Cronograma.pdf	18/11/2018 16:47:54	WELDER ZAMONER	Aceito

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

BOTUCATU, 14 de Março de 2019

Assinado por:
SILVANA ANDREA MOLINA LIMA
(Coordenador(a))

Endereço: Chácara Butignolli, s/n

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8.4. Alteração do título do projeto

Campus de Botucatu

DECLARAÇÃO DE ALTERAÇÃO DE TÍTULO EM PROJETO DE PESQUISA

Objetivo Acadêmico: Dissertação de Mestrado ()
Tese de Doutorado (X)

Título constante no parecer de aprovação do projeto pelo CEP/CEUA:

“Comparação de diferentes esquemas de administração de vancomicina em pacientes com lesão renal aguda em terapia hemodialítica quanto à vancocinemia: um ensaio clínico”

Título final do trabalho (constante na capa da dissertação ou tese):

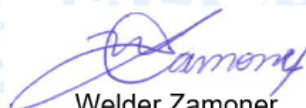
“Comparação quanto à eficácia e segurança de diferentes esquemas de administração de vancomicina em pacientes com injúria renal aguda em hemodiálise: um ensaio clínico randomizado”

Data da reunião do CEP/CEUA que aprovou o projeto **11/03/2019**

Declaramos que o trabalho não sofreu alterações nos objetivos e/ou conteúdo metodológico da época de apresentação para análise do CEP e/ou CEUA.

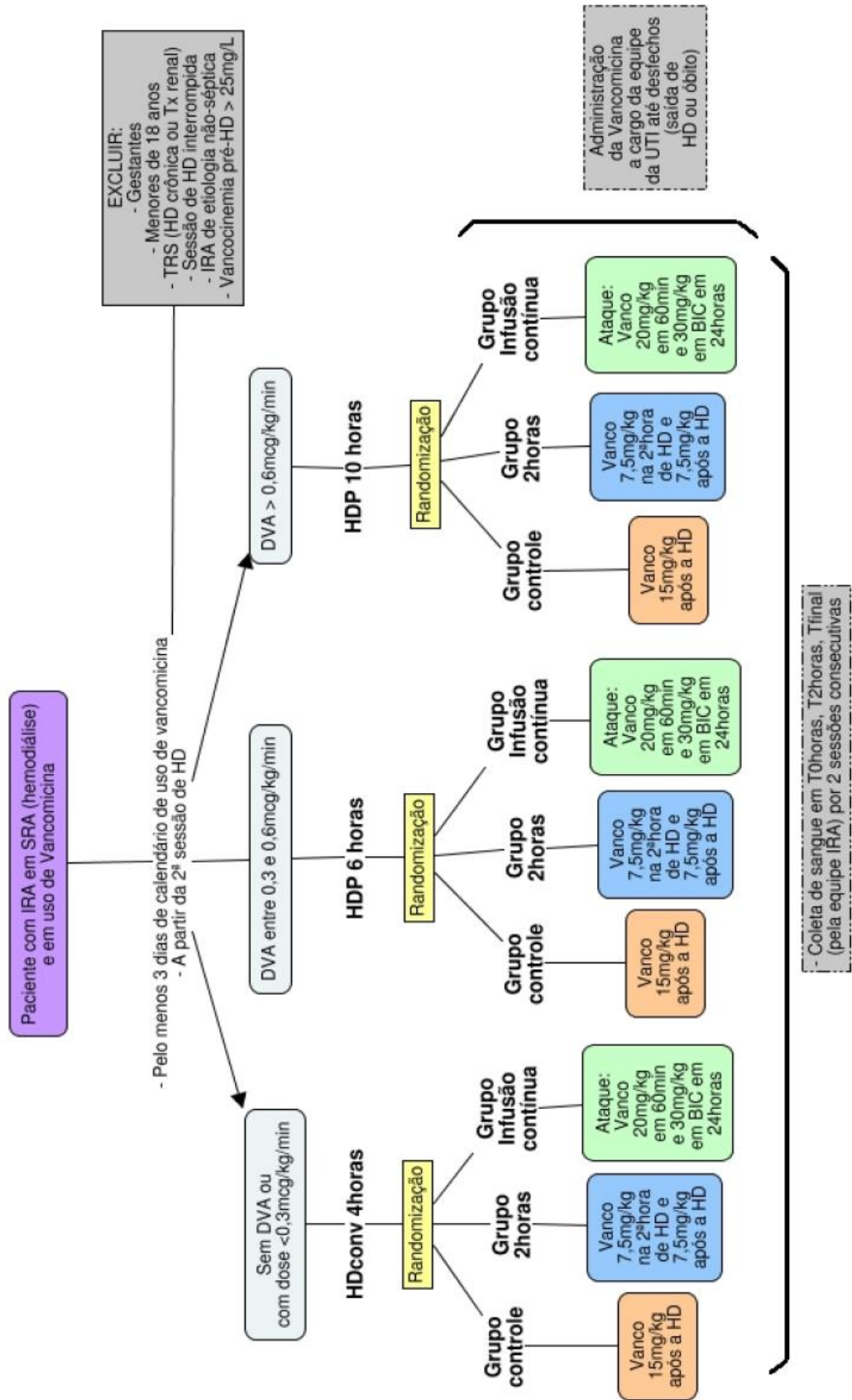


Prof. Dra. Daniela Ponce
Nome/assinatura original do(a) Orientador(a)



Welder Zamoner
Nome/assinatura original do(a) Aluno(a)

8.5. Protocolo clínico



Capítulo II: Artigos publicados na temática

REVIEW

Pharmacokinetics and pharmacodynamics of antibiotics in critically ill acute kidney injury patients

Welder Zamoner, Fernanda M. de Freitas, Durval S. S. Garms, Mariele Gobo de Oliveira, André L. Balbi & Daniela Ponce

Nephrology, University São Paulo State-UNESP, Botucatu, SP 18618-970, Brazil

Keywords

Acute kidney injury, antibiotics, critically ill patients, dialysis, drug toxicity, sepsis.

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Funding Information

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Pharma Res Per, 4(6), 2016, e00280,
doi: 10.1002/prp2.280

doi: 10.1002/prp2.280

Abstract

Sepsis is the most common cause of death in critically ill patients and is associated with multiorgan failure, including acute kidney injury (AKI). This situation can require acute renal support and increase mortality. Therefore, it is essential to administer antimicrobials in doses that achieve adequate serum levels, avoiding both overdosing and drug toxicity as well as underdosing and the risk of antibiotic resistance and higher mortality. Currently, there are no validated guidelines on antibiotic dose adjustments in septic patients with AKI. The current recommendations were extrapolated from studies conducted in noncritical patients with end-stage chronic kidney disease receiving chronic renal replacement therapy. This study aimed to review and discuss the complexity of this issue, considering several factors related to drug metabolism, the characteristics of critically ill patients, the properties of antimicrobial drugs and dialysis methods.

Abbreviations

AKI, acute kidney injury; CRRT, continuous renal replacement therapy; ED, extended dialysis; HD, hemodialysis; HPLC, high-performance liquid chromatography; IHD, intermittent hemodialysis; MDRD, modified diet in renal diseases; MIC, minimum inhibitory concentration; PD, peritoneal dialysis; PK, pharmacokinetic; RRT, renal replacement therapy.

Introduction

The main cause of death in patients in intensive care units is sepsis, with mortality rates ranging from 18.4 (Kaukonen et al. 2014) to 60%, depending on the severity of the condition (Alberti et al. 2002; Zarjou and Agarwal 2011). In recent years the sepsis, severe sepsis and septic shock concepts have been reviewed and updated targeting more accurate diagnosis and best suitable treatment of this condition. In the last update sepsis was defined as an organic life-threatening dysfunction caused by exacerbated response to infection (Singer et al. 2016). Sepsis is a well-known risk factor for the development of acute kidney injury (AKI), taking to 70% mortality rate, greater than other causes of AKI (around 45%; Schier and Wang 2004).

Sepsis is the main cause of AKI in critically ill patients, and half of these patients require acute renal support (Bellomo et al. 2004; Davenport 2011; Zarjou and

Agarwal 2011). Thus, the adoption of measures that lead to decreased mortality and costs associated with treatment and hospitalization has become important. Actions with the greatest impact include early administration of antimicrobials, the choice of which is based on the patient's history, the recent use of antibiotics and the source of community or hospital pathogens (Roberts and Lipman 2009).

In a septic patient, variations in the volume of distribution and clearance can affect the antimicrobial concentration. Patients undergoing acute renal support via dialysis also have an increased risk of receiving a subtherapeutic dose of the antimicrobial (Roberts and Lipman 2009; Lewis and Mueller 2014). Maintaining an adequate antimicrobial dose is key to preventing bacterial resistance, infection by opportunistic bacteria and mortality. This is dependent on microbiological activity, antimicrobial sensitivity, and pharmacokinetics (Roberts and Lipman 2009).

To date, there are no validated guidelines on antibiotic dose adjustments in septic patients with AKI; current recommendations have been extrapolated from studies conducted in noncritical patients with end-stage chronic kidney disease receiving chronic renal replacement therapy (Bellomo et al. 2004; Mueller and Smoyer 2009). This study aimed to review and discuss the complexity of this issue, considering several factors related to drugs metabolism, the characteristics of critically ill patients, the properties of antimicrobial drugs and dialysis methods.

Pharmacokinetics and Pharmacodynamics of Antibiotics in Critically ill Patients

The antimicrobial exert its effect by different mechanisms, primarily by inhibiting the synthesis of the bacterial wall (penicillins, glycopeptides, carbapenems, and cephalosporins), inhibiting DNA replication (quinolones) or its transcription (rifampicin), impairing bacterial ribosomes and protein synthesis (macrolides, linezolid, dalfopristin, tetracyclines, and aminoglycosides), interfering with metabolic pathways (sulfonamides and trimethoprim) or disrupting the cytoplasmic membrane (polymyxin and daptomycin) (Finberg and Guharoy 2012).

The parameter used to measure the microbiological activity of an antimicrobial is the minimum inhibitory concentration (MIC). This is an in vitro measure of the effectiveness of the antimicrobial against the microorganism (Finberg and Guharoy 2012).

Pharmacokinetics and pharmacodynamics are tools that determine how much and how often the drug should be

dispensed (Finberg and Guharoy 2012). Pharmacokinetics describes the absorption, distribution, metabolism, and elimination of a drug, whereas pharmacodynamics describes the impact of serum levels and the drug response (Roberts and Lipman 2009; Finberg and Guharoy 2012). Thus, the pharmacodynamics of an antimicrobial may be time-dependent, that is, related to the time of exposure to a specific MIC, such as beta-lactams, clarithromycin, erythromycin, carbapenems, linezolid, lincosamides (clindamycin) (Finberg and Guharoy 2012), and fluconazol (Fissell 2013); or it may be concentration-dependent, as for aminoglycosides, metronidazole, daptomycin (Finberg and Guharoy 2012), amphotericin B, and echinocandins (Fissell 2013). The effects of some drugs are both concentration- and time-dependent, as for quinolones, azithromycin, glycopeptides, tetracycline (Roberts and Lipman 2009) (Fig. 1).

To optimize antimicrobial therapy and maximize the effect of the drug on the pathogen, as well as to reduce the risk of antimicrobial resistance and avoid drug toxicity (Blot et al. 2014; Lewis and Mueller 2014), the drug with the correct spectrum of action should be selected, initiated early and given at an appropriate dose based on its pharmacokinetics and pharmacodynamics.

Various mechanisms influence antimicrobial pharmacokinetics in critically ill patients (Scoville and Mueller 2013; Blot et al. 2014) (Fig. 2). The absorption of a drug by the oral route of administration may be impaired (Lewis and Mueller 2014) by gastric dysmotility, adherence in circuits, interactions with nutritional components or incorrect gastric pH due to the concomitant use of proton pump inhibitors (Fissell 2013). Similarly, via the subcutaneous route of administration, absorption may be

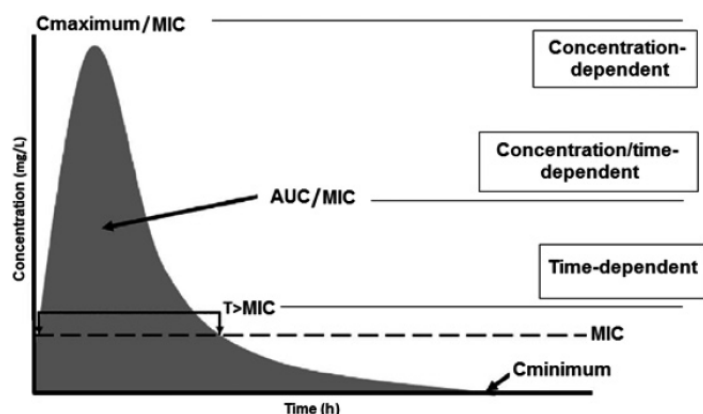


Figure 1. Pharmacodynamics of an antimicrobial drug with respect to its concentration versus time curve. $T > \text{MIC}$: time (T) that the drug concentration remains above the minimum inhibitory concentration (MIC); $C_{\text{maximum}}/\text{MIC}$: maximum concentration rate (C_{maximum}) by the MIC; AUC/MIC : ratio of the area under the curve (AUC) of the concentration versus time above the MIC. Adapted from Roberts and Lipman (2009).

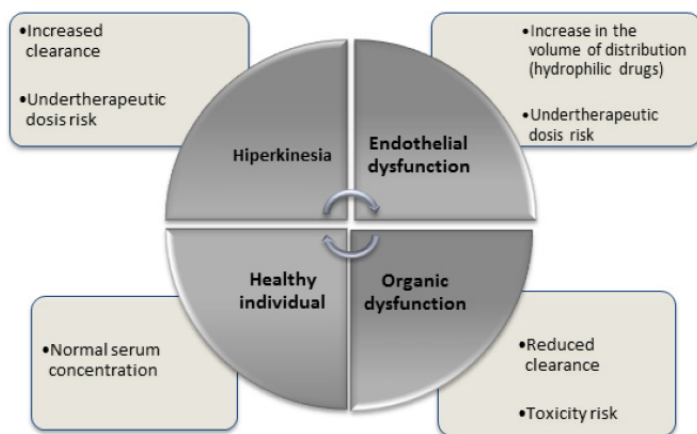


Figure 2. Influence of the patient's clinical status on antimicrobial pharmacokinetics. Adapted from Roberts and Lipman (2009).

impaired by reduced secondary cutaneous circulation and the redistribution of blood flow exacerbated by edema (Lewis and Mueller 2014). Considering these effects on absorption, preference is given to intravenous administration of antibiotics in critically ill patients.

Antimicrobial distribution also undergoes profound changes in critically ill patients: the production of endotoxins by a microorganism during sepsis can lead to the release of various inflammatory mediators that affect the vascular endothelium and culminate in the altered distribution of blood flow, increased capillary permeability, acid/base disorders and endothelial injury. Thus, fluid extravasation from the intravascular to the interstitial compartment occurs, increasing the distribution volume of hydrophilic drugs and decreasing serum levels; this has been shown with beta-lactams, aminoglycosides, glycopeptides, linezolid, and colistin. Changes in the volume of distribution can also be increased in the presence of mechanical ventilation, hypoalbuminemia, and extracorporeal circuits (Roberts and Lipman 2009; Roberts 2011; Lewis and Mueller 2014).

Drug elimination also changes under septic conditions; in the absence of organ dysfunction, there is increased renal perfusion and creatinine clearance, leading to increased hydrophilic drug elimination (Roberts and Lipman 2009) and the optimization of other routes of metabolism and elimination (bile and transintestinal routes) (Lewis and Mueller 2014), leading to reduced serum concentrations of some antimicrobials (Roberts and Lipman 2009).

With deterioration of the patient's health status, myocardial depression, and decreased organ perfusion impair the clearance of the antimicrobial (either due to hepatic or renal impairment), increase the half-life

(defined as the time until the concentration of the drug is reduced by half (Roberts and Lipman 2009)) and increase potential toxicity due to elevated serum concentrations of the drug and/or accumulation of its metabolites (Roberts and Lipman 2009). However, patients on acute kidney support show increased drug clearance, depending on the molecular weight, entrainment of proteins and distribution volume (of the drug), and the heterogeneity of the dialysis method, with increased clearance seen using methods that are prolonged, frequent, or more intense (Kielstein and Burkhardt 2011; Lewis and Mueller 2014). Antimicrobial hepatic metabolism may also be affected in the context of AKI. This is not fully understood, but is likely due to changes in hepatic blood flow and reduced activity of cytochrome P450 enzymes, particularly CYP 3A (Lewis and Mueller 2014).

The standard dose recommendations for antimicrobials were determined in studies performed on healthy young adults and physiologically normal individuals (Roberts 2011). In order to avoid under or overdosing, dose adjustments should be performed in patients with renal or hepatic impairment (Roberts and Lipman 2009; Roberts 2011).

To perform adjustments for renal function, the dosing schedule should be based on the volume of distribution and systemic clearance (Roberts 2011). Estimates of the glomerular filtration rate by indirect methods are not as accurate, despite the ease of monitoring this parameter (Roberts 2011; Blot et al. 2014). Among the available calculations currently used to estimate creatinine clearance, the Cockcroft-Gault equations, the Modified Diet in Renal Diseases (MDRD) score and the Chronic Kidney Disease EPI (CKD EPI) score (Gilbert et al. 2014; Kaukonen et al.

2014) were all validated in patients with stable renal function, which does not occur in the context of AKI (Blot *et al.* 2014). Thus, the antimicrobial doses currently suggested for critically ill patients with AKI were derived in most cases from studies on patients with chronic kidney disease (Blot *et al.* 2014).

An alternative method is to measure clearance directly by collecting urine for 24 h or as samples taken every 2, 4, or 8 h using the formula: urinary creatinine concentration $\times$ urine volume $\times$ time/serum creatinine. The result is expressed in mL/min (Blot *et al.* 2014); however, this method is impractical and limited in anuric patients.

The therapeutic monitoring of drugs can measure the serum concentration of the antimicrobial, and its clearance can be calculated to improve the accuracy of subsequent dose adjustments, providing a lower risk of toxicity due to overdose and a lower risk of uncontrolled infection or bacterial resistance due to underdosing (Roberts 2011). Among the bioanalytical methods used for therapeutic drug monitoring, immunoassays such as fluorescence polarization (FPIA), multiplied by technical enzyme (EMIT), and immunoenzymatic assays (ELISA) are popular methods using the reaction of an antibody to its antigen. However, drug metabolites or drugs with a similar structure can also be recognized by the antibody, resulting in falsely high concentrations.

High-performance liquid chromatography (HPLC) and mass net-spectrometry chromatography (LC/MS) are more specific methods that can separate and quantify drugs based on their molecular polarities and interactions with the stationary phase in a column, but are associated with a high cost and require highly trained technicians, which make these methods difficult to use in medical practice (Liu *et al.* 2011).

The Influence of Acute Renal Supportive Therapy

An important factor that interferes with the removal of drugs is the dialysis technique, which may be based on one of two types of transport: diffusion or convection. Both are effective at removing low molecular weight solutes; however, convective therapy is most effective in removing high molecular weight substances.

The choice of the dialyzing membrane also affects drug removal, since a high flux membrane, with increased permeability of medium size molecules, presents a greater capacity to remove drugs with a high molecular weight compared to low flux membranes (Eyler and Mueller 2011; Lewis and Mueller 2014). This difference was demonstrated in a small prospective cohort study ($n = 9$) carried out in the Czech Republic. The study compared the removal of vancomycin in critically ill patients with

AKI in hemodialysis with high versus low flow membranes. The median percentage removal of vancomycin after dialysis with a low flow membrane was 17%, whereas with a high flux membrane this was 31%. The study concluded that, despite the differences between removal membranes, it was still necessary to monitor serum levels of vancomycin after each dialysis and to provide an additional dose of vancomycin, since all patients showed subtherapeutic antibiotic levels (Petejova *et al.* 2012).

Another feature of the dialyzing membrane is adsorption. Hydrophobic synthetic membranes have a high adsorption capacity, whereas cellulose acetate membranes show less adsorption (Clark *et al.* 1999). The clinical importance of this property of the membrane in relation to interference in serum levels of antimicrobials requires further study, but some evidence suggests early saturation of this process (Schetz 2007).

In critically ill patients, several options for renal replacement therapy (RRT) are available: peritoneal dialysis (PD) and hemodialysis (HD), which can be classified according to their duration and dialysate and blood flow, such as conventional intermittent hemodialysis (IHD), prolonged or extended dialysis (ED), and continuous renal replacement therapy (CRRT) (Pannu *et al.* 2008; Kielstein *et al.* 2010). Currently, there is no consensus in the literature as to which is the best method of dialysis for patients with AKI. Thus, the choice of the method made by nephrologists and intensivists, according to their experience and the clinical condition of the patient at the time of treatment (Gabriel *et al.* 2008). Table 1 shows the types of dialysis and their main features.

Peritoneal dialysis is an option for a selected group of patients. Recent studies have suggested that, when indicated, PD should be performed with large volumes of dialysate, in a continuous manner and through a flexible catheter and cyclor, in order to obtain survival results similar to patients treated with IHD (Ponce *et al.* 2012). In PD, the dialyzing membrane is the peritoneum; little is known about drug removal in high volume therapies.

Intermittent hemodialysis is characterized by high blood and dialysate flow, that is, 300–400 and 500 mL/min, respectively, for 4 to 5 h at an affordable cost. This method uses similar machines and filters to those used in chronic dialysis (Fieghen *et al.* 2010). Intermittent hemodialysis is indicated in hemodynamically stable patients and can be taken on alternate days or daily, according to the clinical and laboratory conditions of the patient, in order to maintain water balance and control the generation of urea (Shingarev *et al.* 2011).

Some authors suggest that critically ill patients with AKI, as they are hemodynamically unstable (using vasoactive drugs) and hypercatabolic should be treated by continuous methods (Yu *et al.* 2007). Continuous renal

Table 1. Antimicrobials used in intensive care and their main characteristics (based on The Sanford Guide to Antimicrobial Therapy, reference Gilbert et al. 2014).

	Vancomycin	Meropenem	Cefepime	Piperacillin Tazobactam	Fluconazole	Micafungin
Pharmacodynamics	AUC/MIC	T > MIC	T > MIC	T > MIC	AUC/MIC	AUC/MIC
Molecular weight (Da)	1485	384.46	571.5	539.5 322.3	306.99	1292.26
Volume of distribution ¹ (L/kg)	0.7	0.23–0.35	0.3	0.24–0.4	0.7–0.8	0.39
Protein binding (%) ¹	10–55	2	20	16–48	10	>99
Clearance	Renal	Renal	Renal	Renal	Renal	Hepatic/Renal
Dose for normal renal function	15–20 mg/kg q8–12 h	1 g q8 h	1–2 g q8–12 h	3.375 g q6 h	100–400 mg q24 h	100–150 mg q24 h
Dose in CRRT	500 mg q24–48 h	500 mg q24 h	2 g q24 h	2.25 g q6 h	200–400 mg q24 h	No dose adjustment
Dose in EHD ²	No data	No data	No data	No data	No data	No dose adjustment
Dose in IHD ³	15 mg/kg after HD	500 mg q24 h	1 g q24 h (+1 g after HD)	2.25 g q12 h (+0.75 g after HD)	100–400 mg q24 h – after HD	No dose adjustment
Dose in PD ⁴	7.5 mg/kg q2–3 days	500 mg q24 h	1–2 g q48 h	2.25 g q6 h	50–200 mg q24 h	No dose adjustment

AUC, area under the curve; MIC, minimum inhibitory concentration; T, time; CRRT, continuous renal replacement therapy; IHD, conventional intermittent hemodialysis; EHD, prolonged or extended hemodialysis; HDI, intermittent hemodialysis; PD, peritoneal dialysis.

¹In healthy individuals.

²Is suggested to be used in the same dosages.

³Considering next IHD in 1 day.

⁴CAPD (continuous ambulatory peritoneal dialysis).

replacement therapy, defined as a prolonged and continuous treatment, lasts for 24 h and uses lower blood and dialysate flow compared to conventional dialysis, that is, 100–150 and 1000–1500 mL/h, respectively (Marshall and Golper 2011). This is an efficient method that provides adequate metabolic and blood volume control without affecting the hemodynamic stability of the patient.

An intermediate method that provides hemodynamic stability and adequate metabolic control of patients with a shorter duration than CRRT is prolonged or ED, lasting between 6 and 18 h. The blood and dialysate flow are lower than in conventional dialysis, that is, 100–200 and 200–300 mL/min, respectively (Kumar et al. 2000; Marshall and Golper 2011).

Intermittent hemodialysis and ED can be performed with low or high capillary flow and efficiency, or with greater or lesser removal means molecules capacity, according to the ultrafiltration and performance coefficients (Kuf and KoA, respectively), the duration of therapy and blood flow variables. Continuous renal replacement therapy is performed using hemofilters (capillaries with a large removal capacity for larger molecules) and low blood flow (Blake and Daugirdas 2008).

Regarding the different dialysis methods, there have been few studies on antibiotic removal in association with DP and ED, and the studies performed on IHD and CRRT were not all done on critically ill patients. So, there are many questions about drug flux in critical patients subjected to the different dialysis modalities.

In clinical practice, the most commonly used guideline is the “Sanford Guide to Antimicrobial Therapy” (Gilbert et al. 2014), which includes CRRT and IHD, and recommends that the dosage of an antimicrobial with ED to be estimated as with CRRT. However, Mushatt et al. (2009) recommend that, for antibiotics administered every 24 h, a supplementary dose should be considered immediately after ED or alternatively, the prescribed daily dose should be given after ED. For drugs administered every 12 h, a dose should be done after ED session and the other after 12 h. Another suggestion is that drugs such as vancomycin and gentamicin, for which serum levels can be measured, should be assessed immediately after ED to determine the need for a further dose after dialysis (Mushatt et al. 2009).

Table 1 shows the pharmacodynamic characteristics (PD) and pharmacokinetic (PK) of the main antibiotics used in clinical practice in intensive care, although the

recommended doses have been extrapolated from studies not conducted with the critical AKI population and acute renal support.

Conclusion

The topics discussed in this review show that the critical patients present several changes in the pharmacokinetics and pharmacodynamics of antibiotics, especially regarding absorption, distribution and metabolism, resulting in variations in serum levels. Thus, there is an increased risk of overdosing and drug toxicity, or a subtherapeutic dose and an increased risk of bacterial resistance, infection by opportunistic germs and mortality.

The removal of antimicrobials by different dialysis therapies in critically ill patients is a complex issue. This depends on the dialyzing membrane characteristics, such as the surface area (efficiency) and size of the pores (flow), as well as drug characteristics, such as water solubility, molecular weight and the extent of protein binding. Moreover, the rate of blood flow, the duration of therapy, and the kind of dialysis (diffusion and/or convection) affect drug removal.

There are no validated guidelines to assist in antibiotic dose adjustment in septic patients on acute renal supportive therapy, and the extrapolated recommendations were obtained from studies on noncritical patients with end-stage chronic kidney disease receiving substitutive renal therapy. Thus, because of the importance of maintaining therapeutic levels of antimicrobial drugs, more studies on this very complex subject are needed in order to reduce microbial resistance and mortality.

Disclosures

None declared.

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The use of antimicrobials in septic patients with acute kidney injury

O uso de antimicrobianos em pacientes sépticos com lesão renal aguda

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ABSTRACT

Sepsis is the most common cause of death in critically ill patients and it may be associated with multiorgan failure, including acute kidney injury (AKI). This situation can require acute renal support and increase mortality. Therefore, it is essential to administer antimicrobials in doses to achieve adequate serum levels, preventing overdosing and drug toxicity or underdosing and risk for resistance to antibiotics and higher mortality. To date, there aren't validated guidelines on antibiotic dosing adjustment in septic patients with AKI and the recommendations are extrapolated from studies conducted in non-critical patients with chronic kidney disease in end stage receiving chronic renal replacement therapy. This study aimed to review and discuss the complexity of that issue, considering the several factors related to the drugs removal: critically ill patient characteristics, antimicrobial properties and dialysis method.

Keywords: acute kidney injury; intensive care units; anti-bacterial agents.

RESUMO

A sepse é a principal causa de óbito em pacientes críticos e pode cursar com falência de vários órgãos, entre eles os rins, requerendo, com frequência, suporte renal agudo e elevando a mortalidade. Assim, torna-se imprescindível a administração de antimicrobianos em dose que garanta nível sérico adequado para evitar superdosagem e toxicidade medicamentosa ou ainda subdosagem e risco de resistência microbiana, ambas as situações contribuindo para maior mortalidade. Até o momento, não há diretrizes validadas para auxiliar no ajuste de dose de antibióticos nos pacientes sépticos com lesão renal aguda em suporte renal, sendo as recomendações extrapoladas de estudos realizados em pacientes não críticos e com doença renal em estágio final recebendo terapia renal substitutiva crônica. Esse estudo teve como objetivo revisar e discutir a complexidade desse assunto, levando em consideração os vários fatores relacionados à remoção de drogas: características do paciente crítico, propriedades dos antimicrobianos e método dialítico utilizado.

Palavras-chave: lesão renal aguda; unidades de terapia intensiva; antibacterianos.

INTRODUCTION

Among patients in intensive care units, the main cause of death is sepsis, with mortality rates ranging between 30 and 60%.^{1,2} Sepsis can occur with failure of several organs, including the kidneys, with a 70% mortality in those cases.³

Sepsis is the main etiology of acute kidney injury (AKI) in critically ill patients, and half of these patients require acute renal support.^{2,4,5} Thus, measures that reduce mortality and costs are paramount. Among the actions with the greatest impact, we stress the early administration of antimicrobials.⁶

In septic patients, there are distribution volume and clearance variations, which may affect antimicrobial concentration. In those under acute kidney support (AKS), there is also clearance by dialyzing membranes, resulting in a risk of subtherapeutic dose and, consequently, antibiotic resistance.^{6,7} Therefore, the use of adequate doses of antimicrobials is key to avoiding the emergence of bacterial resistance, infection by opportunistic germs, as well as mortality reduction.⁶

To date, there are no validated guidelines to assist in the dose adjustment of

antibiotics in septic patients in AKS, and the recommendations are extrapolated from studies performed in non-critical patients with end-stage renal disease receiving chronic renal replacement therapy.^{4,8} Thus, the purpose of this review is to discuss the complexity of this issue, taking into account the various factors related to drug clearance: critical patient characteristics, antimicrobial properties and dialytic method used.

PHARMACOKINETICS AND PHARMACODYNAMICS OF ANTIMICROBIALS IN CRITICAL PATIENTS

The parameter used to measure the microbiological activity of antimicrobials is the minimum inhibitory concentration (MIC), an *in vitro* measure of the antimicrobial effectiveness on the pathogen.

Pharmacokinetics and pharmacodynamics are tools that determine how much and how often the drug should be administered.⁹ Pharmacokinetics describe drug absorption, distribution, metabolism and clearance, while pharmacodynamics describe the impact of serum concentration and response to the drug.^{6,9}

Thus, the pharmacodynamics of an agent can be time dependent ($T > MIC$), related to the time of exposure to a specific MIC, such as beta-lactams, concentration dependent (C_{max}/MIC), for aminoglycosides; concentration/time dependent (AUC/MIC), for the glycopeptides, as shown in Figure 1.

Several mechanisms influence antimicrobial pharmacokinetics in critical patients^{10,11} (Figure 2). Absorption of a drug via the oral route may be impaired⁷ by gastric dysmotility, adherence to the loops, interaction with nutritional components, gastric pH altered by the concomitant use of proton pump inhibitors,¹² as well as in the subcutaneous route of administration, absorption may be decreased due to reduced skin circulation secondary to the redistribution of blood flow and aggravated by edema.⁷ Considering these effects on absorption, preference is given to the intravenous administration of antimicrobials in critically ill patients.

The distribution of antimicrobial agents also undergoes profound changes in critically-ill patients: the production of endotoxins by a microorganism during a septic shock can lead to the release of several inflammatory mediators that affect the vascular endothelium and culminate in poor blood flow distribution, increased capillary permeability, acid changes and endothelial injury.

Figure 1. Pharmacodynamics of an antimicrobial agent in relation to its concentration versus time. $T > MIC$: time (T) that the drug concentration remains above the minimum inhibitory concentration (MIC); C_{max}/MIC : maximum concentration rate (C max) by MIC; AUC/MIC : rate of the area under the curve (AUC) of the concentration versus the time above the MIC. Adapted from Roberts and Lipman.⁶

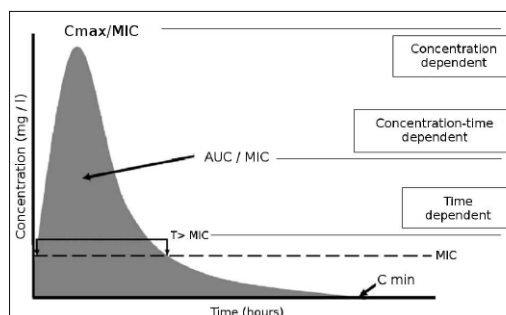
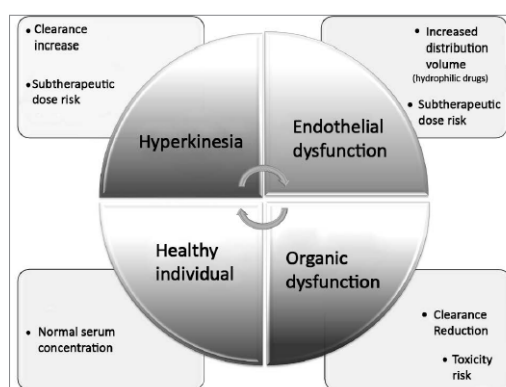


Figure 2. Influence of the patient's clinical status on antimicrobial pharmacokinetics. Adapted from Roberts and Lipman.⁶



Thus, there is extravasation of fluid from the intravascular space to the interstitium, increasing the volume of hydrophilic drug delivery and decreasing its serum concentration, which occurs with beta-lactams, aminoglycosides, glycopeptides, linezolid and colistin. This distribution volume can also be increased in the presence of mechanical ventilation, hypoalbuminemia and extracorporeal circuits.^{6,7,13}

Drug clearance also occurs in septic patients: in the absence of organic dysfunction, there is an increase in renal perfusion and creatinine clearance, leading to an increase in the clearance of hydrophilic drugs,⁶ as well as optimization of other routes of metabolism and clearance (biliary and transintestinal),⁷ causing a reduction in the serum concentration of some antimicrobials.⁶

With the deterioration of the patient's state of health, there is myocardial depression and decreased perfusion, leading to a decrease in antimicrobial

clearance (either due to renal or hepatic dysfunction), an increase in the half-life and the potential toxicity of the high serum concentration of the drug and/or a buildup of its metabolites.⁶

The liver metabolism of antimicrobials may be affected in AKI, although this is not fully elucidated, probably due to changes in hepatic blood flow and reduction in the cytochrome P450 and CYP 3A⁷ enzyme activity.

Regarding renal function adjustments, the regimen is based on distribution volume and systemic clearance¹³. Indirect methods to estimate the glomerular filtration rate are not so precise, despite the ease of monitoring.^{10,13} Among the currently available calculations to estimate creatinine clearance are the Cockcroft-Gault or the Modified Diet in Renal Diseases (MDRD), and the Chronic Kidney Disease EPI (CKD EPI) equations, all of which are validated in patients with stable renal function, which does not occur in the context of AKI.¹⁰

An alternative method is to measure clearance directly in 24-hour urine collection or in 2, 4 or 8-hour samples using the formula: Urinary creatinine concentration x urinary volume x serum time/creatinine, the result being expressed in mL/min, this method is not practical and it is limited in anuric patients.

Therapeutic drug monitoring can measure serum antimicrobial concentration, and its clearance can be calculated to improve the accuracy of subsequent dosing adjustments.¹³ Bioanalytical methods include immunoassays, such as fluorescence polarization (FPIA), multiplied by enzyme (EMIT) and enzyme-linked immunosorbent assay (ELISA), all of which are methods that use the reaction of an antibody to its antigen. However, metabolites of drugs with similar structure may also be recognized by the antibody, resulting in falsely elevated concentration.

High-performance liquid chromatography (HPLC) and liquid chromatography-mass spectrometry (LC/MS) are more specific methods that can separate and quantify drugs based on their molecular polarities and interactions with the stationary phase of a column, but these bear high cost and require highly skilled professionals, which makes it difficult to use them in medical practice.¹⁶

THE INFLUENCE OF ACUTE KIDNEY SUPPORT (AKS)

An important factor for drug clearance is the dialysis technique, based mainly on two types of transport: diffusion or convection, both efficient in the removal

of low molecular weight solutes; but the most effective convective therapy in the clearance of high molecular weight substances.

The selection of the dialyzing membrane also alters clearance, since the high flow ones, with greater permeability to medium-size molecules, have a higher capacity to remove high molecular weight drugs than low-flow membranes.^{7,17}

This difference was demonstrated in a small prospective cohort (n = 9) performed in the Czech Republic, comparing vancomycin clearance in critically ill patients with AKI patients dialyzed with high versus low-flow membranes. The median percentage of vancomycin clearance in low flow membrane dialyses was 17%, while that for high flow membranes was 31%. The study concluded that, despite these differences between membranes, monitoring serum vancomycin levels and dose administration after each dialysis is required, since these patients had sub-therapeutic levels of antibiotics.¹⁸

Another characteristic of the dialyzer membrane under discussion is its adsorption rate. Hydrophobic synthetic membranes have high adsorption, while cellulose acetate membranes have lower adsorption.¹⁹ The clinical importance of this property in relation to serum antimicrobial level interference is still lacking, but some evidence suggests an early saturation of this process.²⁰

The options for AKS in critically ill patients are peritoneal dialysis (PD) and hemodialysis (HD), which can be classified as intermittent (IHD), prolonged (PHD) and continuous (CHD)²¹⁻²³ hemodialysis (Table 1).

PD is an option for a selected group of patients, and recent studies suggest that, when indicated, it should be performed continuously, with large volumes of dialysate and through a flexible catheter and cyclor, with survival results are similar to those from patients treated with IHD.²⁴ In PD the dialyzer membrane is the peritoneum and little is known about the clearance of drugs in high volume therapies.

IHD is characterized by high blood and dialysate fluxes, a 4 to 5 hours duration and an affordable cost.²⁵ IHD is indicated in patients with AKI who are hemodynamically stable, and it can be done on alternate days or daily, according to the patient's clinical and laboratorial conditions.²⁶

CHD is defined as a long and continuous 24-hour treatment that uses dialysate and blood flows lower than the conventional ones.^{27,28} It is an efficient

TABLE 1 TYPES OF DIALYSIS AND ITS MAIN CHARACTERISTICS

	CHD	PHD	IHD	PD
Clearance of uremic toxins	Convection/Diffusion	Diffusion	Diffusion	Diffusion
Membranes	High flow	High flow/Low flow	High flow/Low flow	Peritoneum
Dialysate flow	Low (1000-1500 ml/h)	Low (200-300 ml/min)	High (500 ml/min)	High dialysate volume
Blood flow	Low (100-150 ml/min)	Low (100-200 ml/min)	High (300-400 ml/min)	50-100 ml/min (Blood flow in the peritoneum)
Ultrafiltration and solute clearance	Continuous (24 hours)	Intermittent (6-18 hours)	Intermittent (3-5 hours)	Continuous (24 hours)
Anticoagulation	Continuous	Intermittent	Intermittent	Unnecessary
Hemodynamic stability	Excellent	Good	Bad	Excellent
Use of standard dialysis machine	No	Yes	Yes	Yes
Costs	High	Low	Low	Low

CHD: continuous hemodialysis; PHD: prolonged hemodialysis; IHD: intermittent hemodialysis; PD: peritoneum dialysis.

method because it provides adequate metabolic and volume control without impairing the patient's hemodynamic stability.

An intermediate method that provides hemodynamic stability and adequate metabolic control of the patient with a shorter duration than CHD is prolonged hemodialysis (PHD), lasting between 6 and 18 hours, with lower blood flows and less dialysate than what is conventionally used.^{28,29}

IHD and PHD can be performed with capillaries of low or high flow and efficiency, that is, with greater or lesser capacity for medium-size molecules removal, according to their ultrafiltration coefficients and performance (Kuf and KoA, respectively), and with variable blood flow and treatment duration. CHD is performed by means of hemofilters, that is, capillaries with great capacity to remove larger molecules using low blood flows.³⁰

Regarding the different AKS modalities, there are few antibiotic clearance studies in PD and HD, and the studies in IHD and CHD do not always involve critical patients. Thus, there are many questions regarding drug regimen corrections for critically ill patients in different dialytic modalities.

In clinical practice, one of the most commonly used guidelines is The Sanford Guide to Antimicrobial Therapy,³¹ which considers the IHD and CHD modalities, and there are recommendations that the dose of antimicrobials for PHD be estimated according to

that of CHD. However, Mushatt et al.³² recommend that for antibiotics given every 24 hours, a supplementary dose should be considered immediately after PHD or, alternatively, a daily dose be prescribed after PHD. For those given every 12 hours, keep one dose after the PHD and another after 12h. Another suggestion is that drugs such as vancomycin and gentamicin, which can have their serum levels measured, are measured immediately after PHD to determine the need for supplemental dose after dialysis.³²

Table 2 shows the pharmacodynamic (PD) and pharmacokinetic (PK) particulars of the major antimicrobials used in intensive care. Although the recommended doses have been extrapolated from studies not performed with the critically ill population with AKI and under AKS, they are used in clinical practice.

CONCLUSION

The topics discussed in this review show that critical patients have several changes in the pharmacokinetics and pharmacodynamics of antimicrobials, culminating in variations in their serum concentrations. Thus, there is an increased risk of overdose and drug toxicity, as well as subtherapeutic dosage and risk of bacterial resistance, infection by opportunistic germs and higher mortality.

Moreover, antimicrobial clearance by the different modalities of AKS in critical patients is a complex issue, since, besides being dependent on the

TABLE 2 ANTIMICROBIAL AGENTS USED IN INTENSIVE CARE AND THEIR MAIN CHARACTERISTICS (BASED ON THE SANFORD GUIDE TO ANTIMICROBIAL THERAPY)³¹

	Vancomycin	Meropenem	Cefepime	Piperacillin/ Tazobactam	Fluconazole	Micafungin
PD	AUC/MIC	T > MIC	T > MIC	T > MIC	AUC/MIC	AUC/MIC
Molecular weight	1485	384.46	571.5	539.5 322.3	306.99	1292.26
Distribution volume* (L/Kg)	0.7	0.23-0.35	0.3	0.24-0.4	0.7 - 0.8	0.39
% linked to proteins*	10-55	2	20	16-48	10	> 99
Clearance	Renal	Renal	Renal	Renal	Renal	Hepatic/Renal
Dose in normal kidney function	15-20 mg/kg every 8-12h	1 g every 8h	1-2 g every 8-12h	3,375 g every 6h	100-400 mg every 24h	100-150 mg every 24h
Dose in CHD	500 mg every 24-48h	500mg every 24h	2 g every 24h	2,25g every 6h	200-400 mg every 24h	Without correction
Dose in PHD**	Without information	Without information	Without information	Without information	Without information	Without correction
Dose in IHD***	15 mg/kg after HD	500 mg every 24h	1g every 24h (+ extra 1 g after HD)	2,25 g every 12h (+ extra 0,75g after HD)	100-400 mg every 24h - after HD	Without correction
Dose in PD****	7,5 mg/kg every 2-3 days	500 mg every 24h	1-2 g every 48h	2,25 g every 6h	50-200 mg every 24h	Without correction

PD = pharmacodynamics; AUC = area under the curve; MIC = minimum inhibitory concentration; T = time; CHD = continuous hemodialysis; PHD = prolonged hemodialysis, IHD = intermittent hemodialysis; PD = peritoneal dialysis

*In healthy individuals **The same doses used in CHD are suggested for being used ***Considering the next IHD in 1 day ****Dose in COPD (continuous outpatient peritoneal dialysis).

dialyzing membrane characteristics (surface area and pore size) and drug specificities (water solubility, molecular weight, extension of binding to proteins), it also depends on the blood flow used, treatment duration and the type of transport used, diffusion and/or convection.

There are no validated guidelines to aid in dose adjustment of antibiotics in septic patients in AKS, with recommendations being, so far, extrapolated from studies in non-critical patients and with end-stage renal disease receiving chronic renal replacement therapy. Thus, due to the importance of maintaining the therapeutic level of antimicrobials, more studies on this complex topic are necessary to reduce microbial resistance and mortality.

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Vancomycin Removal During High-Volume Peritoneal Dialysis in Acute Kidney Injury Patients: A Prospective Cohort Clinical Study



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Introduction: Vancomycin pharmacokinetic data in patients with acute kidney injury (AKI) on high-volume peritoneal dialysis (HVPD) are lacking. The aims were to study the pharmacokinetics of i.v. vancomycin in patients with AKI treated by HVPD who received an i.v. dose of vancomycin (15–20 mg/kg), to determine the vancomycin removal, and to establish vancomycin dosing and evaluation pharmacokinetics target attainment achievement for the empirical treatment of patients with AKI treated by HVPD.

Methods: Vancomycin was administered 1 hour before dialysis start. Samples of all dialysate were collected for a 24-hour period. Blood samples were collected after 1, 2, 4, and 24 hours of therapy. Vancomycin concentrations were determined using a liquid chromatographic (high-performance liquid chromatography)–fluorescence method. Pharmacokinetic calculations were completed assuming a 1-compartment model.

Results: Ten patients completed the study. The mean vancomycin dose administered was 18.0 ± 2.95 mg/kg ($14.7\text{--}21.8$ mg/kg) on the day of study (first day) and the mean percentage of vancomycin removal by HVPD was $21.7\% \pm 2.2\%$ (16%–29%). Peritoneal clearance was 8.1 ± 2.2 ml/min (5.3–12 ml/min). The serum vancomycin half-life was 71.2 ± 24.7 hours (42–110 hours) during HVPD session, the maximum serum concentration was 26.2 ± 3.5 mg/l, which occurred 1 hour after vancomycin administration and HVPD start. Area under the curve (AUC)_{0–24}/minimum inhibitory concentration (MIC) ratio ≥ 400 was achieved in all patients when MIC = 1 mg/l was considered.

Conclusion: HVPD removes considerable amounts of vancomycin in septic patients with AKI. Administration of 18 mg/kg vancomycin each 48 to 72 hours in patients with AKI undergoing HVPD was required to reach and maintain therapeutic concentrations.

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KEYWORDS: acute kidney injury; peritoneal dialysis; sepsis; vancomycin

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Sepsis is the main etiology of AKI in critically ill patients and can reach the surprising mortality rate of 70%.^{1–4} Current renal replacement therapy modalities include peritoneal dialysis (PD), intermittent hemodialysis (conventional hemodialysis or prolonged hemodialysis), and continuous renal replacement therapy. Continuous methods are preferred in hemodynamically unstable patients; however, previously published studies have shown no difference in patient survival among

continuous renal replacement therapy, intermittent hemodialysis, or PD.⁵

Recently, the interest in PD to manage patients with AKI has been increased, mainly in developing countries, due to its lower cost and minimal infrastructural requirements. Brazilian studies have shown that, with careful thought and planning, patients with AKI can be successfully treated using PD.^{6,7}

Our previous studies have demonstrated that HVPD can offer adequate small solute clearances and ultrafiltration using a flexible catheter, 2-l exchanges (total dialysate volume ranged from 32 to 44 l per day) and 35- to 60-minute dwell times. HVPD was rapidly effective in the correction of blood urea nitrogen, creatinine, bicarbonate, and fluid overload. The achieved weekly Kt/V

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(K, dialyzer clearance of urea; t, dialysis time; V, volume of distribution of urea) was 3.8 ± 0.6 and the mortality was 57%.⁶⁻⁸

Considering the high mortality rate of septic AKI and its related costs of hospitalization and treatment, the early administration of antimicrobials should be adopted.

Vancomycin is an antibiotic used in the parenteral treatment of infections caused by multidrug-resistant gram-positive bacteria, especially methicillin-resistant *Staphylococcus aureus*. Its antibacterial action is time-dependent and concentration-independent.^{9,10} Based on the pharmacodynamics of vancomycin, an AUC (ratio) is recommended by the MIC (AUC/MIC) of 400 or greater. Due to the logistic challenges of such determination in clinical practice, it was demonstrated that such value could be obtained with trough serum levels of vancomycin between 10 and 20 mg/l.^{9,11} A serum level of less than 10 mg/l does not guarantee an AUC/MIC ratio greater than 400 and may develop bacterial resistance. However, the dosage above 20 mg/l can be nephrotoxic.^{9,10}

Vancomycin has almost exclusive renal elimination, making dosage adjustment during kidney failure obligatory. The half-life of vancomycin is 5 to 8 hours in patients with normal kidney function and higher than 180 hours in patients with advanced chronic kidney disease.¹²⁻¹⁶ Volume of distribution of vancomycin is 0.4 to 1.0 l/kg, molecular weight is approximately 1450 Da, and protein binding from 10% to 50%.¹⁶

Vancomycin is not removed to a significant extent during PD and should be administered each 72 to 120 hours. However, there is no study that evaluated the vancomycin removal during HVPD sessions in patients with AKI and no strategies have been proposed to appropriately dose vancomycin in HVPD.¹⁴⁻¹⁶

Our aim was to study the pharmacokinetics of i.v. vancomycin in patients with AKI treated by HVPD who received a single i.v. dose of vancomycin (15 mg/kg), to determine the vancomycin removal, to compare vancomycin levels obtained in blood with MICs of typical gram-positive bacterial pathogens, to evaluate pharmacokinetic target attainment achievement, and to establish vancomycin dosing guidelines for the empirical treatment of patients with AKI receiving HVPD.

METHODOLOGY

This was a prospective cohort clinical study performed at the University Hospital Sao Paulo State in Botucatu Medical School, Brazil. All procedures performed in studies involving human participants were in

accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by local ethics committees. Written informed consent was obtained from patients or families. It was not registered because it is not a clinical trial study. It is a prospective cohort clinical study.

Ten critically ill adult patients with sepsis and AKI treated by HVPD on vancomycin therapy were included. Classification of AKI was made according to Kidney Disease: Improving Global Outcomes criteria.¹⁷ All patients were oliguric (urine output lower than 0.5 ml/kg per hour). They were followed for 2 days after introduction to the study.

PD was performed using a flexible catheter, an automated cycler (HomeChoice; Baxter, Deerfield, IL), and a high volume of dialysis fluid, as described in our previous studies.⁶⁻⁸ Each session of HVPD lasted 24 hours, and sessions were repeated daily, 7 times per week. The total dialysate volume per session ranged from 32 to 38 l and the prescribed Kt/V was 0.50 per session.

Vancomycin was administered 1 hour before dialysis start. The protocol required that vancomycin 15 to 20 mg/kg was reconstituted with 100 ml 0.9% sodium chloride and was administered for 1 hour. Blood samples were collected after 1, 2, and 4 hours of dialysis start and end of dialysis (after 24 hours). Dialysate samples were collected at the end of each dwell using a sample port directly on the automatic cycler machine for a 24-hour period. Vancomycin concentrations were determined using a liquid chromatographic (high-performance liquid chromatography)-fluorescence method. Blood samples were placed in an ice bath and centrifuged within 3 hours of collection. Serum was transferred to a labeled polypropylene tube and stored frozen at -80°C until assayed. Volumes of dialysate and of ultrafiltration were recorded for each patient.

Throughout, the analysis was carried out using a high-performance liquid chromatography system (Agilent Series 1100; Agilent Technologies, Palo Alto, CA), according to the protocol described by Hu et al.¹⁸ The following pharmacokinetic parameters were calculated for each patient assuming a 1-compartment model: volume of distribution (Vd), dialysis total drug clearance (Cl), and elimination half-life. The AUC was determined using the trapezoidal rule to the last nonzero time point. The AUC from the last nonzero time point was determined by the pharmacokinetic method, concentration/k, where k is the elimination rate constant determined from log-linear regression of the terminal phase of the concentration-time profile. A monoexponential model was used for all pharmacokinetic calculations. The following equations

were used: the serum elimination rate constant (k_{el}) for dwells was obtained by regression of the serum concentrations over the time between the start of the dwell and the end of the dwell. The formula used to determine the approximate serum concentration was $C = C_0 \cdot e^{-k_{el} \cdot t}$, where C = concentration, C_0 = original concentration, $-k_{el}$ = elimination rate constant, and t = time between sampling points. The serum elimination half-life for patients on theycler was calculated as $(0.693)/(\text{mean } k_{el} \text{ dwells})$. The serum elimination half-life for patients off theycler was calculated as $(0.693)/(\text{mean } k_{el} \text{ dwells})$. The serum AUC for the first 24 hours was calculated by summation of the AUC of each dwell, using the trapezoid rule, and from 24 hours to infinity by extrapolation of the serum concentration at 24 hours/ k_{el} last dwell.

Data are expressed as median and range. The vancomycin removal from blood during the HVPD session was calculated from the following formula and expressed as % vancomycin removed:

% Vancomycin removal =
$$\frac{([C_{preHVPD} - C_{24hHVPD}]/C_{preHVPD}) \times 100,$$

where $C_{preHVPD}$ = the concentration of vancomycin before HVPD, and $C_{24hHVPD}$ = the concentration of vancomycin at end of HVPD.

Sample Size Calculation

This study was performed to estimate the mean amount of vancomycin removed by HVPD and to establish an 80% confidence interval about that value such that the width was less than $\pm 20\%$, using $\alpha = 0.05$, $\beta = 0.2$, and standard sample size equations for parametric data; it was estimated that 10 patients were required.¹⁹

RESULTS

Table 1 shows the patients and clinical characteristics. All patients had sepsis or septic shock. The main bacterial agents were gram-positive *Staphylococcus haemolyticus*, methicillin-resistant *S aureus*, and *Enterococcus faecalis*. All patients were in stage 3 according to Kidney Disease:

Improving Global Outcomes criteria of AKI.¹⁷ Mean glomerular filtration rate according to MDRD was 0.3 ml/min (0 to 0.74 ml/min). The mean dwell times for cycles ranged from 35 to 50 minutes and 7 patients were anuric.

Vancomycin removal by HVPD was $21.7\% \pm 2.2\%$ (16%–29%). Vancomycin serum concentrations higher than 15 mg/l at the day of study dialysis were obtained in all patients at the end of dialysis. The median vancomycin dose was 18 ± 2.95 mg/kg (14.7–21.8 mg/kg) on the day of study (first day). In all patients, it was the first vancomycin dose administered.

AUC_{0–24}/MIC ratio ≥ 400 was achieved in all patients on the study days (Table 2), when MIC = 1 mg/l was considered. Table 2 shows the vancomycin pharmacokinetic parameters.

The mean serum and dialysate concentrations remained in excess of MICs for sensitive organisms (approximately 1 mg/l) in all patients during the treatment. The mean vancomycin peak serum concentration was 26.2 ± 3.5 mg/l, which occurred 1 hour after vancomycin administration and HVPD start. The mean dwell dialysate concentration was 7.3 ± 1.77 mg/l. Figure 1 shows serum vancomycin concentrations during HVPD therapy.

Peritoneal clearance was 8.1 ± 2.2 ml/min (5.3–12 ml/min) and vancomycin half-life during dialysis was 71.2 ± 24.7 hours (42–110 hours).

DISCUSSION

The purpose of this study was to characterize the pharmacokinetics of vancomycin and provide dosing recommendations based on a single i.v. 15-mg/kg dose of vancomycin in patients with AKI treated by HVPD (prescribed Kt/V of 0.5 per session) using 18 to 24 cycler exchanges over 24 hours.

Although the pharmacokinetics of vancomycin have been studied in chronic patients on continuous ambulatory PD, the data are limited for automated PD and there were no data in HVPD. Vancomycin clearance is minimal during continuous ambulatory PD and

Table 1. Patients' demographic and clinical characteristics

Patient	Sex	Age, yr	Weight, kg	SOFA	Diagnosis	Pathogen/MIC	Urine output, ml/kg per h
1	F	58	65	11	Pneumonia	MRSA	0
2	F	62	55	12	Endocarditis	Enterococcus	0.32
3	F	59	58	14	Meningitis	MRSA	0.38
4	M	76	71	13	Pneumonia	Staphylococcus haemolyticus	0.40
5	M	72	62	12	Peritonitis	Enterococcus	0
6	M	59	58	14	Meningitis	MRSA	0
7	F	44	75	13	Pneumonia	MRSA	0
8	M	67	68	12	Blood Stream	Enterococcus	0.44
9	M	63	72	13	Blood Stream	MRSA	0
10	M	72	62	14	Peritonitis	Enterococcus	0.42

F, female; M, male; MRSA, methicillin-resistant *Staphylococcus aureus*; SOFA, Sequential Organ Failure Assessment.

Table 2. PK/PD vancomycin parameters of individual patients

Patient	Doses, mg/kg	C Van T1h, mg/l	C Van T2h, mg/l	C Van T4h, mg/l	C Van T24h, mg/l	C Van dialysate, mg/l	Half-life, h	AUC/MIC	Removal, %	Peritoneal Cl, ml/min		Distribution volume, l/kg
										Van	Ur	
1	15.3	22.5	19.4	17.3	16.8	9.5	42.2	424.4	25	12	12.5	0.68
2	21.8	28.6	27.7	25.1	23.8	5.6	64	568	16	8.8	10.8	0.85
3	17.2	24.5	21.3	19.3	17.9	8.2	52.4	424.5	25	9.2	11.5	0.7
4	21.3	28.2	27.6	25	23.1	6.1	105	557.4	18	5.7	8.2	0.74
5	16.1	22.2	19.7	19	17.8	8.1	52.6	422.5	23	8.3	9.7	0.72
6	17	24.5	21.2	17.3	16.9	9.3	65	490	24	6.8	9.1	0.73
7	13.5	32.7	28.6	27.1	25.9	8.1	77.5	605	2	9.7	13.4	0.61
8	19	26.6	22.4	19.6	18.8	9	53.4	448	29	5.3	9.8	0.65
9	14	24.6	22.3	21	20.5	5.2	110	477.5	16	8.1	11.4	0.7
10	22.3	22.1	19.6	19.2	17.7	8.2	77.6	401	22	8.6	10.5	0.62

AUC/MIC, area under the curve/minimum inhibitory concentration; C Van, serum concentration of vancomycin; Cl, clearance; Ur, urea.

should be administered approximately every 5 to 7 days,¹⁴ whereas during an automatic PD treatment, the vancomycin clearance is significant, and should be administered every 3 to 5 days. In a small study of 4 pediatric patients with peritonitis while on automated PD, vancomycin serum concentrations decreased 17% after the automated dialysis session.^{20,21} It was recommended that vancomycin should be readministered to maintain therapeutic serum concentrations. Dialysate concentrations were not provided.

In this study, vancomycin removal mean was 21% during HVPD. Previous study reported that it was 10% in continuous ambulatory PD, 17% in automated PD, and ranged from 17% to 31% in intermittent hemodialysis therapy, according to flux membrane dialysis used.^{14,22} Variability in vancomycin removal in HVPD was modest (16% to 29%), and it is different from that found in studies that described hemodialysis removal using low- and high-flux dialysis. Peritoneal clearance was 8.1 ± 2.2 ml/min (5.3–12 ml/min), whereas

high-flux membranes have estimated vancomycin clearance between 43.3 and 120.0 mL/min. Clearance of vancomycin during PD may be affected by inflammation that affects peritoneal permeability and dialysate flow. These conditions may lead to variability in vancomycin clearance during PD dosage regimens in a critical care setting.

Due to high pharmacokinetic variability in septic patients with AKI, we suggest daily monitoring of vancomycin concentrations to reach optimal trough vancomycin concentrations and its dose may be readministered every 48 to 72 hours to maintain therapeutic serum concentrations in patients with AKI undergoing HVPD. In hybrid and conventional hemodialysis therapies, vancomycin dose should be administered over the last hour of dialysis and vancomycin intradialytic clearance was approximately 2-fold higher with high-flux membrane compared with low-flux membrane.²²

The vancomycin peak serum concentration occurred 1 hour after vancomycin administration and HVPD start, and vancomycin serum concentrations higher than 15 mg/l were obtained in all patients at the end of 1 session of HVPD. Vancomycin half-life during HVPD session was 71.2 ± 24.7 hours (42–110 hours). Serum and dialysate concentrations suggest that i.v. vancomycin 18 mg/kg each 72 hours would provide adequate concentrations over a 24-hour period.

An AUC/MIC ratio ≥ 400 is necessary to achieve clinical effectiveness with vancomycin therapy.⁷ However, because it can be difficult in the clinical setting to obtain multiple serum vancomycin concentrations to determine AUC and subsequently calculate AUC/MIC, trough serum concentration monitoring, which can be used as a surrogate marker for AUC, is recommended as the most accurate and practical method for vancomycin monitoring. Trough vancomycin serum concentrations maintained above 10 mg/l are recommended.^{9,11–13} All our patients having vancomycin after 1 hour of dialysis

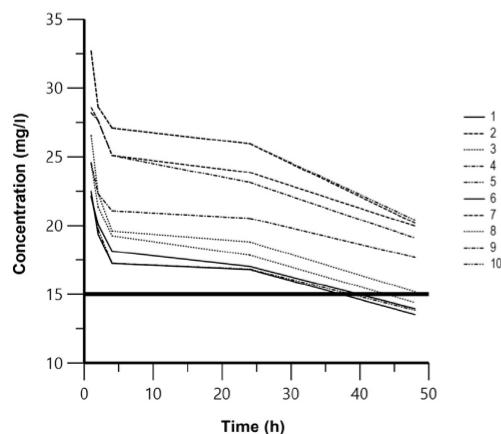


Figure 1. Serum vancomycin concentrations during high-volume peritoneal dialysis therapy.

start serum concentrations above 10 mg/l, and AUC/MIC of at least 400 was achieved in all patients on the study days. This desired AUC/MIC ratio was achieved almost only in patients with vancomycin MIC < 1.0 mg/l. In patients with MIC $\geq$ 1.0 mg/l, higher dosing will be required. A target AUC/MIC of $\geq$ 400 is not achievable with conventional dosing methods if the pathogen vancomycin MIC is $\geq$ 2 mg/l. Achievement of this ratio would lead to undesirable vancomycin toxicity.^{9,11–13,16}

Vancomycin-induced nephrotoxicity has been related to drug plasma concentrations.⁹ Its incidence varies greatly among various studies, with rates as low as zero in the absence of other concomitant nephrotoxins, up to 40%^{23–26} in combination with other potentially nephrotoxic drugs. Among the patient-related factors,^{27–30} the most important are advanced age, reduced kidney function, dehydration, reduced renal mass, sex (women have lower muscle mass and body water quantity), obesity, hypoalbuminemia, and sepsis, whereas drug-related risk factors include administration concomitant with other nephrotoxic drugs, such as aminoglycosides, loop diuretics, amphotericin B, piperacillin-tazobactam, acyclovir, vasopressors, and i.v. contrast media; as well as long treatment duration and high serum dosage of this antimicrobial.^{24–29} Data suggesting a causal relationship between doses and therapeutic targets of vancomycin and nephrotoxicity are conflicting and marked by confounding factors.³⁰ Although there is minimal evidence supporting efficacy in maintaining therapeutic levels between 15 and 20 mg/l, several studies have evaluated the safety of this recommendation, comparing nephrotoxicity rates above and below 15 mg/l levels.³¹ A systematic review and a meta-analysis conducted by van Hal et al.³¹ included 15 studies in which trough serum levels of vancomycin $\geq$ 15 mg/l were associated with a higher risk of nephrotoxicity when compared with levels < 15 mg/l (odds ratio 2.67, $P < 0.01$).

The pharmacokinetic parameters should not change. However, in critically ill patients, drug pharmacokinetic parameters may be expected to change, especially regarding absorption, distribution, and metabolism, resulting in variations in serum levels. Thus, there is an increased risk of overdosing and drug toxicity, or a subtherapeutic dose and an increased risk of bacterial resistance, infection by opportunistic germs, and mortality.^{16,19,21}

The removal of antimicrobials by different dialysis therapies in critically ill patients is a complex issue. This depends on the modality and intensity of dialysis, as well as drug characteristics, such as water solubility, molecular weight, and the extent of protein binding. There are no validated guidelines to assist in antibiotic dose adjustment in septic patients on acute renal supportive therapy, and the extrapolated recommendations were

obtained from studies on noncritical patients with end-stage chronic kidney disease receiving substitutive renal therapy. Thus, because of the importance of maintaining therapeutic levels of antimicrobial drugs, more studies on this very complex subject are needed to reduce microbial resistance and mortality.^{22,32,33}

Our study has some limitations, as the small number of patients studied and the dialysis elimination have been considered the only route of vancomycin elimination. We did not consider the role of renal and biliary elimination of vancomycin as possible confounders in the vancomycin plasma reduction. We also evaluated the pharmacokinetics of i.v. vancomycin in patients with AKI treated by HVPD (prescribed Kt/V of 0.5 per session). However, recent studies have presented similar outcomes of patients with AKI treated with lower PD doses.^{34,35} Paripiboon et al.³⁵ presented a study using PD to treat 80 critically ill patients with AKI. This was a randomized controlled trial comparing the 2 regimens recommended in the International Society for Peritoneal Dialysis guidelines, aimed at achieving target weekly Kt/V of 3.5 and 2.1, respectively.³³ Patients were randomized 1:1 to receive 1.5 l of PD fluid using manual PD and a single-bag open system delivered either hourly (36 l/24 hours) or every 2 hours (18 l/24 hours) for the first 48 hours. Following this, they could perform exchanges less often, based on metabolic parameters and fluid balance. Seventy-five patients were included in the analysis. The achieved weekly Kt/V was 2.26 in the low-intensity group and 3.3 in the high-intensity group. There was no significant difference in metabolic control, although ultrafiltration was higher in the high-intensity group. The mortality was 72% in the high-intensity and 63% in the low-intensity groups ($P = 0.18$), suggesting no advantage to the higher-intensity treatment. Certainly, when lower PD doses are used, the clearance of vancomycin and its pharmacokinetics can be different from our results.

CONCLUSION

HVPD removes considerable amounts of vancomycin in septic patients with AKI, and antibiotic underdosing is undesirable in these patients. Application of 18 mg/kg vancomycin each 48 to 72 hours in patients with AKI undergoing HVPD was required to maintain therapeutic concentrations. Daily vancomycin serum concentration monitoring is recommended to maintain therapeutic concentrations, and vancomycin pharmacokinetics in patients with AKI undergoing HVPD warrants further investigation.

DISCLOSURE

All the authors declared no competing interests.

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COMPLIANCE WITH ETHICS GUIDELINES

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the ethics committee of Brazil Plataforma, under number: 17086413.3.0000.5411. Informed consent was obtained from all individual participants included in the study.

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Vancomycin dosing, monitoring and toxicity: Critical review of the clinical practice

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Summary

Vancomycin is an antibiotic used in the treatment of infections caused by multidrug-resistant Gram-positive bacteria, especially methicillin-resistant *Staphylococcus aureus*. In the last decades, vancomycin has been widely used in hospital environments due to the increasing incidence of sepsis and septic shock. Sepsis may lead to multiple organ failure; it is considered a risk factor for the development of acute kidney injury (AKI), with an overall mortality rate of around 45%, which can reach the surprising rate of 70% with the combination of AKI and sepsis. Considering the high mortality rate of sepsis and its related costs of hospitalization and treatment, specific measures should be adopted, such as early-goal treatment protocols: proper and early administration of antimicrobials, fluids, vasoactive drugs and transfusion support. Besides the careful selection of the antimicrobial, another concern related to critically ill patients is the proper dose of the antimicrobial, since pharmacokinetic changes are observed due to drug absorption, distribution, metabolism and elimination. Gram-positive pathogens are very common in hospitalized patients with septic shock, so vancomycin has been the antimicrobial of choice for more than 60 years. However, discussions about its dosage, administration and monitoring are extremely important, considering the risk of nephrotoxicity and the emergence of resistant *S. aureus*. This narrative review aims to discuss controversial aspects related to the efficacy and safety of vancomycin, correlating them with data available in the literature and identifying knowledge gaps in guide future lines of research.

KEYWORDS

acute kidney injury, efficacy, nephrotoxicity, pharmacodynamics, pharmacokinetics, safety, sepsis, vancomycin

1 | VANCOMYCIN

Vancomycin is a glycopeptide antimicrobial with antibacterial action, acting by inhibition of cell wall synthesis. It was introduced in clinical practice in the mid-1950s for the treatment of bacterial infections caused by Gram-positive bacteria and it is considered by the Infectious Disease Society of America (IDSA) as the first treatment option for methicillin-resistant *Staphylococcus aureus* (MRSA) infections.^{1,2} However, it also presents action against *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*,

Streptococcus bovis, *Streptococcus viridans*, *Enterococcus*, species of *Clostridium*, *diphtheroids*, *Listeria monocitogenes*, *Actinomyces*, and species of *Lactobacillus*. The antimicrobial activity against *S. aureus*, *S. bovis*, *Enterococcus* and *S. viridans* can be improved by combining vancomycin and an aminoglycoside.³

1.1 | Pharmacokinetics

The pharmacokinetic scheme is described using the two-compartment model with biphasic elimination half-life (Figure 1). Drug

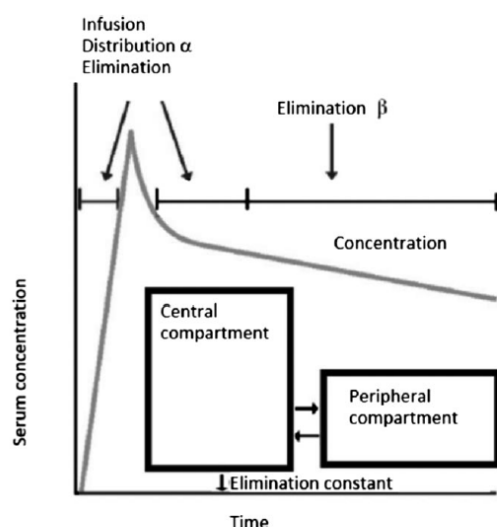


FIGURE 1 Schematic representation of the pharmacokinetic two-compartment model. Adapted from Rybak⁵

distribution occurs rapidly in healthy subjects with a volume of distribution (V_d) of 0.4–1.0 L/kg. Critically ill patients present altered V_d and may reach two or three times the typical value. Its protein binding ranges from 10% to 50% and depends on the total serum concentration of proteins. The drug is not metabolized and its excretion is 80%–90% renal, with elimination half-life highly dependent on renal function.^{4–6} In subjects with normal creatinine clearance, vancomycin has a distribution phase of 30 minutes to 1 hour and a half-life elimination of 6–12 hours.^{4,5,7}

Vancomycin penetrates most tissues although its concentration is variable and often depends on the degree of inflammation present. Its penetration into the lung and central nervous system is poor, with a higher risk of subtherapeutic tissue concentration at lower doses.⁵ Skin penetration is significantly lower in patients with diabetes when compared to patients without diabetes.⁸

Its antibacterial action is time and concentration dependent.^{4,6} Based on the pharmacodynamics of vancomycin, an area under the curve (ratio) is recommended by the minimum inhibitory concentration (AUC/MIC) of 400 or greater for *S. aureus* with MIC $\leq$ 2 mg/L. In a prospective study, Moise-Broder et al⁹ identified in patients with pulmonary sepsis that time above MIC was 100% in all patients, but clinical success was about six times higher in those with AUC/MIC above 400. This finding was obtained again in later studies, and AUC/MIC is now considered the best predictor of clinical outcomes.⁴

A multicenter prospective cohort study conducted by Song et al¹⁰ analyzed the association between 24-hour AUC and MIC with clinical outcomes in 117 patients with sepsis and infections caused by MRSA. Treatment failure, defined as 30-day mortality, persistent bacteraemia for more than 7 days, or recurrent infection in less than

30 days of treatment end was observed in 32.5% and was associated with low AUC/MIC ratio (OR 3.50 for microdilution method, and 5.61 for Etest, with minimum values of 392.7 and 397.2, respectively), concluding that values above 400 could improve treatment outcomes.

A meta-analysis conducted by Men et al¹¹ included nine cohorts. Mortality rates were lower (RR = 0.47, CI 0.31–0.70, $P < 0.001$), as well as the treatment failure rates (RR = 0.39, CI 0.28–0.55, $P = 0.001$) in the group with higher AUC/MIC, with 400 considered a reasonable target.

In 2006, the Clinical and Laboratory Standards Institute (CLSI) reduced the susceptibility and resistance limits for vancomycin MIC from ≤ 4 to ≤ 2 mg/L (classified as susceptible), from 8–16 to 4–8 mg/L (intermediate), and from ≥ 32 to ≥ 16 mg/L (resistant). Studies have suggested that serum levels of vancomycin < 10 mg/L may predict therapeutic failure and the selection of vancomycin-resistant *S. aureus* (VRSA) or vancomycin-intermediate *S. aureus* (VISA).^{12–14} Another emerging population of *S. aureus* is heteroresistant vancomycin-intermediate *S. aureus* (hVISA), considered to be the precursor of the VISA population. Although uncommon, this subpopulation seems to predict vancomycin treatment failure.^{7,14}

Some clinical situations may require the combined use of vancomycin for the treatment of complicated infections, for example, vancomycin combined with rifampicin to treat prosthetic infections; with gentamicin in MRSA bacteraemia; and with clindamycin to reduce toxin produced by *S. aureus*.⁷

The two most common ways to determine the MIC of *Staphylococcus* sp. are by microdilution (results by dilution performed twice) or Etest (continuous gradient describing fractional dilutions).⁶ Determining the AUC and subsequently the AUC/MIC ratio is impossible under normal circumstances due to the large number of serum samples that should be collected after a single dose. Then, the standard recommendation is the use of serum trough level in a stable condition as a marker.⁶

A meta-analysis conducted by van Hal et al¹⁴ included 22 studies and found that, in *S. aureus* infections, MIC ≥ 2.0 mg/L was a predictor of treatment failure (OR 2.69, $P < 0.01$). Lodise et al,¹⁵ in a retrospective cohort study involving 92 patients, found that MIC ≥ 1.5 mg/L had a 2.4 times greater risk of treatment failure when compared to MIC ≤ 1.0 mg/L (36.4% and 15.4%, respectively, $P = 0.049$), indicating that MIC ≥ 1.5 mg/L was independently associated with treatment failure (RR 2.6, $P = 0.01$), suggesting that another antimicrobial should be considered in this context.

A prospective study conducted by Song et al¹⁶ evaluated a cohort of 1027 cases of invasive infection caused by *S. aureus* and identified that all-cause mortality rates at day 30 and due to bloodstream infection from the group of high MIC (≥ 1.5 mg/L) did not differ from the group of low MIC (< 1.5 mg/L).

Patel et al¹⁷ conducted a Monte Carlo simulation series to identify the probability of reaching AUC/MIC ≥ 400 and trough concentration of 15–20 mg/L with different MICs and dosing regimens. Their analysis suggested that with MIC ≥ 2 , a higher dose regimen (4 g/d) showed 57% efficacy and nephrotoxicity risk of

35%. In addition, with MIC ≤ 1.0 mg/L, a trough concentration of 15–20 mg/L was not always required to reach AUC/MIC ≥ 400 . A great variability was observed between AUC and trough concentration, the relationship between them being dependent on the dosage regimen.

Considering AUC/MIC as target, larger doses with longer maintenance intervals or smaller doses with shorter intervals could be used, supporting the continuous infusion regimen of vancomycin.

According to the Sanford Guide to Antimicrobial Therapy,¹⁸ the attack dose should be 25–30 mg/kg, followed by maintenance of 15–20 mg/kg every 8–12 hours for intermittent administration, or the attack dose of 15–20 and 30 mg/kg in 24 hours for continuous infusion regimens.

The use of attack dose has been proposed as a strategy to avoid subtherapeutic levels in the early stages of the treatment, soon achieving an AUC/MIC over 400, and without evidence of impact on nephrotoxicity.^{13,19,20}

A retrospective study conducted by Rosini et al²¹ evaluated 2131 patients at three academic centres and compared the vancomycin dose of >20 to ≤ 20 mg/kg, and found a lower incidence of nephrotoxicity in the higher dose group (5.8% vs 11.1%, $P < 0.001$). After adjustment for age, sex and baseline creatinine, exposure to high dose of vancomycin was not initially associated with nephrotoxicity (RR = 0.60). The authors performed a sensitivity analysis to determine if the usual dose of 25 mg/kg would have an impact on the results, but such data were not presented in the study; it only reported no statistically significant changes.

Later, Rosini et al²² conducted another prospective study, randomizing 99 patients who came to the emergency service to receive the attack dose of 30 mg/kg or 15 mg/kg. The first concentration before the second dose was 15–20 mg/L in 34% compared to 3%, respectively ($P < 0.01$). The study found no difference between the rates of nephrotoxicity, hospitalization period or mortality between the two groups.

1.2 | Special situations

1.2.1 | Patients with kidney disease

For patients with impaired kidney function, dosage adjustment based on estimated glomerular filtration is recommended.¹⁹ For clearance of 10–50 mL/min/1.73 m², the dose of 15 mg/kg is recommended every 24–96 hours and, for clearances of less than 10 mL/min/1.73 m², the dose of 7.5 mg/kg every 48–72 hours. Some authors suggest nomograms to help adjust dosage, without evidence to date that shows superiority of one method in relation to another.^{4,6,24} However, the studies that guided these dose adjustments are based on stable creatinine situations, a context that does not occur in patients with acute kidney disease.

Some websites help adjust such dosing, such as vancomycin-calculator.com, developed by Baue's pharmacokinetic method, the only one that adjusts doses for obese and underweight patients.²⁴

1.2.2 | Obese patients

In subjects with moderate to severe obesity (BMI greater than 35 kg/m²), the standard recommendation is to use the current weight for dose calculation. However, some pharmacokinetic studies do not support this practice.^{4,19,20} Vancomycin concentrations are impacted by increased clearance and volume of distribution and shorter half-life, related to greater vancomycin clearance due to higher cardiac output in these patients.¹³

A retrospective cohort analyzed by Davies et al²⁵ included 530 patients, of whom 207 were obese, with similar groups, except for a higher female prevalence ($P = 0.042$), diabetes mellitus ($P = 0.018$) and hypertension ($P = 0.0009$) in the obese group. Obesity was not associated with an increased risk of nephrotoxicity (RR 0.98, CI 0.93–1.04, $P = 0.59$), unlike the APACHE II >21 severity score, which was correlated with nephrotoxicity ($P = 0.039$).

The most frequent recommendations for obese patients are an initial dose based on the current weight, not exceeding 2000 mg and adjustments of subsequent doses based on the therapeutic serum level.^{6,26,27}

Some specific populations require individual assessment, such as those with large burns.²⁸ In this population, a shorter administration interval and larger doses may be required; however, nomograms or therapeutic drug monitoring are recommended for adjustments.

1.3 | Intermittent vs continuous administration

Vancomycin administration via continuous infusion seems to be an attractive option for critically ill patients because of the variable volume of distribution and drug clearance. The literature shows several dosing regimens to maintain serum levels between 15 and 25 mg/L, as well as nomograms to guide the clinical use of this antimicrobial.⁴

A retrospective study conducted by Eldemiry et al²⁹ included 40 critically ill patients with pulmonary sepsis caused by a vancomycin-sensitive germ (MIC <2 mg/L), with Cr >1.4 mg/dL and oliguria <0.5 mL/kg/h in 6 hours. The patients were divided into two groups, one received intermittent standard dose and the other, continuous infusion. After the treatment, the continuous infusion group showed, in relation to the intermittent dose group, lower levels of urea ($P = 0.041$), creatinine ($P = 0.009$), leukocytes ($P = 0.001$), pCO₂ ($P = 0.025$) and body temperature ($P = 0.0001$), as well as higher pO₂ and saturation ($P = 0.038$). In addition, continuous infusion resulted in lower sub therapeutic level rates (30% vs 55%), higher optimal level rates (40% vs 10%) and similar toxic rates (30% vs 35%), as well as shorter treatment duration ($P = 0.0001$).

A study conducted by Cataldo et al³⁰ reviewed the literature on vancomycin administration. They evaluated a randomized clinical study and five observational studies and found an association between continuous infusion and a lower risk of nephrotoxicity (RR 0.6, $P = 0.02$), with no difference in mortality between the groups.

A prospective study conducted by Duszynska et al³¹ compared 21 septic patients receiving vancomycin continuously to 21 patients receiving intermittent vancomycin. They found no difference

between the groups regarding mean AUC/MIC, therapeutic success rate and nephrotoxicity; however, the mean cost was lower in the continuous infusion group (377 vs 552 Euros, $P = 0.04$). Wysocki et al⁴³ identified a lower cost per patient over 10 days of continuous infusion, 23% lower when compared to intermittent administration ($P < 0.0001$), with comparable efficacy and tolerance, suggesting continuous administration as a cost-effective option.

A literature review conducted by DiMondi et al⁴ included 14 studies: two prospective, 11 retrospective and one meta-analysis that compared continuous to intermittent vancomycin infusion. No difference was observed in efficacy when comparing both treatments. The prospective studies did not show different nephrotoxicity rates, and the retrospective studies showed heterogeneous results, without determining which subgroups could benefit from continuous infusion. In addition, questions were raised regarding compatibility, safety and efficacy using this type of administration, and further studies are needed.

Continuous infusion may be of interest for patients presenting high risk for nephrotoxicity, such as those in concomitant use with aminoglycosides and loop diuretics and those with septic shock or receiving higher doses of vancomycin. It has the advantage of easy monitoring and lower cost, with comparable efficacy to intermittent infusion. It may also require less therapeutic monitoring, and samples may be collected at any time after 18–24 hours of administration.

Continuous infusion of vancomycin can reach therapeutic levels more rapidly and more consistently. The American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), and the Society of Infectious Diseases Pharmacists (SIDP) do not recommend continuous infusion of vancomycin due to the lack of robust data showing better outcomes. However, some centres have administered continuous infusion of vancomycin with inconclusive results.³¹

Despite its wide use in clinical practice, there are unresolved concerns about its effectiveness and safety. Regarding efficacy, mainly in critically ill patients, its pharmacokinetics is altered, due to drug distribution, metabolism and elimination,^{1,32–34} which could lead to subtherapeutic serum concentration and develop bacterial resistance, with possible increased mortality.³⁵ In terms of safety, its main side effect—nephrotoxicity—has been widely discussed, with risk of AKI and complications in the short and long term.³⁶

1.4 | Serum monitoring

Considering the great heterogeneity of patients, different degrees of organic dysfunction and pathophysiological changes in critically ill patients, therapeutic drug monitoring should be considered to achieve pharmacokinetic goals in ICUs; however, no study considers the costs of implementing such monitoring in hospital routines.³⁷

A randomized clinical study and five cohort studies were included in a meta-analysis conducted by Ye et al,³⁸ which showed therapeutic drug monitoring associated with higher clinical efficacy rates (OR 2.62, $P = 0.005$) and lower nephrotoxicity rates (OR 0.25,

$P < 0.0001$). No difference was observed in vancomycin treatment duration or hospitalization period.

Based on animal and clinical studies, since 2009 the optimum activity has been defined as the area under the curve divided by the minimum inhibitory concentration (AUC/MIC) equal to or greater than 400. Due to the logistic challenges of such determination in clinical practice, it was demonstrated that such value could be obtained with trough serum levels of vancomycin between 10 and 20 mg/L.^{8,20} Larger concentrations were studied, but without evidence of better therapeutic outcomes.³⁹

A clinical study conducted by Shahrami et al³⁹ showed that, after 20 critically ill patients received an attack dose of 25 mg/kg vancomycin, the strategy that best guarantees AUC/MIC ≥ 400 and serum level ≥ 15 mg/L are individual doses based on serum vancomycin concentration.

A serum level of less than 10 mg/L does not guarantee an AUC/MIC ratio greater than 400 and may develop bacterial resistance.⁸ Therefore, a level above 10 mg/L is recommended. For more serious infections^{40,41} (bacteraemia, endocarditis, osteomyelitis, meningitis and nosocomial pneumonia), a level between 15 and 20 mg/L is recommended. However, some studies indicate that up to 50% of patients with a ratio greater than 400 had a serum level lower than 15 mg/L. In case of serum level of vancomycin below the desired values, it was advised to increase the dose. When level is high, especially above 30 mg/L, the adjustment is in the opposite direction.¹² Patients with a level above 20 mg/L should be monitored for kidney function.^{23,40–42}

It is recommended the monitoring of serum level of vancomycin in patients with high risk of kidney failure: patients critically ill, who are receiving high doses of medication or undergoing treatment for more than 3–5 days, making concomitant use of other nephrotoxic drugs, patients with obesity or low body weight, patients with large fluctuations in the volume of drug distribution such as pregnant women and children, patients with previous chronic kidney disease or acute kidney injury or in those who are in dialysis therapies.^{8,37,40,41,43–45}

The monitoring must be performed when the serum level of vancomycin reaches a steady state, that is, after a minimum of three doses infused intravenously every 12 hours. In order to ensure the trough status, the sample must be collected 30–60 minutes before the administration of any dose between the third and the fifth, if the kidney function is normal; or collected in up to 48 hours after starting the administration if creatinine clearance lower than 10 mL/min/1.73 m².^{8,28,37,40–44}

The frequency of monitoring, after reaching the therapeutic target, may be on a weekly basis for haemodynamically stable patients. In unstable patients, more frequent evaluations (in some situations on a daily basis) should be performed, but there is no exact frequency, and monitoring should be based on clinical judgment.^{27,37}

A systematic review and a meta-analysis conducted by Steinmetz et al²⁶ evaluated the impact of low (<15 mg/L) vs high (≥ 15 mg/L) trough level on the efficacy of the treatment against MRSA. In total, 12 retrospective and four prospective studies were evaluated,

including 2003 participants. There was no significant difference between the levels for outcomes of all causes of mortality (OR 1.07, CI 0.78–1.46, $I^2 = 28\%$). In the studies evaluating pneumonia caused by MRSA, a higher mortality rate was observed in the group of low vancomycin level (OR 1.78, CI 1.11–2.84). No difference was observed in treatment failure rates, but after the exclusion of a discrepant study from the analysis, a higher failure was observed in the group of low vancomycin level (OR 1.56, CI 1.08–2.26, $I^2 = 16\%$).

A meta-analysis of 14 cohorts conducted by Prybylski⁴⁵ showed that trough serum levels greater than 15 mg/L were not associated with reduced treatment failure, persistent bacteraemia or mortality. On the other hand, higher AUC/MIC values were associated with reduced treatment failure (OR 0.41, CI 0.31–0.53), persistent bacteraemia (OR 0.53, CI 0.33–0.86), and mortality (OR 0.47, CI 0.33–0.65).

Different nomograms have been developed to individualize pharmacokinetic monitoring of vancomycin, possibly with more cost-effectiveness in relation to serum level monitoring. However, many are based on linear and non-linear regression and become complex models that require specific information on pharmacokinetics as well as computer programs.²⁴

1.5 | Toxicity

Since 1958, there have been reports of toxicity related to the administration of vancomycin. The initial preparations were called 'Mississippi mud' and had significant amounts of impurities (70% pure), which was the main reason for toxicity. With purification techniques, current preparations have 90%–95% vancomycin B (active portion).^{6,46}

Vancomycin has almost exclusive renal elimination; however, the mechanism through which nephrotoxicity occurs is still not well understood. Studies in experimental animals suggest that oxidative stress induced by the drug in proximal renal tubule cells may lead to tubular ischaemia and acute tubulointerstitial damage.^{47,48} Both vancomycin build-up in kidney cells and alteration of mitochondrial function in proximal tubule cells have been proposed as the main factors of nephrotoxicity.^{48–51} Vancomycin crosses the basolateral membrane of the proximal tubular epithelium via organic acid transport system and via transport mediated by receptor megalin on the apical surface. Then, its injury to the tubule is mediated by oxidative stress, activation of inflammatory pathways and complement.^{45,52} Superoxides produced by vancomycin cause depolarization of the mitochondrial membrane potential, with release of cytochrome C and subsequent activation of caspases 3 and 9, related to cellular apoptosis.⁴⁵ Another potential mechanism of injury is tubular obstruction with cylinders containing vancomycin precipitates.⁵²

The incidence of nephrotoxicity caused by vancomycin varies greatly among various studies, with rates as low as zero in the absence of other concomitant nephrotoxins, up to 40%^{8,45,51,53} in combination with other potentially nephrotoxic drugs, with a higher prevalence frequently described from 5% to 7%,⁴⁵ involving different factors that may speed up or enhance the occurrence

of nephrotoxicity, which may be related to the patient and/or the drug.⁵¹ Among the patient-related factors,^{48,51,54} the most important are advanced age, reduced kidney function, dehydration, reduced renal mass, sex (women have lower muscle mass and body water quantity), obesity,⁵⁵ hypoalbuminemia,⁵⁴ and sepsis, while drug-related risk factors include administration concomitant with other nephrotoxic drugs such as aminoglycosides, loop diuretics, amphotericin B, piperacillin-tazobactam, acyclovir, vasopressors and intravenous contrast media^{41,45}; as well as long treatment duration and high serum dosage of this antimicrobial.^{48,51}

Especially in septic patients admitted to the ICU, the presence of other factors concomitantly with the use of vancomycin makes it difficult to assess nephrotoxicity as the aetiology of AKI, since they act as confounding factors and make these patients more susceptible to kidney damage due to the severity of the underlying disease, and not due to the treatment. Then, some authors question whether high serum levels of vancomycin are the cause (due to higher serum concentration) or a consequence of AKI (drug build-up due to impaired kidney function as a consequence of other factors).²¹

Data suggesting a causal relationship between doses and therapeutic targets of vancomycin and nephrotoxicity are conflicting and marked by confounding factors.⁸ Although there is minimal evidence supporting efficacy in maintaining therapeutic levels between 15 and 20 mg/L, several studies have evaluated the safety of this recommendation, comparing nephrotoxicity rates above and below 15 mg/L levels.⁵³ A systematic review and a meta-analysis conducted by van Hal et al⁵⁶ included 15 studies in which trough serum levels of vancomycin ≥ 15 mg/L were associated with a higher risk of nephrotoxicity when compared to levels < 15 mg/L (OR 2.67, $P < 0.01$). A multicenter prospective study conducted by Bosso et al,⁴³ when assessing 288 patients receiving vancomycin, found an association between the incidence of nephrotoxicity and vancomycin concentrations, with AKI occurring in 29.6% of patients with serum vancomycin levels above 15 mg/L and in 8.9% of the group of patients with vancomycin levels below 15 mg/L.

Ten other studies reviewed by Gupta et al⁴⁷ identified vancomycin levels > 15 mg/L as a predictor of nephrotoxicity, with AKI incidence of 27%. A retrospective analysis conducted by Su et al⁵⁷ included 251 patients, with nephrotoxicity occurring in 19.5% of them. A creatinine clearance below 34.46 mL/min presented odds ratio of 4.5 (CI 2.27–8.88) for nephrotoxicity. The concomitant use with loop diuretics (63.3% vs 32.7%, $P < 0.001$) was identified with nephrotoxicity. A multivariate analysis showed that vancomycin-related nephrotoxicity was independently associated with congestive heart failure (OR 7.08, CI 1.973–25.408, $P = 0.003$). Based on the results of this study, it seems prudent to maintain a serum level below 19.6 mg/L to prevent vancomycin-induced nephropathy.⁵⁶ A Brazilian retrospective cohort analyzed by Araújo et al⁵⁹ included 127 patients who had more than three cases of serum level of vancomycin and correlated creatinine levels. The sample was divided into two groups based on the creatinine value ($Cr \leq 1.4$ and > 1.4 mg/dL), and these groups were subdivided into two subgroups, with a serum level of vancomycin ≤ 20 and > 20 mg/L. AKI occurred in 65.7%

of the cases, and in the group with Cr >1.4 mg/dL and vancomycin >20 mcg/mL, the odds ratio adjusted for the development of AKI was 3.17 (CI 1.05-9.56; $P = 0.041$).

Another study conducted by Iwamoto et al⁴² also found that patients who were not monitored for therapeutic levels of vancomycin had a significant decrease in creatinine clearance values and, therefore, presented a higher risk of nephrotoxicity when compared to those who were monitored (OR = 0.25; $P < 0.05$).

In a recent publication,⁵⁶ researchers from the United Kingdom evaluated a retrospective cohort of 1430 severe patients who received vancomycin between 2004 and 2009. The multivariate analysis of the study identified three independent risk factors associated with nephrotoxicity by vancomycin: extended use of antibiotic (OR 1.04 for each day); concomitant use of vasopressors (OR, 1.63); and the need for elevated serum levels of the drug (between 15 and 20 mg/L) (OR, 1.11). Jeffres et al³⁷ found a risk of nephrotoxicity by vancomycin 2.55 times greater after 14 days of treatment, and Hydayat et al¹³ found a higher prevalence of nephrotoxicity as the vancomycin use was extended in patients with therapeutic levels at the upper limit (15-20 mg/L): 6% for ≤ 7 days; 21% for 8-14 days; and 30% for 14 days.

Lodise et al³⁹ observed that patients hospitalized in ICU have an increased risk of 20% for the development of nephrotoxicity when compared to patients not hospitalized in ICU, both groups with serum concentration below the toxic level, which suggests the presence of other risk factors for AKI in critically ill population.

A retrospective study conducted by Choi et al⁵³ identified in 62 cases of nephrotoxicity that 8.7% of them occurred in non-obese individuals, 14.3% in patients with obesity class I and II, and 26.3% in patients with obesity class III ($P = 0.002$). Patients with obesity class III presented three times more nephrotoxicity when compared to non-obese patients (OR 2.99, CI 1.12-7.94), and patients with obesity class I and II (OR 3.14, CI 1.27-7.75).

A systematic review conducted by O'Donnell et al⁵⁸ analyzed 15 pre-clinical studies and identified that an increase in the total daily dose of vancomycin had a correlation with the dose-response curve (50% of maximum toxic response = 130.4 mg/kg/d) of urine concentration of KIM-1, a tubular injury biomarker. In female participants ($P = 0.05$) and therapies for more than 7 days ($P = 0.02$), a deviation of the dose-response curve to the left was observed.

A single-centre retrospective study conducted by Koppula et al⁶⁰ evaluated 54 high serum levels of vancomycin and classified the aetiology of toxic levels into four groups: (a) inadequate moment of collection (21%); (b) inadequate dose (19%); (c) change in renal function (23%); and (d) altered pharmacokinetics/pharmacodynamics (36%), which suggests that the first three situations could be prevented and/or corrected through educational programs, and the fourth situation, through therapeutic drug monitoring or administration of another antimicrobial.

High doses of vancomycin, associated with systemic inflammation and ischaemic insults in the septic patient, increase the risk of nephrotoxicity, which occurs 4 to 8 days after starting the use.⁵¹ Nephrotoxicity is associated with longer hospitalization, higher

TABLE 1 Measures to reduce nephrotoxicity

Recommendations
Use a dose of 15-20 mg/kg of current weight (even in obese patients), combining therapeutic drug monitoring. Consider nomograms if kidney function changes
Consider an attack dose of 25-30 mg/kg for serious infections (bacteraemia, endocarditis, pneumonia, osteomyelitis, meningitis)
Use intermittent dose of vancomycin
Do not reach peak concentrations
Maintain a therapeutic level between 10 and 15 mg/L for non-serious infections and between 15 and 20 mg/L for serious infections
Consider interrupting vancomycin if AKI development after at least 2 d of therapy, changing to another antimicrobial therapy
Concomitant use with piperacillin-tazobactam or aminoglycoside should be monitored with serum level dosage due to toxicity synergism
Therapeutic drug monitoring should be used in patients presenting a high risk for toxicity, extended therapy or impaired kidney function, collecting it before the fourth dose if stable kidney function is observed

Adapted from Fillippone et al⁶

expenses and mortality.⁶¹ Kidney function recovery occurs in 44%-75% of the patients with nephrotoxicity after 1 week of drug discontinuation.⁶² Table 1 summarizes the main recommendations for the prevention of nephrotoxicity found in the literature.

Defining vancomycin-associated nephrotoxicity can be a challenge. The most frequent definition is an increase of 0.5 mg/dL in serum creatinine or 50% increase above baseline in two consecutive measurements after several days of vancomycin and no other apparent causes.⁸ Worsening of kidney function may be defined according to the most current criteria for acute kidney injury (AKI) by the Kidney Disease Improving Global Outcomes (KDIGO)³⁵ as an increase greater than 0.3 mg/dL in baseline creatinine in 48 hours; increase of 1.5 times the baseline creatinine within 7 days; and/or reduction of urinary output to <0.5 mL/kg/h in 6 hours. However, serum creatinine may remain unchanged despite significant tubular injury, increasing only after 48-72 hours. Biomarkers that identify proximal tubular dysfunction, such as NGAL, KIM-1 and IL-18, can be used for early diagnosis of kidney injury and to establish prognosis.⁴⁵

The two most common ways of kidney function impairment by vancomycin are acute tubular necrosis (ATN) and acute interstitial nephritis (ASN).^{45,54} NIA is an immune-mediated reaction that presents symptoms and signs of hypersensitivity: temperature increase, maculopapular rash, eosinophilia, urinary sediments.^{62,63}

The most common adverse events related to the administration of vancomycin and not related to serum concentration are linked with red man syndrome, associated with histamine release, developing paresthesia and redness of the face, neck and thorax, when the administration of large doses occurs very fast (more than 500 mg in less than 30 minutes⁸); suggested infusion period: 1 to 2 hours. Other forms of toxicity include hypersensitivity reactions, such as

DRESS (drug rash with eosinophilia and systemic symptoms), which includes fever, erythema, eosinophilia, atypical lymphocytes, lymphadenopathy and visceral involvement (10% renal with acute interstitial nephritis).⁴⁴

Regarding ototoxicity, despite reports of cases relating it to serum concentration of vancomycin with a variable incidence of 1%-9%, there are no animal experiments that have demonstrated this relationship.⁶⁶ However, there seems to be synergism when concomitant use occurs with other potentially ototoxic drugs, such as aminoglycosides.⁸ It would cause damage to the auditory nerve, which would initially affect high-frequency sounds in the cochlea. Some studies report tinnitus related to the use of vancomycin.

As future perspectives, there are descriptions of liposomal modification of vancomycin, with experimental studies identifying in rats a greater area under the curve with reduced distribution in renal tissue, besides the use of antioxidant substances to reduce toxicity by vancomycin, but with conflicting results so far.⁴⁴

1.6 | Elimination through dialysis

Among patients with stage 5 chronic kidney disease receiving some renal replacement therapy or critically ill patients on acute renal support therapy and concomitant administration of vancomycin, the drug elimination during therapy should be based on dose adjustment.^{21,63-75} Vancomycin clearance by dialysis depends on the type of dialysis membrane, dialysis fluxes and duration, ultrafiltration rate, and Kt/V .⁶⁵⁻⁶⁹ There are no data confirming that levels between 15 and 20 mg/L related to AUC in haemodialysis patients.²¹

In haemodialysis therapies, vancomycin is not significantly removed when using a low-flux capillary, such as cuprophan. In this context, a weekly dose of vancomycin was recommended for many years.^{66,67} However, when using a high-flux capillary, such as polysulfone, polyacrylonitrile or polymethylmethacrylate, vancomycin is significantly dialyzed, with rates ranging from 30% to 46%,^{67,68} with pharmacokinetic studies showing a rebound effect of 16%-36%⁶⁹ at the end of the session, lasting between 3 and 6 hours, a result of drug recirculation from protein binding sites (redistribution phase), as illustrated in Figure 2. Then, for serum level monitoring in these

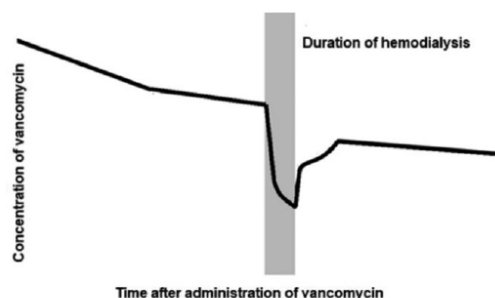


FIGURE 2 Schematic representation of the pharmacokinetic model of vancomycin during chronic haemodialysis. Adapted from Welage et al⁶⁹

patients, blood sampling should happen before the haemodialysis session.⁶⁹

A study conducted by Quale et al⁶⁵ identified 37% vancomycin elimination in six patients receiving conventional haemodialysis with polyacrylonitrile membranes. An *in vitro* analysis, comparing high flux with low flux (cellulose) membranes, identified elimination of 61% and 9%, respectively. Pai et al⁶⁶ evaluated 28 patients and identified vancomycin elimination of $39 \pm 13\%$ through conventional haemodialysis with high-flux capillaries. In patients receiving extended HD, despite a few studies evaluating the removal of vancomycin, Petejova et al⁶⁷ evaluated five patients receiving HD for 6 hours with low-flux membrane and four patients with high-flux membrane, and vancomycin administered in the last hour of therapy; the elimination rates were 17% (8%-38%) and 31% (13%-43%), respectively. Kielstein et al⁷⁷ found that the fraction of drug removed by extended therapy was 26%.

In continuous venovenous therapies, there is no rebound effect on serum concentration, and the level can be determined at any time.^{70,71} Continuous infusion seems to be more successful in fulfilling pharmacokinetic/pharmacodynamic needs in this population, but few studies have addressed this theme.²¹ DeIDot et al⁷⁴ studied 10 critical patients with AKI receiving hemodiafiltration, showing 50% elimination in a 12-hour period and suggesting a 750 mg dose every 12 hours.

In peritoneal dialysis, since 1956, after a study conducted by Geraci et al,⁷⁸ vancomycin diffuses with the dialysate, reaching the concentration of 51% (23%-75%) of simultaneous serum level, with collections performed 1-2 hours after intravenous administration of 500 mg vancomycin. However, the literature has no current studies addressing this topic in details.

In septic patients with AKI, the prevention of new kidney issues, such as nephrotoxicity, is essential. Then, antimicrobial dose should be corrected, but there are no validated guidelines so far to help adjust antimicrobial doses in patients with AKI. In patients with SARS, except for continuous venovenous therapies with more antimicrobial dose studies, studies are scarce for other dialysis types, with recommendations from studies performed in non-critically ill patients and stable kidney function or with chronic kidney disease in the final stage receiving chronic renal replacement therapy.⁷⁶⁻⁷⁹

According to a narrative review conducted by Freitas et al,⁷¹ the dose of 15 mg/kg should be administered after the dialysis for conventional HD therapies in daily regimen (or according to serum level), 500 mg every 24-48 hours in continuous venovenous therapies, 7.5 mg/kg every 2-3 days for continuous ambulatory peritoneal dialysis (CAPD). There is no specific information about doses for patients receiving extended HD therapy or high volume PD.

Ahem et al⁷⁶ studied the pharmacokinetics of vancomycin in patients receiving extended HD and found a half-life of 43.1 ± 21.6 hours for administrations every 24-72 hours. The authors suggested, in their conclusion, the administration of 15 mg/kg as the starting dose and, given the high variability of the antimicrobial half-life during the therapy, serum monitoring after 24 hours of the initial dose and adjustments according to the results.

A narrative review conducted by Crew et al⁷⁰ reported dose regimens based on therapeutic drug monitoring with individual administrations are more interesting to ensure the level of treatment and not involve risk of nephrotoxicity. The proposed scheme, considering elimination between 30% and 40%: for pre-haemodialysis serum level less than 10 mg/L, administer 1,000 mg after the session; between 10 and 15 mg/L, administer 750 mg after the session; between 15 and 25 mg/L, administer 500 mg after the session; and for pre-session level higher than 25 mg/L, do not administer any dose and, after starting next session, administer 500 mg after the session.

A randomized, three-way crossover study conducted by Mason et al⁷⁹ compared infusion of 15 mg/kg vancomycin after dialysis in nine patients receiving haemodialysis, the same dose during the last hour of therapy, and 30 mg/kg during the last 2 hours of dialysis. Vancomycin was significantly eliminated during the third to fourth hour of the session (33.4%-39.5%) and the administration of 30 mg/kg in the last two hours of the dialysis produced serum concentrations similar to the conventional 15 mg/kg dose after dialysis. However, the administration of 15 mg/kg in the last hour resulted in much lower pre-dialysis concentration.

2 | CONCLUSION

Vancomycin is still one of the most widely used antimicrobials in hospital environments and in critically-ill populations, but studies involving the safety and efficacy of vancomycin in septic patients are still inconclusive, especially in patients with acute kidney injury and/or concomitant dialysis therapies. Then, further studies are required to fill such knowledge gaps.

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Vancomycin Removal During High-Volume Peritoneal Dialysis in Acute Kidney Injury Patients

Studies on vancomycin pharmacokinetics in acute kidney injury (AKI) patients on high-volume peritoneal dialysis (HVPD) are lacking. We studied the pharmacokinetics of intravenous (IV) vancomycin in AKI patients treated by HVPD who received a prescribed single IV dose of vancomycin (15–20 mg/kg total body weight) to determine the extent of vancomycin removal and to establish vancomycin dosing guidelines for the empirical treatment of AKI patients receiving HVPD. The application of 18 mg/kg vancomycin every 48–72 hours in AKI patients undergoing HVPD was required to maintain therapeutic concentrations.

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KEY WORDS: AKI; sepsis.

Sepsis is a frequent cause of acute kidney injury (AKI) (1). Recently, there has been a growing interest in the use of peritoneal dialysis (PD) to treat AKI patients, and PD is now frequently used in developing countries because of its lower cost and minimal infrastructural requirements. Studies from Brazil, India, and Africa have shown that, with careful thought and planning, patients can be successfully treated using PD (2–5).

Brazilian studies have demonstrated that AKI patients can be successfully treated with high-volume PD, which is performed using a Tenckhoff catheter, 2-L exchanges, 35–60 min dwell times, prescribed Kt/V value of 0.5 per 24-h session, and a total dialysate volume of 32–44 L/day (3–5).

Serious infections are common in critically ill patients and require prompt treatment to decrease mortality. According to the Surviving Sepsis Campaign, intravenous antibiotics should be administered as soon as the diagnosis of sepsis is made (6).

Vancomycin is indicated for treating patients with a risk of infection caused by resistant gram-positive groups such as coagulase-negative *Staphylococci*, *Enterococcus faecium*. For achieving clinical effectiveness, the target of vancomycin area under the curve/minimum inhibitory concentration (AUC/MIC) ratio is ≥ 400 and the more practical method for monitoring its effectiveness is serum vancomycin concentration >10 mg/L (7,8).

Vancomycin is not metabolized, and its excretion is 90% renal, with elimination half-life highly dependent on renal function (7–10), making dosage adjustment during renal failure obligatory. In addition, it is nephrotoxic. Its half life ranged from 5 to 8 hours in patients with normal kidney function; however it is greater than 180 hours in stage-5 chronic kidney patients (8). Its volume of distribution ranged from 0.4 to 1 L/kg, its molecular weight is around 1,450 Da, and protein binding between 10% and 50% (10).

Vancomycin is not removed significantly during PD and should be administered every 72 to 120 hours. However, there is no study that evaluated the removal of vancomycin

during HVPD sessions in AKI patients and no strategies have been proposed to administer the appropriate dose of vancomycin in HVPD (11). Moreover, critically ill patients are often hemodynamically unstable and can have alterations in drug pharmacokinetics due to multiorgan dysfunction and acute changes in volume state (12,13). These conditions may change the vancomycin clearance during PD, and dose adjustments may be necessary.

Our aim was to study the pharmacokinetics of intravenous (IV) vancomycin in AKI patients treated by HVPD who received a single IV dose of vancomycin (15–20 mg/kg total body weight) to determine the amount of vancomycin removal, to compare vancomycin levels obtained in blood with MICs of typical gram-positive bacterial pathogens, and to establish vancomycin dosing for the treatment of AKI patients receiving HVPD.

METHODOLOGY

This is a prospective cohort clinical study performed at University Hospital Sao Paulo State in Botucatu Medical School, Brazil. The study protocol was approved by local ethics committees. Written informed consent was obtained from patients or family.

Ten critically ill adult patients with sepsis and AKI requiring HVPD on vancomycin therapy were included. Classification of AKI was made according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria (14). All patients were oliguric (urine output lower than 0.5 mL/kg/h). They were followed up for 2 days after introduction to the study.

Peritoneal dialysis was performed using a flexible catheter, an automated cycler, and a high volume of dialysis fluid, as described in our previous studies (3–5). Each session of HVPD lasted 24 hours, and sessions were repeated daily, 7 times per week. The total dialysate volume per session ranged from 32 L to 38 L, the number of cycles ranged from 16 to 19, and dwell time was from 60 to 80 min. Peritoneal access was established by the nephrology team through a percutaneous Tenckhoff catheter and the prescribed Kt/V was 0.50 per session.

Vancomycin 15 mg/kg was administered 1 hour before dialysis start. Blood and dialysate samples were collected after 1, 2, and 4 hours of dialysis start and at the end of dialysis (after 24 h). All dialysate was collected at the end of each dwell using a sample port directly on the automatic cycler machine for a 24-hour period. Vancomycin concentrations were determined using a liquid chromatographic (HPLC)-fluorescence method. Blood samples were centrifuged within 4 hours of collection and serum was stored frozen at -80°C until assayed. Volumes of dialysate and of ultrafiltration were recorded for each patient.

The analysis was carried out using an HPLC system (Agilent Series 1100, Agilent Technologies, Palo Alto, CA, USA), according to the methodology described by Silva *et al.* (15). Forty samples were analyzed. The following pharmacokinetic parameters were calculated for each patient assuming 1-compartment model: volume of distribution (V_d), dialysis total drug clearance (Cl) and elimination half life ($T_{1/2}$). The AUC was determined using the trapezoidal rule to the last non-zero

time point. The AUC from the last non-zero time point was determined by the pharmacokinetic method, concentration/k, where k is the elimination rate constant determined from log-linear regression of the terminal phase of the concentration-time profile. We also compared vancomycin levels obtained in blood (AUC) with MICs of typical gram-positive bacterial pathogens.

Data are expressed as median and range. The elimination of vancomycin from blood during HVPD sessions was calculated from the following formulas and expressed as % removal and peritoneal clearance:

$$\% \text{ vancomycin removal} = [(C_{\text{preHVPD}} - C_{24\text{h HVPD}}) / C_{\text{preHVPD}}] \times 100$$

where C_{preHVPD} = concentration of vancomycin before HVPD, $C_{24\text{h HVPD}}$ = concentration of vancomycin at end of HVPD.

$$\text{Peritoneal vancomycin clearance} = \text{Vanc D} / \text{Vanc P} \times \text{total V} / t$$

where vanc = vancomycin, D = dialysate, P = plasma, V = dialysate drain volume (mL) and t = 1,440 min (1 day).

Sample size calculation: We calculated the sample size estimating the amount of vancomycin removed by PD and establishing a 90% confidence interval about that value such that the width was less than $\pm 20\%$. We used intersubject variability (CV%) of 40%, $\alpha = 0.05$, $\beta = 0.2$, and it was estimated that 10 patients were required (16).

RESULTS

Table 1 shows patient and clinical characteristics. All patients had sepsis or septic shock. All bacterial agents were gram-positive. The median sequential organ failure assessment (SOFA) score was 13. All patients were in AKI-3 according to KDIGO. The median estimated glomerular filtration rate (eGFR) according to the modification of diet in renal disease (MDRD)

was 0.3 mL/s (0 – 0.74 mL/min). The mean dwell times for cycles were 40 – 55 minutes and the total dialysate volume per session ranged from 18 to 32 L. Five patients were anuric. In 5 patients, the urine output ranged from 0.32 to 0.44 mL/kg/h.

Median percentage of vancomycin removal by HVPD was $21.7\% \pm 2.2\%$ (16% – 29%). Vancomycin serum concentrations above 15 mg/L at the day of study dialysis were obtained in all patients at the end of dialysis. The median vancomycin dose was 18 ± 2.95 mg/kg (14.7 – 21.8 mg/kg) on the day of study. In all patients, it was the first vancomycin dose administered.

We did the Pearson correlation between individual patient peritoneal vancomycin clearance and % vancomycin removal and it was excellent ($r = 0.73$, $p = 0.001$), suggesting minimal extra peritoneal elimination (Figure 1).

The ratio of $\text{AUC}_{0-24} / \text{MIC} \geq 400$ was achieved in all patients in the study (Table 2), when $\text{MIC} = 1$ mg/L was considered. Summaries of vancomycin pharmacokinetic parameters are shown in Tables 2 and 3. No significant difference between anuric and nonanuric patients was observed for any pharmacokinetic parameter.

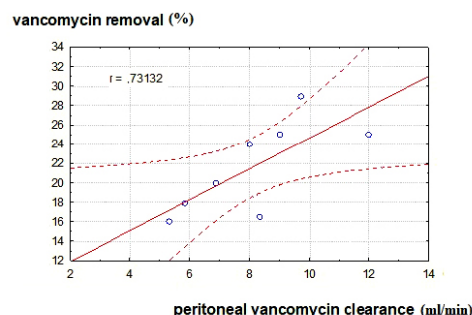


Figure 1 — Pearson correlation between peritoneal vancomycin clearance and vancomycin removal.

TABLE 1
Patient Demographics and Clinical Characteristics

Patient	Sex	Age (years)	Weight (kg)	SOFA	Diagnosis	Pathogen/MIC	Urine output (mL/kg/h)
1	F	58	65	11	Pneumonia	MRSA	0
2	F	62	55	12	Endocarditis	<i>Enterococcus</i>	0.32
3	F	59	58	14	Meningitis	MRSA	0.38
4	M	76	71	13	Pneumonia	<i>Staph haemolyticus</i>	0.40
5	M	72	62	12	Peritonitis	<i>Enterococcus</i>	0
6	M	59	58	14	Meningitis	MRSA	0
7	F	44	75	13	Pneumonia	MRSA	0
8	M	67	68	12	Blood stream	<i>Enterococcus</i>	0.44
9	M	63	72	13	Blood stream	MRSA	0
10	M	72	62	14	Peritonitis	<i>Enterococcus</i>	0.42

SOFA = sequential organ failure assessment; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*.

TABLE 2
PK/PD Vancomycin Parameters of Individual Patients

Patient	Doses administrated (mg/kg)	C Van		C Van		C Van dialysate (mg/L)	Removal (%)	Peritoneal Cl (mL/min)		Distribution volume (L/kg)
		T1h (mg/L)	T2h (mg/L)	T4h (mg/L)	T24h (mg/L)			Van	Ur	
1	15.3	22.5	19.4	17.3	16.8	9.5	25	12	12.5	0.68
2	21.8	28.6	27.7	25.1	23.8	5.6	16	8.8	10.8	0.85
3	17.2	24.5	21.3	19.3	17.9	8.2	25	9.2	11.5	0.7
4	21.3	28.2	27.6	25	23.1	6.1	18	5.7	8.2	0.74
5	16.1	22.2	19.7	19	17.8	8.1	23	8.3	9.7	0.72
6	17	24.5	21.2	17.3	16.9	9.3	24	6.8	9.1	0.73
7	13.5	32.7	28.6	27.1	25.9	8.1	2	9.7	13.4	0.61
8	19	26.6	22.4	19.6	18.8	9	29	5.3	9.8	0.65
9	14	24.6	22.3	21	20.5	5.2	16	8.1	11.4	0.7
10	22.3	22.1	19.6	19.2	17.7	8.2	22	8.6	10.5	0.62

PK = pharmacokinetics; PD = peritoneal dialysis; C Van = serum concentration of vancomycin; Cl = clearance; Ur = urea.

TABLE 3
Vancomycin Half Life and Area Under Curve of Individual Patients

Patient	Half life (h)	AUC/MIC
1	42.3	424.4
2	64	568
3	52.4	424.5
4	105	557.5
5	52.6	422.5
6	65	490
7	77.5	605
8	53.4	448
9	110	477.5
10	77.6	401

AUC/MIC = area under the curve/minimum inhibitory concentration.

The mean vancomycin peak serum concentration was 26.2 ± 3.5 mg/L, which occurred 1 hour after vancomycin administration and HVPD start. The mean dwell dialysate concentration was 7.3 ± 1.77 mg/L. Figure 2 shows serum vancomycin concentrations during HVPD therapy. Peritoneal clearance was 8.1 ± 2.2 mL/min (5.3 – 12 mL/min) and vancomycin half life during dialysis was 71.2 ± 24.7 hours (42 – 110 hours).

DISCUSSION

The purpose of this study was to characterize the pharmacokinetics of vancomycin and provide dosing recommendations based on a single IV 15 – 20 mg/kg dose of vancomycin in AKI patients treated by HVPD (prescribed Kt/V of 0.5 per session) using 18 – 32 L over 24 hours.

We observed a total vancomycin removal of 21% during HVPD, compared with 10% of vancomycin removal found in continuous ambulatory PD (CAPD), 17% in automated PD (APD), and 37% in intermittent hemodialysis (HD) therapy (11,17–19).

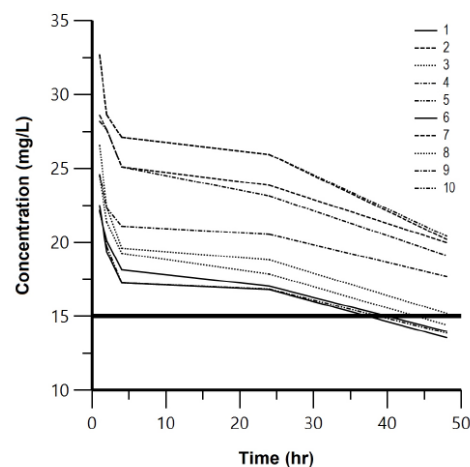


Figure 2 — Serum vancomycin concentrations during high-volume peritoneal dialysis therapy.

Septic patients often present severe hypercatabolism and require a higher dose of renal replacement therapy (17,19). Moreover, the volume of distribution of hydrophilic drugs can differ substantially in AKI patients from that reported in healthy or chronic kidney disease (CKD) patients (17,20). Thus, patients with AKI appear to eliminate vancomycin differently from CKD patients.

Due to high pharmacokinetic variability in AKI septic patients, we recommend daily monitoring of vancomycin concentrations to achieve optimal vancomycin concentrations, and the vancomycin dose can be readministered every 48 – 72 hours to maintain therapeutic serum concentrations in AKI patients undergoing HVPD. In hybrid and conventional HD therapies, the vancomycin dose should be administered

over the last hour of dialysis. This strategy is more practical and the loss of vancomycin may be compensated for by administration of higher vancomycin doses based on therapeutic drug monitoring (17–20). About a 2-fold higher vancomycin intradialytic clearance with high-flux membrane compared to low-flux membrane was observed (18).

The vancomycin concentrations may be lower in patients with residual renal clearance. Clinicians need to evaluate the patients' residual kidney function and properly adjust vancomycin doses. In our study, half of the patients were anuric and the urine output of the oliguric ones ranged from 0.32 to 0.44 mL/kg/h. No significant difference between anuric and nonanuric patients was observed for any pharmacokinetic parameter.

Variability in vancomycin removal in HVPD was modest (16% to 29%) and it is different from that found in studies that described HD removal using low- and high-flux dialysis. Contemporary high-flux membranes eliminate vancomycin with an estimated vancomycin clearance of 43.3 – 120 mL/min, while peritoneal clearance was 8.1 ± 2.2 mL/min ($5.3 - 12$ mL/min).

The vancomycin peak serum concentration occurred 1 hour after vancomycin administration and HVPD start, and vancomycin serum concentrations above 15 mg/L were obtained in all patients at the end of 1 session of HVPD. Vancomycin half life during HVPD sessions was 71.2 ± 24.7 hours (42 – 110 hours). Serum and dialysate concentrations, predicted using a 1-compartment model, suggest that IV vancomycin 18 mg/kg every 72 hours would provide adequate concentrations for susceptible organisms over a 24-hour period.

For achieving clinical effectiveness, the target of vancomycin AUC/MIC ratio is ≥ 400 and the more practical method for monitoring its effectiveness is serum vancomycin concentration >10 mg/L (10–13). All our patients having vancomycin after 1 hour of dialysis start had serum concentrations above 10 mg/L, and a AUC/MIC ratio of at least 400 was achieved in all patients on the study days. The target AUC/MIC ratio was achieved almost only in patients with vancomycin MIC ≤ 1.0 mg/L. In patients with MIC ≥ 1.0 mg/L, a higher vancomycin dose can be necessary, although to achieve this ratio, undesirable vancomycin toxicity can occur (10–13,17).

The remaining pharmacokinetic parameters should not change. However, in critically ill patients, drug pharmacokinetic parameters may be expected to change, especially regarding absorption, distribution, and metabolism, resulting in variations in serum levels. Thus, there is an increased risk of overdosing and drug toxicity, or a subtherapeutic dose and an increased risk of bacterial resistance, infection by opportunistic germs, and mortality (17,19,21).

The removal of antimicrobials by different dialysis therapies in critically ill patients is a complex issue. It depends on the modality and intensity of dialysis, as well as drug characteristics such as water solubility, molecular weight, and the extent of protein binding. There are no validated guidelines to assist in antibiotic dose adjustment in septic patients on acute renal supportive therapy, and the extrapolated recommendations were obtained from studies on noncritical

patients with end-stage CKD receiving substitutive renal therapy (17,20).

CONCLUSIONS

Our study has some limitations, such as the small number of patients studied and the fact that dialysis elimination was considered the only route of vancomycin elimination. We did not consider the role of renal and biliary elimination of vancomycin as possible confounders in the vancomycin plasma reduction. We did not measure urinary vancomycin in nonanuric patients. However, we did the Pearson correlation between individual patient peritoneal vancomycin clearances and % plasma removal and it was excellent ($r=0.73$, $p=0.001$), suggesting minimal extra peritoneal elimination.

One useful outcome of our study is that significant vancomycin removal can be achieved by the HVPD method (around 25%). Occasionally, patients with vancomycin toxicity can be treated with PD, avoiding the need for acute HD. In conclusion, HVPD removes considerable amounts of vancomycin in septic patients with AKI, and antibiotic underdosing is undesirable in these patients. Application of 18 mg/kg vancomycin every 48 – 72 hours in AKI patients undergoing HVPD was required to maintain therapeutic concentrations. Daily vancomycin serum concentration monitoring is recommended to maintain therapeutic concentrations, and vancomycin pharmacokinetics in AKI patients undergoing HVPD warrant further investigation.

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DISCLOSURES

The authors have no financial conflicts of interest to declare.

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Article

Vancomycin for Dialytic Therapy in Critically Ill Patients: Analysis of Its Reduction and the Factors Associated with Subtherapeutic Concentrations

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Abstract: This study aimed to evaluate the reduction in vancomycin through intermittent haemodialysis (IHD) and prolonged haemodialysis (PHD) in acute kidney injury (AKI) patients with sepsis and to identify the variables associated with subtherapeutic concentrations. A prospective study was performed in patients admitted at an intensive care unit (ICU) of a Brazilian hospital. Blood samples were collected at the start of dialytic therapy, after 2 and 4 h of treatment and at the end of therapy to determine the serum concentration of vancomycin and thus perform pharmacokinetic evaluation and PK/PD modelling. Twenty-seven patients treated with IHD, 17 treated with PHD for 6 h and 11 treated with PHD for 10 h were included. The reduction in serum concentrations of vancomycin after 2 h of therapy was $26.65 \pm 12.64\%$ and at the end of dialysis was $45.78 \pm 12.79\%$, higher in the 10-h PHD group, 57.70% (40, 48–64, 30%) ($p = 0.037$). The ratio of the area under the curve to minimal inhibitory concentration (AUC/MIC) at 24 h in the PHD group was significantly smaller than at 10 h ($p = 0.047$). In the logistic regression, PHD was a risk factor for an AUC/MIC ratio less than 400 (OR = 11.59, $p = 0.033$), while a higher serum concentration of vancomycin at T0 was a protective factor (OR = 0.791, $p = 0.009$). In conclusion, subtherapeutic concentrations of vancomycin in acute kidney injury (AKI) patients in dialysis were elevated and may be related to a higher risk of bacterial resistance and mortality, besides pointing out the necessity of additional doses of vancomycin during dialytic therapy, mainly in PHD.

Keywords: sepsis; acute kidney injury; dialysis; vancomycin; pharmacokinetic-pharmacodynamic

1. Introduction

Sepsis is an important cause of acute kidney injury (AKI) in critically ill patients (over 50% of cases), and half of these patients require acute renal support (ARS) [1–4]; therefore, the adoption of measures that aim to reduce mortality, as well as the costs associated with treatment and hospitalization, remain a huge challenge.

Among these measures, early administration of antimicrobial in the appropriate dose is highly impactful [5–7]. However, the pharmacodynamics of antibiotic drugs in critically ill patients are greatly modified and poorly known due to alterations in their absorption, distribution, metabolism and elimination [8–10]. Another as yet unclarified question is the correct adjustment of the antimicrobial dosage in AKI patients and in dialytic therapy [4,11], aiming to avoid toxicity and subtherapeutic concentrations, which may contribute to higher mortality [12].

Vancomycin is a widely used drug in intensive care units (ICUs), as oxacillin-resistant Gram-positive cocci are of the main infectious etiological agents. Vancomycin is a 10–50% protein-bound

glycopeptide with a molecular weight of 1485 Da and a distribution volume of 0.4–1 L/kg, which acts to inhibit cell wall synthesis in Gram-positive bacteria. Regarding its pharmacodynamics, vancomycin is an antimicrobial whose action is both time- and concentration dependent, and the best predictor of its activity is the ratio of the area under the concentration curve (AUC) to minimal inhibitory concentration (MIC) [13].

Due to its molecular weight and partial linkage to proteins, vancomycin is poorly removed by intermittent haemodialysis (IHD) utilizing low-flux dialyzers ($\text{kuf} < 20 \text{ mmHg}$), justifying, in the past, its administration every 7–10 days [14]. However, with the frequent use of high-flux dialyzers, this dosing frequency of vancomycin is being re-evaluated, since 30–40% of the dose might be removed per session in patients in a scheme of chronic intermittent HD, with a likely increase in the amount removed by therapies of longer duration [15–17], such as prolonged HD (PHD) and continuous HD (CHD).

Thus, the objective of this study was to evaluate the reduction in vancomycin by different methods of dialysis (IHD and PHD) in critical patients with AKI associated with sepsis, through a pharmacokinetic approach and pharmacokinetic-pharmacodynamic modelling, in order to identify the factors related to subtherapeutic concentrations.

2. Methods

This was a prospective cross-sectional clinical study that included patients hospitalized in an ICU of the Brazilian University Hospital, over 18 years of age, with AKI and a clinical presentation suggestive of acute tubular necrosis associated with sepsis, in acute renal support (IHD or PHD) and on administration of vancomycin. The following groups were excluded from the study: pregnant women, patients who were not using vancomycin, those that presented AKI of other aetiologies and those in chronic renal replacement therapy (dialysis or renal transplant). Patients who had their dialytic session interrupted for clinical or technical reasons were also excluded. The research project was approved by the local Commission of Ethics in Research in March of 2015 (protocol 1,477,511). Free and informed consent was given in writing by each patient before the start of the study procedures.

Patients were allocated into three groups according to the type of dialytic treatment prescribed by the nephrology assistant team, based on the patient's hemodynamic conditions and on the indications and contraindications of each dialysis method: IHD, 6-h PHD and 10-h PHD.

The prescription of vancomycin followed a protocol instituted by the institution's Commission of Control of Infections Related to Health Assistance, being administered in an initial dose of 20 mg/kg and 15 mg/kg/day after haemodialysis session, since all patients utilized high-flux hemodialysis membranes [15]. The dosage was adjusted according to the serum levels of vancomycin, which were assayed on alternate days.

Proportion machines (*Fresenius 4008*) and high-flux hemodialysis membranes (FX 60, FX 80 or FX 100), with surface areas of 1.8, 2.0 and 2.2 m², respectively, were used in IHD and PHD sessions. The IHD sessions were carried out with blood flow of 250 to 300 mL/min; a dialysate flow of 500 mL/min and FX 60, FX 80 or FX 100 hemodialysis membranes for 4 h. The PHD session was carried out with a blood flow of 200 mL/min, a dialysate flow of 300 mL/min and an FX 80 hemodialysis membrane when the prescribed duration was 6 h and an FX 60 hemodialysis membrane when the prescribed time was 10 h.

During the sessions, patients were anticoagulated with 50–100 UI/kg of heparin in a bolus, and 500–1000 UI/hour in the remaining hours. When anticoagulation was contraindicated, the system was cleaned with 50–100 mL of 0.9% sodium chloride every 30 min during the procedure. Concentrations of bicarbonate (28–36 mEq/L), potassium 1–4 mEq/L, sodium (135–142 mEq/L) and calcium (2.5 or 3.5 mEq/L) in the dialysis bath were adjusted according to the patients' individual requirements and examinations.

A serialized collection of blood samples (2 mL each) was carried out through a central venous catheter for the determination of serum concentrations of vancomycin before starting dialysis, 2 and

4 h after the beginning of therapy and at the conclusion of therapy. The previous vancomycin dose was received 24 h before the dialysis session. Figure 1 depicts the dialysis procedure, administration of vancomycin and sampling moments.

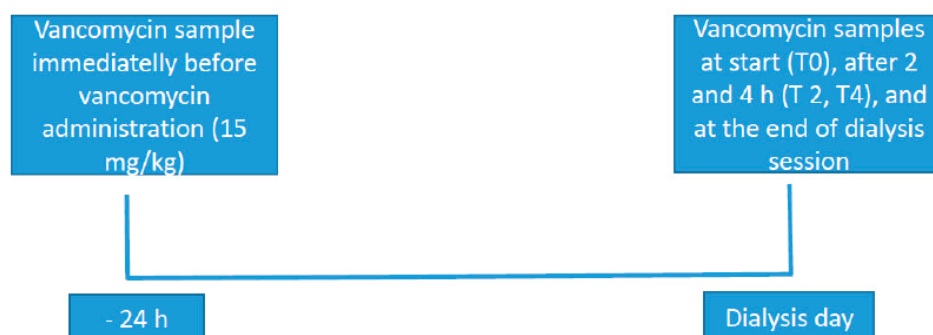


Figure 1. Dialysis procedure, administration of vancomycin and sampling.

The collected blood was transferred to vacuum collection tubes (10 mL) containing Benton Dickinson (BD) gel and kept in styrofoam or in a refrigerator until the last collection of the day, when they were forwarded to the laboratory. There, serum was separated by centrifugation (3000 g, 20 min) and transferred to properly labelled 2-mL microcentrifuge tubes (Eppendorf). Serum samples were stored in a temperature-controlled freezer at -20°C .

Vancomycin concentrations were determined using a liquid chromatographic (HPLC)-fluorescence method as reported previously by Lopez et al. [18]. Blood samples were centrifuged within 4 h of collection and serum was stored frozen at -80°C until assayed. The pharmacokinetic (PK) parameters volume of distribution (Vd) and elimination half-life ($T_{1/2}$) were calculated for each patient assuming a 1-compartment model. The area under the curve (AUC) was determined using the trapezoidal rule to the last non-zero time point. The AUC from the last non-zero time point was determined by the pharmacokinetic method, concentration/k, where k is the elimination rate constant determined from log-linear regression of the terminal phase of the concentration-time profile. Table 1 shows the formulas utilized for the calculation of vancomycin pharmacokinetic (half-life time, volume of distribution (L), dialytic clearance of vancomycin (L/h) and % reduction in vancomycin).

Table 1. Formulas utilized for the calculation of Vancomycin pharmacokinetic [18–20].

Pharmacokinetic	Formula
Distribution Volume (L)	$VD = \text{Vancomycin dose (mg)} / \text{concentration of vancomycin (mg/L)}$
Dialytic Clearance of vancomycin (L/h)	$Cl_{\text{vanco}} = (\text{Initial} - \text{final concentration}) / \text{Initial concentration} \times QD/t$
Half-life time	$T_{1/2} \text{ life} = 0.693 \times VD / Cl$
% reduction in vancomycin	$\% \text{ red} = (C_{\text{pre HD}} - C_{\text{final HD}}) / C_{\text{pre HD}} \times 100$

VD: Distribution volume. Cl_{vanco} : Dialytic Clearance of vancomycin. QD: Dialysate fluxo (L/h). t: time h). $T_{1/2}$ life: half-life time. $C_{\text{pre HD}}$: concentration of vancomycin pre hemodialysis. $C_{\text{final HD}}$: Concentration of vancomycin at the end of hemodialysis.

Pharmacodynamic (PD) data are related to the MIC obtained by the antimicrobial susceptibility testing done for each pathogen in the Microbiology Laboratory after the strain documentation. The predictive index of vancomycin effectiveness is expressed by AUC 0-24/MIC ratio >400 [21,22]. The MIC considered for the calculation of AUC/MIC was 1, since not all patients had positive cultures, and the majority of works consider this MIC in their models.

3. Statistical Analysis

A sample size calculation was performed [23], considering the removal of 20% of the drugs by the high-flux membranes during the first 2 h of the IHD session and of at least 40% at the end of the session, with an alpha error of 0.05 and a study power of 80%. A minimum samples size of 50 patients was determined.

The data obtained in the study were organized in Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA, USA) sheets and posteriorly analysed with the statistical program *Sigma stat* 3.5.

Patients were compared initially according to the modality of HD (IHD vs. 6-h PHD vs. 10-h PHD). Since the best predictor of vancomycin activity is AUC/MIC and, in the literature [24], it is recommended that this ratio be maintained above 400 for the best clinical outcomes, this cut-off point was utilized to compare the patients in which it was possible to construct the 24-h AUC from clinical data.

In the descriptive statistics, data were analysed initially regarding distribution. For continuous variables, as measures of central tendency, the mean and standard deviation were used for normally distributed data, and the median and interquartile range for data with a non-normal distribution. For categorical variables, the measures of frequency and the chi-squared test were used for between-group comparisons. For comparison of continuous variables, the parametric Student's *t*-test and ANOVA and the non-parametric Wilcoxon and Mann–Whitney tests were used. From the univariate analysis, the variables that presented $p < 0.1$ and were not co-linear were included in the multiple logistic regression analysis.

4. Results

From March 2015 to August 2017, 27 patients treated with IHD, 17 patients treated with PHD for 6 h and 11 patients treated for PHD for 10 h were included.

Tables 2 and 3 show the clinical, laboratory and dialytic characteristic of the 55 analysed patients. The mean age was 62 ± 13.12 years, with a predominance of the male sex (67.3%); the main comorbidities were systemic arterial hypertension (72.2%), diabetes mellitus (50%) and cardiovascular disease (49.1%). The most prevalent hospitalization diagnosis was sepsis (63.6%), and the lungs were the most frequent focus (67.2%). When compared with respect to their clinical characteristics, the groups were statistically significantly different regarding the prevalence of systemic arterial hypertension ($p = 0.03$), cardiovascular disease ($p = 0.035$) and sepsis as a hospitalization diagnosis ($p = 0.02$), all of which were more frequent in the IHD group when compared with the other groups.

The illness severity of the studied patients was evaluated by using the prognostic score APACHE II, which obtained a mean of 29.64 ± 7.56 , and the prognosis regarding acute renal lesion by the LIANO score, which obtained a median of 0.75 (0.6–0.87). The groups differed significantly regarding APACHE II score and noradrenaline dose, which were higher in the 6-h PHD and 10-h PHD groups, respectively ($p = 0.042$ and $p < 0.001$). There was no difference ($p = 0.27$) between groups with respect to mortality, the frequency of which was 74.54% in the study population.

In the 55 patients analysed, the mean dose of vancomycin was 15.51 ± 7.35 mg/kg/day, with no significant difference between dialytic treatments ($p = 0.053$). During the study period, the median number of days of vancomycin administration was 5 (2–10), with no difference between dialytic treatment groups ($p = 0.393$) and with the patients who were already in dialytic therapy for 4 days (3–7), with no difference between dialytic treatment groups ($p = 0.152$).

Table 2. Clinical characteristics of the general population and of the groups according to the different dialytic treatments.

Variables	General (n = 55)	IHD (n = 27)	PHD 6 h (n = 17)	PHD 10 h (n = 11)	p
Age (Years)	62.61 ± 13.12	63.30 ± 13.86	61.94 ± 14.15	62 ± 10.36	0.934
Male sex (%)	37 (67.3)	17 (62.86)	13 (76.47)	6 (54.54)	0.457
Weight (kg)	75.07 ± 24.20	71 (64–84.75)	69 (57.32–77.75)	62 (58.50–85.75)	0.594
Comorbidities					
Diabetes (%)	28 (50.0)	13 (48.15)	10 (58.82)	5 (45.45)	0.726
Hypertension (%)	40 (72.72)	24 (88.89) ^a	10 (58.82) ^b	6 (54.54) ^b	0.030
Cardiovascular disease (%)	27 (49.09)	18 (66.67) ^a	5 (29.41) ^b	4 (36.36) ^{ab}	0.035
Obesity (%)	9 (16.36)	3 (11.11)	2 (11.76)	4 (36.36)	0.134
Neoplasia (%)	6 (10.90)	2 (7.41)	2 (11.76)	2 (18.18)	0.621
Smoking (%)	25 (45.45)	11 (40.74)	8 (47.06)	6 (54.54)	0.731
Chronic Kidney Disease (%)	4 (7.27)	2 (7.40)	1 (5.88)	1 (9.09)	0.950
Other (%)	30 (54.54)	13 (48.15)	10 (58.82)	7 (63.64)	0.626
Hospitalization Diagnostic					
Sepsis (%)	35 (63.64)	22 (81.48) ^a	7 (41.18) ^b	6 (54.54) ^b	0.02
Acute abdomen (%)	7 (12.73)	3 (11.11)	3 (17.65)	1 (9.09)	0.754
Acute Coronary Syndrome (%)	6 (10.90)	5 (18.6)	1 (5.88)	0	0.183
Trauma (%)	3 (5.45)	1 (3.70)	1 (5.88)	1 (9.09)	0.799
Elective Surgery (%)	7 (12.73)	2 (7.41)	3 (17.65)	2 (18.18)	0.508
Other (%)	3 (5.45)	1 (3.70)	0	2 (18.18)	0.100
Arterial Thrombosis (%)	7 (12.73)	5 (18.52)	2 (11.76)	0	0.172
Infectious Focus					
Lung (%)	37 (67.27)	21 (77.78)	9 (52.94)	7 (63.64)	0.223
Urinary (%)	3 (5.45)	2 (7.41)	1 (5.88)	0	0.657
Abdominal (%)	6 (10.90)	1 (3.70)	3 (17.65)	2 (18.18)	0.242
Cutaneous (%)	5 (9.09)	1 (3.70)	1 (5.88)	3 (27.27)	0.062
Other (%)	6 (10.90)	3 (11.11)	3 (17.65)	0	0.343
APACHE II	29.64 ± 7.56	27.16 ± 7.930 ^a	33.06 ± 7.07 ^b	30.00 ± 5.59 ^{ab}	0.042
LIANO	0.75 (0.6–0.87)	0.72 (0.54–0.78)	0.78 (0.71–0.84)	0.89 (0.44–0.89)	0.163
Death (%)	41 (74.54)	19 (70.37)	15 (88.23)	7 (63.63)	0.27

^a significantly different from ^b. ^{ab}: similar to ^a and ^b. IHD: conventional intermittent dialysis. PHD 6 h: Hemodialysis prolonged for 6 h. PHD 10 h: Hemodialysis prolonged for 10 h.

Table 3. Laboratory and dialytic characteristics of the general population and of the groups according to different dialytic treatments on the day of the study.

Variables	General (n = 55)	IHD (n = 27)	PHD 6 h (n = 17)	PHD 10 h (n = 11)	p
Noradrenaline (mcg/kg/min)	0.25 (0.05–0.5)	0.05 (0.0–0.14) ^a	0.5 (0.33–0.8) ^b	0.45 (0.38–0.57) ^b	<0.001
Urinary Volume (mL/24 h)	200 (50–650)	300 (133–950)	150 (27.5–800)	100 (0.0–260)	0.072
Hematocrit (%)	27.85 ± 3.89	26.5 (23.8–28.9)	27.9 (26.75–30.35)	27.8 (26.8–29.9)	0.062
PCR (mg/L)	27.1 (7.3–33.7)	25.8 (5.50–31.82)	23.2 (8.12–35.3)	27.8 (23.8–35.1)	0.518
Albumin (g/dL)	2.18 ± 0.49	2.21 ± 0.43	2.17 ± 0.51	2.11 ± 0.67	0.049
Ultrafiltration (mL)	1901.82 ± 1148.19	2018.52 ± 1138.84	1564.71 ± 1225.22	2136.36 ± 1026.91	0.339
Kt/V	0.89 ± 0.33	0.86 ± 0.28	0.82 ± 0.35	1.08 ± 0.36	0.093
Intradialytic hypotension	9 (16.36)	4 (14.81)	4 (23.52)	1 (9.09)	0.574

^a significantly different from ^b. IHD: conventional intermittent dialysis. PHD 6 h: Hemodialysis prolonged for 6 h. PHD 10 h: Hemodialysis prolonged for 10 h. PCR: reactive protein C.

The distribution volume was higher and the half-life of vancomycin was longer in the PHD group when compared with the IHD group ($p < 0.001$); however, the dialytic clearance of vancomycin was lower in the PHD group, calculated in L/h, as described in Table 4. In the beginning of dialysis, serum concentrations of vancomycin were higher in patients treated with IHD, and this difference was maintained after 2 h ($p < 0.001$) and at the end of dialysis ($p < 0.001$). Groups were similar regarding AUC/MIC during HD but differed statistically significantly with respect to AUC/MIC at 24 h, this ratio being smaller in the 10-h PHD group ($p = 0.047$).

Table 4. Characteristics associated with the prescription of vancomycin and to the pharmacodynamic and pharmacokinetic of the drug in the general population and on the groups according to different dialytic treatments on the day of the study.

Variables	General (<i>n</i> = 55)	IHD (<i>n</i> = 27)	PHD 6 h (<i>n</i> = 17)	PHD 10 h (<i>n</i> = 11)	<i>p</i>
Vancomycin days	5 (2–10)	7 (3–12)	5 (2–6.5)	4 (2–12)	0.39
Vancomycin dose (mg/kg/dia)	15.5 ± 7.3	13.9 (8.6–15.4)	14.7 (13.5–18.0)	18.7 (12.0–24.6)	0.05
Vancomycin concentration before analysis (mg/L)	19.6 (16–27.8)	20.9 (17.8–31.5)	20.2 (15.4–27.7)	17.9 (14.1–23.0)	0.61
Distribution volume (L/Kg)	0.6 (0.4–0.85)	0.40 (0.29–0.62) ^a	0.8 (0.61–1.0) ^b	0.7 (0.59–1.29) ^b	<0.001
Half-life time (h)	17.4 (6.7–32.6)	6.70 (4.2–11.9) ^a	27.6 (19.5–74.4) ^b	38.4 (30.62–74.78) ^b	<0.001
Vancomycin dialytic Clearance (L/h)	1.9 (1.13–3.23)	3.2 (2.54–3.68) ^a	1.3 (0.93–1.72) ^b	1.0 (0.75–1.15) ^b	<0.001
Vancomycin concentration (mg/L) at T0	26.0 (15.9–35.9)	34.2 (22–44) ^a	13.4 (10.7–18.4) ^b	23.1 (13.6–31.0.6) ^{ab}	<0.001
Vancomycin concentration at T 2 h (mg/L)	17.7 (11.39–28.2)	22.8 (17.45–33.04) ^a	11.1 (8.36–15.26) ^b	16.6 (9.45–19.03) ^b	<0.001
Vancomycin concentration at T final (mg/L)	14.2 (8.7–20.9)	20.26 ± 9.91 ^a	11.32 ± 5.71 ^b	10.6 ± 5.96 ^b	<0.001
% of reduction in 2 h	26.6 ± 12.6	25.5 ± 12.5	25.3 ± 13.3	31.5 ± 11.8	0.36
% Total reduction	45.7 ± 12.79	43.1 (33.2–49.8) ^a	44.7 (32.9–57.9) ^{ab}	57.7 (40.5–64.3) ^b	0.03
AUC/MIC 24 h	411.37 (326.64–580.17)	504.2 (409.8–840.1) ^a	410.65 (336.34–565.39) ^{ab}	328.53 (302.36–372.39) ^b	0.04
AUC/MIC during analysis	138.0 (99.6–215.2)	169.8 (112.5–235.3)	103.0 (94.8–178.1)	124.7 (92.8–185.1)	0.13

^a significantly different from ^b. ^{ab}: similar to ^a and ^b. IHD: conventional intermittent dialysis. PHD 6 h: Hemodialysis prolonged for 6 h. PHD 10 h: Hemodialysis prolonged for 10 h. T final: final time of dialysis. AUC/MIC: area under the curve/minimum inhibitory concentration.

After 2 and 4 h of dialysis, there was no difference between groups regarding the reduction in the serum concentration of vancomycin (25.49 ± 12.49 vs. 25.32 ± 13.32 vs. 31.54 ± 11.86, *p* = 0.363 and 43.07 ± 10.06 vs. 39.28 ± 12.11 vs. 41.54 ± 12.69, *p* = 0.720, respectively). Vancomycin reduction during dialytic therapy was significantly higher in the 10-h PHD group when compared with the IHD group (43.07 ± 10.06 vs. 57.7 ± 12.13, *p* = 0.003; Figure 2). Before the dialysis session, 43 patients (78.2%) presented therapeutic vancomycin concentrations. At the end of dialysis, only 23 (41.8%) had therapeutic levels and there was a significant difference between patients treated by IHD vs. PHD (74 vs. 20%, *p* = 0.004). Of the 32 patients who had subtherapeutic concentrations, most of them were treated by PHD (68 vs. 32%, *p* = 0.004).

In order to identify the factors related to the therapeutic subconcentration of vancomycin, patients were analysed according to AUC/MIC, with a cut-off of 400, as recommended in the literature [24].

The AUC at 24 h was determined for 41 patients, 19 (46.34%) of whom presented AUC/MIC ratios less than 400. In the univariate analysis, the factors associated are highlighted in Table 5. The variables modality of dialytic therapy, distribution volume (L/kg), dialytic clearance (L/h) and serum concentration of vancomycin at T0 were included in the logistic regression model. The variables half-life and AUC/MIC during dialysis were excluded from the model because they were covariable with the rest. PHD was associated with AUC/MIC smaller than 400 (OR = 11.59, IC 95% 1.219–110.171, *p* = 0.033), while the higher serum concentration of vancomycin at T0 was a protective factor for AUC/MIC smaller than 400 (OR = 0.791, IC 95% 0.664–0.942, *p* = 0.009) (Table 6).

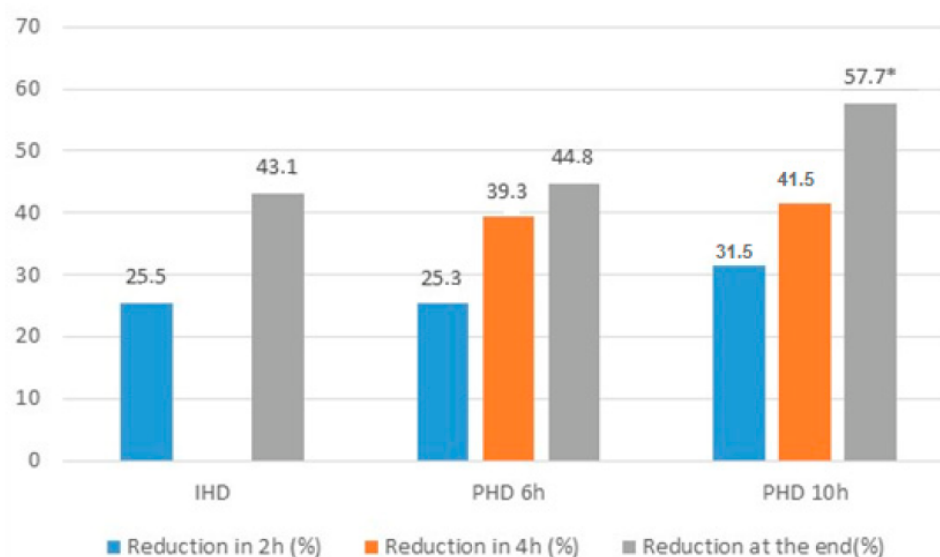


Figure 2. Reduction of vancomycin in 2 h, 4 h and at the end of dialysis in the groups HDI, HDP 6 h and HDP 10 h. * $p < 0.05$ PHD 10 h vs. IHD, $p < 0.05$.

Table 5. General characteristics of the population according to the area under the curve/minimum inhibitory concentration of Vancomycin.

Variables	General Population (<i>n</i> = 41)	AUC/MIC 24 h <400 (<i>n</i> = 19)	AUC/MIC 24 h >400 (<i>n</i> = 22)	<i>p</i>
Age (years)	65.00 (56.50–72.50)	65.00 (57.00–74.00)	65.00 (53.75–72.25)	0.724
Male sex (%)	15 (36.41)	14 (73.68)	12 (54.54)	0.345
Weight (kg)	70.00 (60.50–82.50)	71.00 (62.00–86.00)	70.00 (54.25–74.25)	0.36
APACHE II	32.00 (26.00–36.00)	32.47 ± 6.04	28.91 ± 7.79	0.114
LIANO	0.77 (0.61–0.89)	0.83 ± 0.72	0.75 ± 0.51	0.123
Noradrenaline (mcg/kg/min)	0.33 (0.06–0.53)	0.38 (0.20–0.57)	0.15 (0.00–0.52)	0.11
Urinary volume (ml/24 h)	200.00 (40.00–425.00)	100.00 (25.00–450.00)	200.00 (45.00–500.00)	0.591
Hematocrite (%)	28.10 ± 3.87	27.39 ± 3.75	28.71 ± 3.95	0.281
PCR (mg/L)	24.80 (6.60–33.65)	25.78 ± 14.67	19.12 ± 14.30	0.15
Albumin (g/dL)	2.18 ± 0.49	2.14 ± 0.51	2.23 ± 0.48	0.587
Conventional hemodialysis (%)	16 (39.02)	3 (15.79)	13 (59.10)	0.012
Prolonged hemodialysis 6 and 10 h (%)	25 (60.98)	16 (84.21)	9 (40.90)	0.012
Kt/V	0.89 ± 0.33	0.90 ± 0.35	0.88 ± 0.31	0.814
Dose of Vancomycin (mg/kg/day)	14.71 (12.69–19.37)	14.71 (10.71–20.00)	14.60 (13.29–17.86)	0.734
Volume of distribution (L/Kg)	0.67 (0.45–0.87)	0.73 (0.61–1.34)	0.56 (0.34–0.83)	0.018
Half-life time	19.67 (9.36–38.14)	28.38 (17.51–79.69)	11.22 (5.99–26.28)	0.004
Vancomycin dialytic clearance(L/h)	1.69 (1.03–3.05)	1.19 (0.95–1.70)	2.39 (1.15–3.55)	0.017
Vancomycin concentration (mg/L) at T0	23.59 (14.92–33.87)	14.96 (13.19–24.20)	32.83 (21.47–37.95)	0.001
% of reduction in 2 h	26.52 ± 13.29	27.18 ± 12.23	25.94 ± 14.41	0.771
% Total reduction	46.98 ± 13.05	50.56 ± 14.62	43.90 ± 10.95	0.104
AUC/MIC during dialysis	120.44 (94.85–211.45)	103.07 (87.35–169.25)	172.43 (108.01–252.98)	0.016
Death (%)	30 (73.17)	16 (84.21)	14 (63.64)	0.259

AUC/MIC: area under the curve/minimum inhibitory concentration.

Table 6. Logistic regression of the variables associated to AUC/MIC < 400.

Variables	Odds Ratio	Confidence Interval	<i>p</i>
Prolonged hemodialysis	11.59	1.219–110.171	0.033
Distribution volume (L/Kg)	0.197	0.0123–3.153	0.251
Dialytic clearance of vancomycin (L/h)	1.614	0.391–6.672	0.508
Serum concentration of vancomycin (mg/L) at T0	0.791	0.664–0.942	0.009

5. Discussion

The objective of this study was to evaluate the reduction in plasma vancomycin concentration during different dialytic modalities and to identify the factors associated with the therapeutic concentration. Although the literature about vancomycin is vast, few studies have taken this approach. Most of the existing studies about antimicrobial dosage in critically ill patients in dialytic therapy were carried out on a population treated with continuous therapy [25–27]. This haemodialytic method is utilized most often by nephrologists and intensivists in developed countries, on top of being a therapy that frequently utilizes convective processes, which have a high capacity to remove molecules with higher molecular weights, like vancomycin.

On the other hand, IHD is still the main dialytic method utilized in developing countries. The majority of studies about the use of antimicrobials in IHD were realized in patients with chronic kidney disease (CKD) receiving a treatment plan of HD three times per week [28]. Although there are many studies and developed protocols, even for the CKD patients, there are still variations, controversies and inconsistencies in the literature regarding the dosage of vancomycin, involving the dosage and administration interval and the monitoring of its serum levels [28]. Even then, these recommendations are also utilized for AKI patients, despite the pharmacokinetic and pharmacodynamic alterations of the drugs used in these critically ill patients.

PHD consists of a hybrid method, with characteristics of IHD and continuous HD, and also gives adequate blood volume and metabolic control to the critically ill patient at a lower cost than continuous HD, thus being an alternative therapy to it. Studies that deal with antimicrobial dosage are still rare in this modality of HD [29,30], because they present parameters such as blood flow and dialysate and the duration of therapy as being too variable, making it difficult to design studies and protocols. Thus, generally, antibiotic dosage recommendations are utilized for IHD and CHD; however, as shown in the studies of Keough et al. [31] and Harris et al. [32], there is a great variation in the prescription of antibiotics in prolonged haemodialysis patients and the utilized dosages are frequently inadequate, possibly resulting in subtherapeutic concentrations. Lewis and Muller [33], using a mathematical model of Monte Carlo simulation applied to four different PHD prescriptions, showed that vancomycin administered at an initial dose of 15–20 mg/kg followed by 15 mg/kg after PHD would effectively reach the pharmacodynamic target in patients with *S. aureus* infections with an MIC of vancomycin ≤ 1 mg/L during the first 48 h of therapy. After this period, it is recommended that dosages be individualized according to the serum concentrations of vancomycin and that they follow the nomogram from the AUC/MIC in 24 h. However, those recommendations are not validated by clinical studies. The patients in our study received a dose of vancomycin of, on average, 15.51 ± 7.35 mg/kg after dialysis and, even within the doses recommended by previous studies, we found 46.34% of patients to have subtherapeutic concentrations of vancomycin (AUC/MIC < 400), 84.2% of whom were receiving prolonged haemodialysis. If an MIC of 2 was utilized, practically all patients would be below the recommended value. When the modalities of HD were compared, 10-h PHD showed the lowest ASC/MIC in 24 h (504.2 (409.8 – 840.1) vs. 410.65 (336.34 – 565.39) vs. 328.53 (302.36 – 372.39), $p = 0.0473$), lower than what is recommended as therapeutic by the majority of the infectiology guidelines²⁶.

When the pharmacokinetic and pharmacodynamic parameters were analysed comparing the methods of HD, PHD patients were observed to have a higher distribution volume and longer half-life. Ahern et al. [34], upon analysing the pharmacokinetics of vancomycin in prolonged haemodialysis patients, also saw a prolonged and variable half-life (43.1 ± 21.6 h) and higher distribution volume

(0.84 ± 0.17 L/kg). It is possible that the findings of our work are related to a higher disease severity, characterized by higher APACHE II scores in the 6-h and 10-h PHD groups. In critical patients, due to the decrease in albumin synthesis, the passing of more protein into the extracellular space related to alterations of permeability and to uraemia itself, there is less binding of the drug to proteins, contributing to the increase in distribution volume [10] and, thus, to the higher serum concentration of vancomycin at the start of dialysis in the patients of the present study. It is important to highlight that the 6-h and 10-h PHD groups did not differ from the IHD group with respect to the administered vancomycin dose ($p = 0.053$), but there was a statistical tendency toward a higher dosage in the 10-h PHD group. PHD presented smaller dialytic *clearance* in L/h but a higher reduction in vancomycin at the end of dialysis, probably related to the longer duration of dialysis.

Despite AUC/MIC being the best predictor of the efficacy of vancomycin, there are few studies in the literature that utilize this parameter in patients undergoing renal replacement therapy, and these works focus on a treatment plan of haemodialysis for chronic renal disease [35], since *Staphylococcus aureus* infections are frequent in these patients. Thus, our study stands out by analysing the factors associated with lower AUC/MIC in 400 AKI patients in different dialytic modalities. In the multiple logistic regression, 10-h PHD was independently associated with an AUC/MIC lower than 400, while a higher serum concentration of vancomycin at the start of dialysis was a protective factor.

In contrast to previous studies that examined the removal of vancomycin during HD in critical patients, the present study included only patients in whom high permeability was used for all modalities, allowing for the evaluation of other factors such as time and dialytic *clearance*. The reduction in vancomycin at the end of therapy, calculated from the serum dosage of vancomycin at the start, at 2 h and at the end of dialytic therapy, was 43.13% for IHD, 44.23% for 6-h PHD and 57.70% for 10-h PHD, $p = 0.042$. Our results were higher than those found by Golestaneh et al. [36], which presented a reduction of 36% in 10 patients receiving PHD with a duration of at least 8 h. When they analysed the removal of vancomycin from dialysate in patients with sepsis and AKI treated with PHD using high-flux membranes, Kielstein et al. [37] observed 26% removal of vancomycin from the dialysate. In a study by our group, the removal of vancomycin through high-volume peritoneal dialysis was 21.7% [38].

Our study presents some limitations. Its design was cross-sectional, since patients were analysed in a single moment. It was realized in a single centre, including only 55 patients. A backfire effect was not considered, given by the redistribution of vancomycin from the tissues to the bloodstream, which may lead to an increase of 30–40% in serum levels of vancomycin 4–6 h after the end of intermittent haemodialysis [39]. This effect is lower in PHD, due to the higher duration of dialysis, resulting in a higher distribution of the drugs through the tissues along the therapy. Vancomycin was not dosed in the dialysate for the calculation of its removal by dialytic therapy, because, on top of the increased costs that this would have incurred, our study included only high-flux membranes and evaluated different durations of PHD with the goal of identifying the factors associated with higher reduction and therapeutic concentrations. Moreover, the obtained results serve as orientation for new studies and proposals of antimicrobial dosage in critically ill patients, those with AKI and undergoing renal replacement therapy, which are difficult to evaluate from the point of view of drug pharmacokinetics and pharmacodynamics, since they are subjected to various alterations, many of which are still not fully understood in the literature.

6. Conclusions

Our study in septic AKI patients treated by HD with high-flux membranes showed a high prevalence of patients that do not reach therapeutic concentrations, especially in the population treated by PHD. Such results may be related to a higher risk of bacterial resistance and mortality, besides pointing out the necessity of additional doses of vancomycin during prolonged haemodialysis and not only at the end of therapy as realized in clinical practice. However, future studies are necessary to evaluate vancomycin dosage protocols in critical patients in IHD or PHD that have the objective of

guaranteeing therapeutic concentrations. These will be of great relevance for developing countries, where such dialytic methods are more often utilized, and serum analysis of vancomycin for the adjustment of the drug is not always available.

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Serum Concentration of Vancomycin Is a Diagnostic Predictor of Nephrotoxic Acute Kidney Injury in Septic Patients in Clinical and Surgical Wards

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Introduction and Aim: 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.

Methodology: This was a cohort-unicentric study that evaluated septic patients aged >18 years using vancomycin admitted to clinical and surgical wards of a Brazilian university center from August 2016 to July 2017 in a daily and uninterrupted way. We excluded patients with AKI prior to the introduction of vancomycin or with AKI development <48 hours after use, patients with AKI of other etiologies, stage V chronic kidney disease, and pregnant women.

Results: We evaluated 225 patients, and 135 were included. Evaluation of serum concentration of vancomycin was realized in 94.1%, and of those, 59.3% presented toxic concentrations. The prevalence of AKI was 27.4% and happened on average on the ninth day of vancomycin usage. Between the fourth and sixth days, vancomycin serum concentration of >21.5 mg/L was a predictor of AKI, with area under the curve of 0.803 (95% CI 0.62–0.98, $p=0.005$), preceding the diagnosis of AKI by at least 3 days. Of these patients, 20.7% died, and serum concentrations of vancomycin between the fourth and sixth days were identified as risk factors associated with negative outcomes.

Conclusion: Serum concentration of vancomycin is an excellent predictor of AKI in patients admitted to wards, preceding the diagnosis of AKI by at least 72 hours. Toxic concentrations of vancomycin are associated with AKI, and AKI was a risk factor for death. Also, serum concentration of vancomycin >21.5 mg/L was the only variable associated with death in the Cox model.

Keywords: sepsis, acute kidney injury, vancomycin, nephrotoxicity

Introduction

Sepsis is defined as an organic dysfunction that threatens life, caused by an exacerbated response to an infection.^{1,2} It implies the failure of multiple organs, including the kidneys.^{3–5} As such, the adoption of measures that lead to decreased mortality and reduced costs related to treatment and hospitalization, such as early administration of antimicrobials, the choice of which should be based on the patient's history, the recent use of antibiotics and the origin of the pathogens (community or hospital), are justified.⁶

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The main polemic points on vancomycin relate to its efficacy and safety.^{5–9} Regarding efficacy, the concern is the alteration in pharmacokinetics, usually related to the distribution, metabolism, and elimination of the drug,^{6,8} which can lead to subtherapeutic concentrations, leading to the emergence of bacterial resistance due to the inefficacy of the treatment and consequently leading to higher mortality. Regarding safety, emphasis has been given to the main side effect of the medication — nephrotoxicity — which can aggravate the clinical picture and contribute to unfavorable outcomes.

Based on studies of animal and clinical experimentation, in 2009 it was determined that optimum activity occurs with an area under the curve divided by the minimum inhibitory concentration value of equal or greater than 400. It was identified that this value is reached when trough serum concentrations of vancomycin (when the medicine is at a lower concentration) is 15–20 mg/L for major infections.^{10,11} However, there have been few studies to evaluate monitoring of its serum concentration and association with clinical outcomes, requiring improvement in knowledge regarding the safe and effective use of vancomycin.

Methodology

This was a prospective observational cohort study of adult patients diagnosed with sepsis defined using the quick SOFA² and admitted to four wards at the Clinics Hospital of Botucatu Medical School (two clinical and two surgical) 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 antimicrobial. We excluded patients aged <18 years, pregnant patients, those with chronic kidney disease stage 5 (classified according to estimated serum-creatinine clearance or measured

at <15 mL/min), renal transplant recipients, patients already admitted with an acute kidney injury (AKI) of any etiology, vancomycin use <48 hours, and those who had developed AKI from another etiology (prerenal or ischemic, glomerular, and vascular renal causes).

The study was approved by the local research ethics committee and registered in the Brazilian Registry of Clinical Trials (ReBEC) under number RBR-4zrwzt. Patients or legal guardians signed the informed consent form. From the time of prescription of vancomycin, the patient was included in the study and their electronic medical record consulted, and daily evolution data obtained, always by the same observer, until the end of the use of vancomycin and its hospital outcome (discharge or death).

The AKI definitions used were those of the organization Kidney Disease: Improving Global Outcomes (KDIGO):⁵ baseline creatinine being the lowest value in 6 months if no prior data available or lower creatinine levels during hospitalization as long as the patient was not on dialysis. Therapeutic, subtherapeutic, and toxic serum concentrations were defined as two consecutive trough concentrations of 15–20 mg/L, <15 mg/L, and >20 mg/L, respectively.

Central tendency and dispersion were calculated as continuous and frequency values for the categorical variable and occurrence of AKI and death were established as dependent variables. ROC curves were built to evaluate the cutoff points for serum-vancomycin concentration as predictors of diagnosis and prognosis of AKI during T0–T2, T2–T4, and T4–T6. Areas under the curve of 0.7–0.79 were considered satisfactory and 0.8–0.89 as optimum. Sample-size calculation was performed using Lee's formula, and considering that the prevalence of AKI would be 20% higher in patients with toxic concentrations of vancomycin, with α -error of 0.05 and 80% study power, 64 patients were estimated for each group (total 128: 64 with toxic concentrations and 64 without).

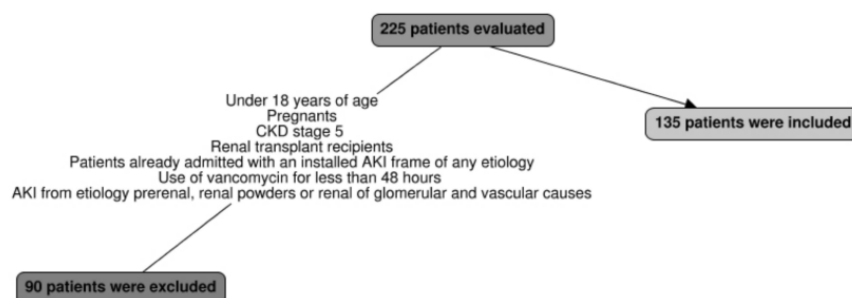


Figure 1 Flow diagram of patients included and excluded.

Results

We included 135 patients from clinical and surgical wards (Figure 1), of which 94.1% had serum concentrations of vancomycin measured during the use of the antimicrobial. Of these, 75.6% received adjustments in dosage and 59.3% presented a toxic serum concentration of vancomycin. The mean higher value for serum concentration was 22.07 ± 14.77 mg/L, 27.4% of the patients presented with AKI, of which KDIGO stage 1 was the most frequent (54.05%), and 20.7% evolved to death.

Table 1 presents clinical and laboratory characteristics of the patients and Table 2 vancomycin-related characteristics,

both regarding the presence or absence of AKI. In Cox regression analysis, serum concentration of vancomycin during 96–144 hours (T4–T6, HR 1.06; $p=0.038$) was identified as the only risk factor for AKI, as indicated in Table 3. The rest of the variables did not present statistically significant differences between the groups.

ROC-curve analysis (Figure 2) showed that serum concentration >21.5 mg/L between the fourth and sixth days was a good predictor of AKI, with area under the curve of 0.8 (95% CI 0.62–0.98), sensitivity of 81.1%, specificity of 73.7%, and preceding diagnosis of AKI by at least 3 days (AKI happened on average at the ninth day of vancomycin use). After

Table 1 Clinical and Laboratory Characteristics of Patients Using Vancomycin Hospitalized in Surgical and Clinical Wards Regarding the Presence or Absence of AKI

	General (n=135)	with AKI (n=37)	Without AKI (n=98)	p-value
Age (years)*	56.12±17.35	56.03±17.5	56.1±17.3	0.836
Weight (kg)*	65.5±16.4	72.3±16.8	65.6±15.8	0.036
Male sex (%)	93 (68.9)	28 (75.6)	65 (66.3)	0.402
GFR baseline (CKD-EPI), mL/min*	106±25.7	106.6±28.4	108.5±24.7	0.811
Arterial hypertension (%)	62 (45.9)	15 (40.5)	47 (47.9)	0.563
Diabetes mellitus (%)	44 (32.6)	13 (35.13)	31 (31.63)	0.856
CKD (%)	4 (3)	1 (2.7)	3 (3.06)	1
CVD (%)	14 (10.4)	4 (10.81)	10 (10.2)	1
Mechanical ventilation (%)	12 (8.9)	10 (27.03)	2 (2.04)	<0.001
Vasoactive drugs (%)	11 (8.1)	7 (18.9)	4 (4.08)	0.014
Contrast (%)	21 (15.6)	6 (16.2)	15 (15.3)	1
Diuretic (%)	33 (24.4)	17 (45.9)	16 (16.3)	0.001
Other nephrotoxic drugs (%)	18 (13.3)	8 (21.62)	10 (10.2)	0.145
Hospitalization category				0.36
Surgical (%)	70 (51.9)	19 (51.3)	51 (52.04)	
Clinical (%)	65 (48.1)	32 (49.5)	33 (50.8)	
Hospitalization diagnostic				
Infection (%)	76 (53.6)	15 (40.5)	61 (62.2)	0.038
Cardiovascular (%)	5 (3.7)	3 (8.1)	2 (2.04)	0.248
Postoperative (%)	28 (20.7)	8 (21.62)	20 (20.4)	1
Other (%)	26 (19.3)	11 (29.73)	15 (15.3)	—
Infection focus				
Cutaneous (%)	53 (39.3)	14 (37.8)	39 (39.7)	0.992
Urine (%)	5 (3.7)	—	5 (5.1)	0.374
Blood (%)	4 (3)	—	4 (4.08)	0.497
Lungs (%)	27 (20)	9 (24.3)	18 (18.3)	0.596
Central nervous system (%)	21 (15.6)	6 (16.2)	15 (15.3)	1
Undetermined (%)	25 (18.4)	6 (16.2)	19 (19.3)	0.92
Hospitalization time (days)*	22±16.2	29.9±17.8	24.27±15.3	0.053
Death (%)	28 (20.7)	14 (37.8)	14 (14.2)	0.006

Notes: *Mean ± SD. Values in bold denote significance.

Abbreviations: GFR, glomerular filtration rate; CKD, chronic kidney disease; CVD, cardiovascular disease; AKI, acute kidney injury.

Table 2 Characteristics Related to the Use of Vancomycin in Hospitalized Patients in Clinical and Surgical Wards Regarding the Presence or Absence of AKI

Variables	General	with AKI	Without AKI	p-value
	(n=135)	(n=37)	(n=98)	
Vancomycin usage (days)*	11±7.4	13.14±7.7	12.3±7.3	0.478
Absolute attack dosage (mg)*	1,500±394.4	1,651.3±320.4	1,513.01±414.1	0.031
Attack dosage (mg/kg)*	24.3±6.2	23.9±5.5	23.3±6.6	0.27
Mean maintenance dosage (mg/kg)*	16.9±5.6	18.6±5.5	16.2±5.6	0.047
Dose adjustment (%)	102 (75.6)	32 (86.4)	70 (71.4)	0.112
Number of dose adjustments*	2±1.6	2.38±1.7	1.6±1.58	0.021
Toxic serum concentration (%)	80 (59.3)	32 (86.4)	48 (48.9)	<0.001
Subtherapeutic serum concentration (%)	75 (55.6)	17 (45.9)	58 (59.1)	0.235
Higher value of vancomycin (mg/L)*	22.07±14.7	32.6±17.3	20.8±12.3	<0.001
Vancomycin T0–T2 (mg/L)*	13.14±6.9	18.60±8.1	10.85±5.2	0.09
Vancomycin T2–T4 (mg/L)*	11.9±11.6	16.1±15.2	11.3±10.18	0.138
Vancomycin T4–T6 (mg/L)*	17.93±7.94	21.52±7.38	16.50±7.77	0.014
Vancomycin T6–T8 (mg/L)*	21.33±10.97	28.83±11.18	17.95±7.14	0.008
Number of collected serum concentrations*	4±3.034	4.46±3.07	3.77±3.015	0.171

Notes: T0–T2, serum concentration between the start and the second day of usage of vancomycin (0–48 hours); T2–T4, serum concentration between the second and fourth days of usage of vancomycin (48–96 hours); T4–T6, serum concentration between the fourth and sixth days of usage of vancomycin (96–144 hours); T6–T8, serum concentration between the sixth and eighth days of usage of vancomycin (144–192 hours). *Mean ± SD. Values in bold denote significance.

Abbreviation: AKI, acute kidney injury.

Table 3 Cox Regression of Variables Associated with the Presence of AKI in Patients Using Vancomycin Hospitalized in Clinical and Surgical Wards

Variables	HR	CI	p-value
Number of adjustments	1.17	0.91–1.5	0.21
Vasoactive drug	1.004	0.96–1.2	0.953
Mechanical ventilation	1.007	0.97–1.118	0.947
Attack dosage (mg)	1.001	1.000–1.002	0.87
Vancomycin T4–T6 (mg/L)	1.064	1.003–1.128	0.038

Notes: T4–T6, serum concentration between the fourth and sixth days of usage of vancomycin (96–144 hours). Values in bold denote significance.

construction of the free time curve for AKI, based on cutoff values obtained by the ROC curve for 4–6 days, it was observed that in the group with serum concentrations > 21.5 mg/L, the free time for the development of AKI was smaller than the group with serum concentrations <21.5 mg/L (log rank 0.026, Figure 3).

Table 4 presents clinical and laboratory characteristics of patients and Table 5 characteristics related to vancomycin, both regarding the outcome of death. After analysis of both groups through Cox regression, it was observed that serum concentration of vancomycin between the fourth and sixth days (HR 1.078, $p=0.039$), was the sole predictor of death, as shown in Table 6. After construction of the free time curve for death, based on the cutoff values obtained by the ROC

curve for 4–6 days, it was observed that free time for death was smaller for the group with serum concentration >21.5 mg/L than the group with serum concentration <21.5 mg/L (log rank 0.006, Figure 4).

Discussion

Despite vancomycin's ample use in clinical practice, two concerns still permeate its use: efficacy and safety. Regarding efficacy, it is known that there are alterations in the pharmacokinetics of septic patients, which may lead to subtherapeutic serum concentrations and emergence of bacterial resistance, with a possible increase in mortality. Regarding safety, focus has been put on its main collateral effect, nephrotoxicity, with risks of AKI and complications on the short and long term.

This cohort study had as an objective to evaluate the prevalence of monitorization of serum concentrations at adequate, subtherapeutic, and toxic levels, on top of analyzing the impact of the inadequacy of these serum levels on clinical outcomes, like development of AKI and mortality. Despite the literature about vancomycin being vast, there have been few studies to correlate serum levels with clinical outcomes.

A total of 225 patients were evaluated, but only 135 were included in the analysis. This reflects the difficulty of studying the role of nephrotoxicity of vancomycin, for it is

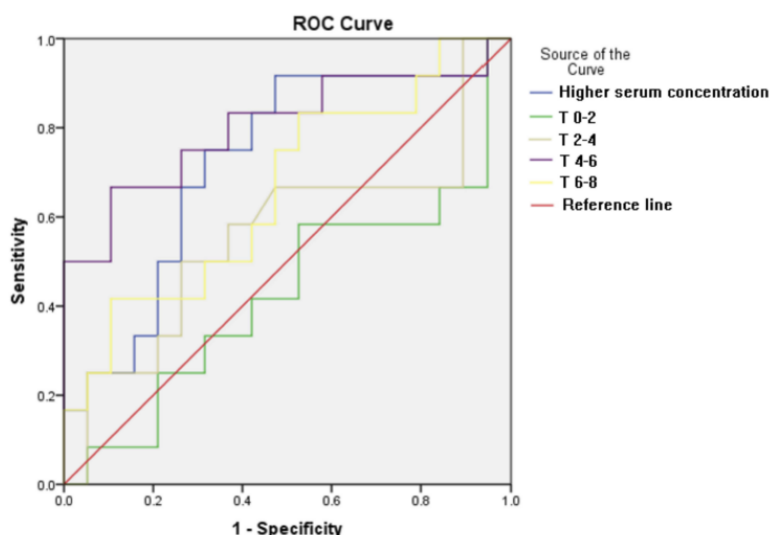


Figure 2 ROC curve for AKI outcome in septic patients using vancomycin hospitalized in clinical and surgical wards. T0–T2, serum concentration between the start and second day of usage of vancomycin (0–48 hours); T2–T4, serum concentration between the second and fourth days of usage of vancomycin (48–96 hours); T4–T6, serum concentration between the fourth and sixth days of usage of vancomycin (96–144 hours); T6–T8, serum concentration between the sixth and eighth days of usage of vancomycin (144–192 hours).

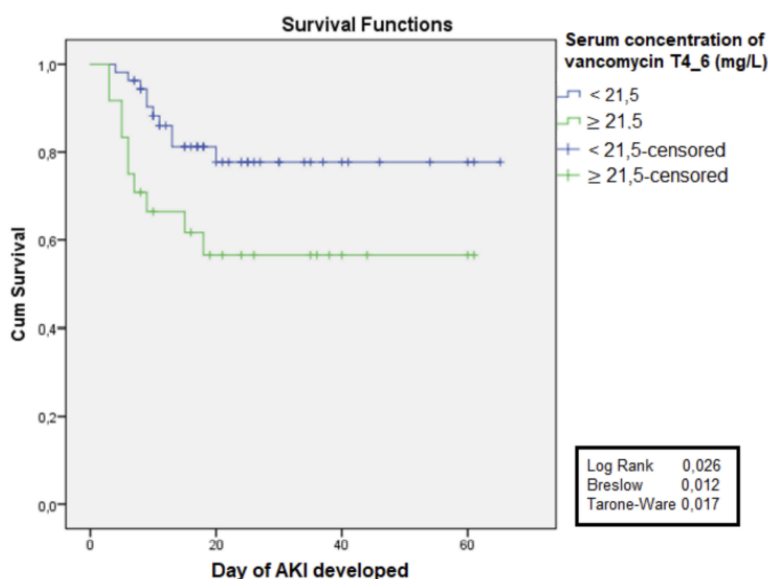


Figure 3 Free time for acute kidney injury (AKI) according to serum concentration (cutoff 21.5 mg/L) during T4–T6 days (96–144 hours) for use of vancomycin in septic patients in clinical and surgical wards.

questionable if high serum levels of vancomycin are the cause (due to elevated serum concentration) or consequence of AKI (accumulation of the drug due to the impaired renal

function from other injuries), as covered by the consensus of the American Society of Health-System Pharmacists, the Infectious Society of America, and the Society of

Table 4 Clinical and Laboratory Characteristics of Patients Using Vancomycin Hospitalized in Clinical and Surgical Wards According to Outcomes

	General (n=135)	No Death (n=107)	Death (n=28)	p-value
Age (years)*	60±17.3	54.8±17.2	61.1±17.1	0.061
Weight (kg)*	65±16.4	67.3±16.2	68.4±17.4	0.783
Male sex (%)	93 (68.9)	71 (66.3)	22 (78.5)	0.311
GFR baseline (CKD-EPI)*	106±25.7	108.8±23.7	104.6±25.7	0.296
Arterial hypertension (%)	62 (45.9)	47 (43.9)	15 (53.5)	0.485
Diabetes mellitus (%)	44 (32.6)	39 (36.4)	5 (17.8)	0.101
CKD (%)	4 (3)	3 (2.8)	1 (3.5)	1
CVD (%)	14 (10.4)	8 (7.5)	6 (21.4)	0.071
Mechanical ventilation (%)	12 (8.9)	7 (6.5)	5 (17.8)	0.134
Vasoactive drugs (%)	11 (8.1)	5 (4.6)	6 (21.4)	0.013
Contrast (%)	21 (15.6)	19 (17.7)	2 (7.1)	0.277
Diuretic (%)	33 (24.4)	24 (22.4)	9 (32.1)	0.414
Other nephrotoxic drugs [#] (%)	18 (13.3)	14 (13.08)	4 (14.2)	1
Hospitalization unit				0.003
Clinical (%)	65 (48.1)	44 (41.1)	21 (75)	—
Surgical (%)	70 (51.9)	63 (58.8)	7 (25)	—
Hospitalization diagnostic				
Infection (%)	76 (53.6)	60 (56.07)	16 (57.1)	1.00
Cardiovascular (%)	5 (3.7)	2 (1.8)	3 (10.7)	0.100
Postoperative (%)	28 (20.7)	25 (23.36)	3 (10.7)	0.227
Other (%)	26 (19.3)			
Infection focus				
Urine (%)	5 (3.7)	4 (3.7)	1 (3.5)	1.00
Blood (%)	4 (3)	4 (3.7)	0	0.680
Lungs (%)	27 (20)	16 (14.9)	11 (39.2)	0.009
Abdomen (%)	6 (4.4)	4 (3.7)	2 (7.1)	0.616
Undetermined (%)	15 (11.1)	11 (10.2)	4 (14.2)	0.510
Nephrological segment (%)	13 (9.6)	7 (6.5)	6 (21.4)	0.044
Hospitalization time (days)*	22±16.2	26.09±16.3	24.8±15.9	0.658
AKI (%)	37 (27.4)	23 (21.5)	14 (50)	0.006
KDIGO (%)				
1	21 (56.7)	16 (69.6)	5 (35.7)	0.09
2	7 (19)	4 (17.4)	3 (21.4)	0.316
3	9 (24.3)	3 (13)	6 (42.8)	0.05

Notes: *Mean ± SD; [#]nonhormonal anti-inflammatory, amphotericin B, acyclovir, amycacin. Values in bold denote significance.

Abbreviations: GFR, glomerular filtration rate; CKD, chronic kidney disease; CVD, cardiovascular disease; AKI, acute kidney injury.

Infectious Diseases Pharmacists.¹¹ Therefore, one of the exclusion criteria of this study was the presence of AKI before the use of vancomycin or at 48 hours after starting its use.

In sum, 75.6% of the patients had their antimicrobial doses adjusted, with the mean number of realized adjustments being 2±1.65. Iwamoto et al¹² noticed that patients

Table 5 Characteristics Related to the Use of Vancomycin in Hospitalized Patients on Surgical and Clinical Wards Regarding Outcome

	General (n=135)	No Death (n=107)	Death (n=28)	p-value
Time of usage of vancomycin (days)*	11±7.4	13.3±7.5	9.5±6.07	0.016
Absolute attack dosage (mg)*	1,500±394.4	1,554.6	1,536.6	0.962
Attack dosage (mg/kg)*	24.31±6.3	23.52±6.4	23.59±6.02	0.847
Mean maintenance dose (mg/kg)*	16.9±5.7	18.02±5.5	17.6±6.5	0.422
Dose adjustment (%)	102 (75.6)	82 (76.6)	20 (71.4)	0.746
Number of dose adjustments*	2±1.6	1.8±1.6	1.9±1.7	0.87
Toxic serum concentrations (%)	80 (59.3)	62 (57.9)	18 (64.2)	0.695
Subtherapeutic serum concentrations (%)	75 (55.6)	61 (57.01)	14 (50)	0.652
Higher serum concentrations (mg/L)*	22.07±14.7	23.3±13.8	27.06±17.8	0.229
Vancomycin T0–T2 (mg/L)*	13.1±6.9	12.3±6.9	18.03±6.9	0.324
Vancomycin T2–T4 (mg/L)*	11.6±11.9	11.9±10.2	15.3±16.8	0.677
Vancomycin T4–T6 (mg/L)*	17.9±7.9	16.5±7.1	22.7±9.1	0.005
Vancomycin T6–T8 (mg/L)*	9.29±11.9	9.96±11.7	6.71±12.5	0.064
Number of collected serum concentrations*	4±3.03	4.07±3.04	3.54±3.02	0.29

Notes: *Mean ± SD. T0–T2, serum concentration between the start and second day of usage of vancomycin (0–48 hours); T2–T4: serum concentration between the second and fourth days of usage of vancomycin (48–96 hours); T4–T6: serum concentration between the fourth and sixth days of usage of vancomycin (96–144 hours); T6–T8: serum concentration between the sixth and eighth days of usage of vancomycin (144–192 hours). Values in bold denote significance.

that were not submitted to monitoring of therapeutic concentrations of vancomycin presented a significant reduction in depuration values of creatinine and thus higher risk of nephrotoxicity than those that were monitored (OR 0.25, $p<0.05$). Davis et al¹³ evaluated adherence to guidelines instituted by the consensus of 2009¹¹ regarding the use of vancomycin, and showed that despite the recommendations, only 19% of institutions questioned claimed to use a standard definition to identify vancomycin-associated nephrotoxicity.

Despite having the availability to realize therapeutic monitoring of the drug, which is not unanimous in all centers, difficulties have been observed with reaching and sustaining adequate serum concentrations, due to factors related to collection, patients, and pharmacokinetic variation of the drug in septic patients.⁸ In our study, this

Table 6 Cox Regression of Variables Associated with Death in Patients Using Vancomycin Hospitalized in Clinical and Surgical Wards

	HR	CI	p-value
Diabetes mellitus	2.434	0.637–9.294	0.193
SOFA score	1.169	0.99–1.38	0.066
Serum concentration, T4–T6 days (mg/L)	1.078	1.004–1.157	0.039
Age	0.992	0.959–1.025	0.63
Follow-up with nephrologist (due to AKI)	0.934	0.243–3.584	0.92

Notes: T4–T6, serum concentration between the fourth and sixth days of usage of vancomycin (96–144 hours). Values in bold denote significance.

Abbreviation: AKI, acute kidney injury.

difficulty was also present, with elevated rates of subtherapeutic and toxic concentrations.

The incidence of AKI found in this study was 27.4%, which happened on average 9 days after the start of usage of vancomycin, with mortality of 20.7%. Data from the literature suggest variable nephrotoxicity prevalence: from 5% to 40% in the presence of other nephrotoxins in concomitant use.^{11,14–16} On Cox regression analysis, only the higher value of serum concentration between the fourth and sixth days was a factor associated with the development of AKI in this population, with serum concentration >21.5 mg/L

showing to be a good predictor of AKI, with an area under the curve of 0.8, sensitivity of 81.1%, specificity of 73.7%, and preceding the diagnosis of AKI by 3 days (AKI happened on average on the ninth day of use of vancomycin).

A prospective multicentric study conducted by Bosso et al¹⁷ evaluating 288 patients using vancomycin found an association between nephrotoxicity incidence and vancomycin concentrations, with AKI occurring in 29.6% of patients with serum concentrations of vancomycin >15 mg/L and 8.9% of patients with vancomycin concentrations <15 mg/L. Ten other studies reviewed by Gupta et al¹⁶ identified concentrations of vancomycin >15 mg/L as a predictor of nephrotoxicity, with AKI incidence of 27%. As such, the ideal therapeutic concentrations aimed at preventing nephrotoxic AKI are questionable. On Cox regression analysis, the higher concentration of vancomycin between the fourth and sixth days was the only predictor of death in the population.

This study presents some limitations, such as the small sample obtained, reflecting the difficulty of studying nephrotoxicity; the data being obtained from a single center; the fact of bacterial vancomycin resistance not having been studied; and the role of serum concentration as a prognostic predictor of AKI (eg, gravity and necessity of acute renal support). Despite these limitations, it was the first study to present cutoff

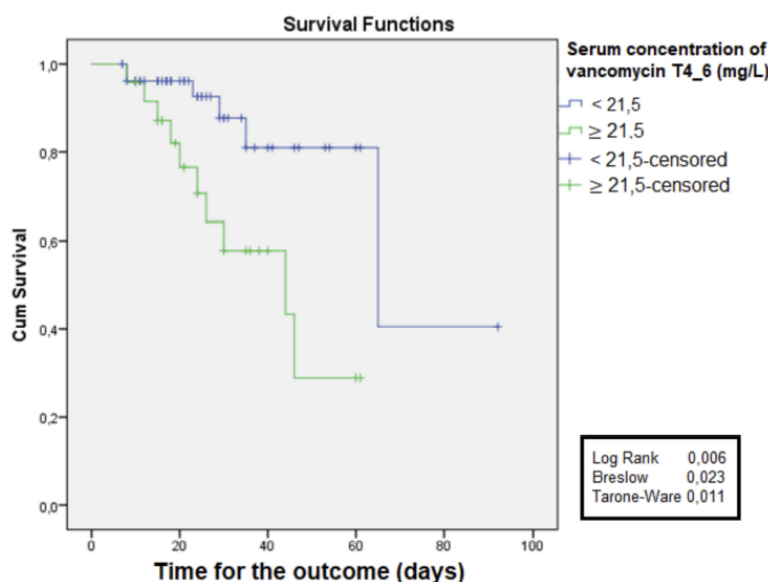


Figure 4 Free time for death outcome according to serum concentration (cutoff 21.5 mg/L) during T4–T6 for vancomycin in patients hospitalized in surgical and clinical wards. T4–T6, serum concentration between the fourth and sixth days of usage of vancomycin (96–144 hours).

values with an objective of refining the use and monitoring of vancomycin in septic patients in clinical and surgical wards.

Conclusion

This study showed that the prevalence of AKI associated with the use of serum concentration of vancomycin was elevated and that serum concentrations >21.5 mg/L between the fourth and sixth days were an independent predictor of AKI, presenting sensitivity and specificity >80% and preceding AKI diagnosis by at least 3 days. It was also shown to be associated with death on uni- and multivariate analysis, remaining the single predictor of death even after adjustment by the Cox model for the variables that also showed statistical significance. Therefore, early identification of serum concentrations of vancomycin can make adequate therapeutic interventions possible, eg, with adjustment of doses or administration intervals, with the goal of preventing AKI or modifying its natural history, resulting in a possible reduction in mortality.

Human Rights

This study was approved by the Ethics Committee of the Brazil Platform under number 65827117.4.0000.5411.

Informed Consent

Participants provided written informed consent to participate at the time of enrollment. Data were anonymized for privacy. The study was conducted according to good clinical practice and the Declaration of Helsinki, and was registered in the Brazilian Registry of Clinical Trials (ReBEC) under number RBR-4zrwztz.

Data-Sharing Statement

No further data will be shared.

Disclosure

The authors have declared they have no conflicts of interest.

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Article

The Serum Concentration of Vancomycin as a Diagnostic Predictor of Nephrotoxic Acute Kidney Injury in Critically Ill Patients

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Abstract: The impact of serum concentrations of vancomycin is a controversial topic. Results: 182 critically ill patients were evaluated using vancomycin and 63 patients were included in the study. AKI occurred in 44.4% of patients on the sixth day of vancomycin use. Vancomycin higher than 17.53 mg/L between the second and the fourth days of use was a predictor of AKI, preceding AKI diagnosis for at least two days, with an area under the curve of 0.806 (IC 95% 0.624–0.987, $p = 0.011$). Altogether, 46.03% of patients died, and in the Cox analysis, the associated factors were age, estimated GFR, CPR, and vancomycin between the second and the fourth days. Discussion: The current 2020 guidelines recommend using Bayesian-derived AUC monitoring rather than trough concentrations. However, due to the higher number of laboratory analyses and the need for an application to calculate the AUC, many centers still use therapeutic trough levels between 15 and 20 mg/L. Conclusion: The results of this study suggest that a narrower range of serum concentration of vancomycin was a predictor of AKI in critically ill septic patients, preceding the diagnosis of AKI by at least 48 h, and it can be a useful monitoring tool when AUC cannot be used.

Keywords: acute kidney injury; nephrotoxicity; vancomycin; sepsis

1. Introduction

The impact of the serum concentrations of vancomycin in hospitalized patients in intensive care units (ICU) is a controversial topic, and it is necessary to improve the knowledge of sepsis and the safe and effective use of vancomycin.

Sepsis is a frequent diagnosis in ICUs and corresponds to the primary etiology of acute kidney injury in this scenario with a high mortality [1–5]. Thus, the early administration of broad-spectrum antibiotics is justified [6].

Vancomycin is widely used in ICUs. Due to the pharmacokinetic changes of the critical patient related to the distribution, elimination, and metabolism of the drug, there is an increased risk of subtherapeutic concentrations, which may compromise the treatment and induce bacterial resistance. On the other hand, it is a drug whose main side effect is nephrotoxicity [5–9].

An area under the curve over the minimum inhibitory concentration (AUC/MIC) equal or greater than 400, determining the optimum activity of the antimicrobial, is usually obtained in patients with a vancomycin serum concentration in the trough of 15 to 20 mg/L. Such troughs are rarely needed to achieve this AUC target and may exceed and cause toxicity [10,11]. The association between serum vancomycin concentration and clinical outcomes is poorly studied.

2. Materials and Methods

The patients who entered the hospital's ICU of Botucatu Medical School from August 2016 to July 2017 and initiated vancomycin in the preceding 48 h were included in a prospective cohort study. The quick-SOFA tool was used to identify patients with sepsis [2]. The initial dose of vancomycin was 25 mg/kg at a maintenance of 15 mg/kg. The dosing interval was 12/12 h up to 96/96 h, varying according to the serum concentration.

The following patients were excluded: patients who developed AKI in less than 48 h from the start of vancomycin use, patients with installed AKI before the introduction of vancomycin, patients with AKI of other etiologies (obstructive, vascular, glomerular, or ischemic AKI), kidney transplant, or stage V of chronic kidney disease (with estimated or measured serum creatinine clearance less than 15 mL/min), patients who were pregnant, or under 18 years old.

This study was registered in the Brazilian Registry of clinical trials (ReBEC) under Number RBR-4zrwzt and was approved by the Research Ethics Committee of Botucatu School of Medicine with number CAAE 65827117.4.0000.5411. All the research was performed following current regulations and a written informed consent statement was obtained from all participants or their legal guardians.

The patient included in the study had his clinical and laboratory evaluation taken daily by the same observer, who consulted his electronic medical record until his treatment with vancomycin or his clinical outcome ended.

The lowest value baseline creatinine was considered in 6 months if the prior creatinine or lower creatinine were available during hospitalization since the patient was not on dialysis. KDIGO used the AKI definitions as any of the following: increase in serum creatinine by 0.3 mg/dL or more within 48 h, or increase in serum creatinine to 1.5 times baseline or more within the last 7 days, or urine output less than 0.5 mL/kg/h for 6 h [5].

The serum toxic, subtherapeutic, and therapeutic concentrations were defined as trough concentrations higher than 20 mg/L, lower than 15 mg/L, and between 15 and 20 mg/L, respectively, in two consecutive dosages.

Frequency and measures of central tendency and dispersion were calculated for the categorical and continuous variables, respectively, and established as outcome variables: AKI and death. Student's t-test was used to compare parametric variables between two groups and the Mann-Whitney test was used for non-parametric variables. Categorical variables were compared with the chi-square or Fisher's exact test. Variables with significant univariate associations were considered as candidates for Cox regression analysis, which was performed using backward variable selection, with the exit criteria set at $p < 0.20$.

ROC curves were built to evaluate the cutoff points of serum concentration of vancomycin as predictors of the diagnosis and prognosis of AKI in the moments until the second day (T0-2), between the second and the fourth days (T2-4), and between the fourth and the sixth days (T4-6).

Areas under the curve (AUC) between 0.7 and 0.79 were considered a satisfactory performance and between 0.8 and 0.89 an optimum performance.

Using Lee Formula for an alpha error of 0.05 and study power of 80%, the sample size calculation was performed, and considering that the prevalence of the AKI outcome would be 30% higher in patients with a toxic concentration of vancomycin [12], 30 patients were estimated with toxic concentrations and 30 without toxic concentrations (total of 60 patients).

3. Results

We evaluated 63 patients (Figure 1), aged 54.67 ± 18.7 years, with a male predominance (66.7%), BMI 26.1 ± 6.8 , and the use of vancomycin for 11.4 ± 7.33 days. The vast majority of patients (92%) had performed the serum vancomycin measurement, the number of serum concentrations dosages and the number of posologic adjustments were 3.87 and 1.84, respectively; 53.96% were in concentrations considered toxic (higher than 20 mg/L), an

average of 25.5 ± 11.90 mg/L. AKI prevalence was 44.4%, with the stage KDIGO 3 being most common (46.4%), and 46% died.

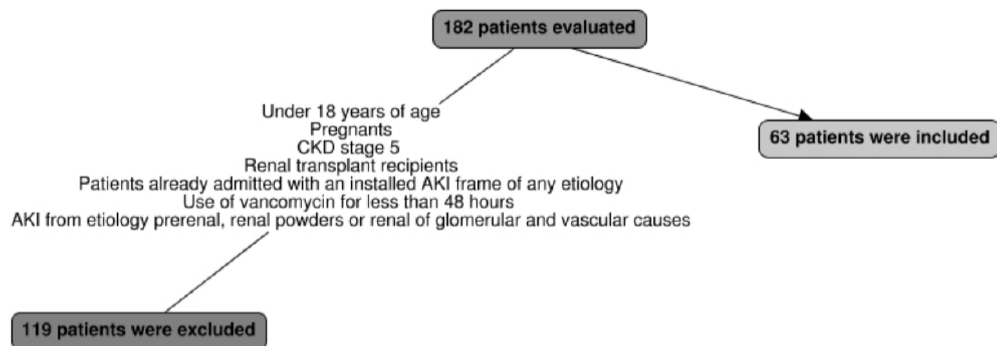


Figure 1. Flow diagram of patients included and excluded.

Clinical and laboratory variables are shown in Table 1, and vancomycin characteristics are shown in Table 2, distinguishing patients who developed AKI or not.

Table 1. Clinical and laboratory characteristics of patients hospitalized in an intensive care unit, using vancomycin for the presence or absence of AKI.

Variable	General	With AKI	Without AKI	p-Value
	(N = 63)	(N = 28)	(N = 35)	
Age (years) *	54.6 $\pm$ 18.7	58.1 $\pm$ 17.2	51.9 $\pm$ 19.7	0.19
Male	42 (66.7)	19 (67.8)	23 (65.7)	0.89
Weight (kg) *	72.6 $\pm$ 18.6	71.4 $\pm$ 17.05	73.5 $\pm$ 19.9	0.66
GFR baseline—CKD-EPI (mL/min) *	108.9 $\pm$ 28.9	98.4 $\pm$ 29.3	117.3 $\pm$ 26.1	0.009
Urinary Output (mL/kg/h) *	1.1 $\pm$ 0.5	1.08 $\pm$ 0.5	1.1 $\pm$ 0.5	0.50
CPR (mg/dL) **	16.4 (11.2–25.9)	16.2 (11.7–25.8)	12.94 (6.4–23.6)	0.13
Mean arterial pressure *	105.9 $\pm$ 11.9	78.7 $\pm$ 8.7	80.8 $\pm$ 9.3	0.37
Albumin (g/dL) *	2.25 $\pm$ 0.38	2.18 $\pm$ 0.3	2.32 $\pm$ 0.44	0.027
SOFA	8.5 $\pm$ 5.95	9.5 $\pm$ 5.54	7.0 $\pm$ 7.07	0.81
Hospitalization days *	36.1 $\pm$ 21.1	33.5 $\pm$ 20.5	30 $\pm$ 20.2	0.71
Arterial hypertension (%)	32 (50.8)	14 (40)	18 (51.4)	0.88
Diabetes Mellitus (%)	18 (28.6)	8 (28.5)	10 (28.5)	0.77
Chronic kidney disease (%)	3 (4.8)	2 (7.1)	1 (2.8)	0.58
Cardiovascular disease (%)	7 (11.1)	4 (14.2)	3 (8.5)	0.69
Mechanical Ventilation (%)	51 (81)	25 (89.2)	26 (74.2)	0.24
Vasoactive drug (%)	35 (55.6)	20 (71.4)	15 (42.8)	0.04
Contrast (%)	7 (11.1)	3 (10.7)	4 (11.4)	1.00
Diuretic (%)	24 (38.1)	15 (53.5)	9 (25.7)	0.04
Other nephrotoxic drugs (%) #	5 (7.9)	3 (10.7)	2 (5.7)	0.65
Diagnosis of hospitalization (%)				
Infection	22 (34.9)	12 (42.8)	10 (28.5)	0.36
Cardiovascular	4 (6.3)	3 (10.7)	1 (2.8)	0.31
Postoperative	22 (34.9)	7 (25)	15 (42.8)	0.22
Other	15 (23.8)	6 (21.43)	9 (25.7)	0.92
Death (%)	29 (46)	15 (53.5)	14 (40)	0.34

KDIGO: Clinical Practice Guideline for Acute Kidney Injury; AKI: Acute kidney injury; CPR: C-protein reactive; GFR: glomerular filtration rate estimated by CKD-EPI; * Average and standard deviation; ** Median and quartiles; # Non-hormonal anti-inflammatory, amphotericin B, Acyclovir, amikacin.

Table 2. Features related to vancomycin in patients hospitalized in an intensive care unit for the presence or absence of AKI.

Variables	General	With AKI	Without AKI	<i>p</i> -Value
	(N = 63)	(N = 28)	(N = 35)	
Vancomycin use time (days) **	11.4 (8.1–15.2)	10 (7.5–15)	9 (6–13.7)	0.25
Attack dose (mg/kg) *	24.8 ± 5	24.42 ± 5.15	25.13 ± 4.93	0.58
Vancomycin doses (First) (mg/kg) **	15.3 (12.9–19.4)	15.2 (13.3–18.3)	15.7 (14.6–19.2)	0.21
Number of doses adjustments **	1.8 (0–3)	1 (0.5–3)	2 (0–3)	0.88
Toxic serum level (%)	34 (54)	22 (78.5)	15 (42.8)	0.009
Subtherapeutic level (%)	32 (50.7)	12 (42.8)	30 (85.7)	<0.001
Vancomycin T0–T2 (mg/L) *	16.08 ± 8.3	17.4 ± 11.7	14.7 ± 5.5	0.73
Vancomycin T2–T4 (mg/L) **	19.1 (7.1–26.6)	22.1 (9.1–29.6)	9.1 (6.03–13.4)	0.002
Vancomycin T4–T6 (mg/L) *	17.1 ± 8.9	20.4 ± 11.04	14.02 ± 5.08	0.051

T0–T2: Serum concentration between the beginning and the second day of use of vancomycin (0–48 h); T2–T4: serum concentration between the second and fourth day of use of vancomycin (48–96 h); T4–T6: serum concentration between the fourth and sixth day of use of vancomycin (96–144 h); AKI: Acute Kidney Injury; * Average and standard deviation; ** Median and quartiles.

The only variable identified as a risk factor for AKI was the vancomycin concentration between the second and the fourth days (T2–4) in the Cox regression analysis (HR = 1.086, *p* = 0.009), without statistically significant differences in other variables, as shown in Table 3.

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

Variables	HR	Confidence Interval	<i>p</i> -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 use	1.004	0.27–3.71	0.99
Serum concentration T2–T4 (mg/L)	1.086	1.02–1.15	0.009

AKI: acute kidney injury; ICU: intensive care unit; GFR: glomerular filtration rate (CKD-EPI); T2–T4: Serum concentration between the second and fourth day of use of vancomycin (48–96 h).

Vancomycin serum concentration in T2–4 days higher than 17.53 was a predictor of AKI with a sensitivity of 79.7% and specificity of 83.3% by ROC curve analysis, with an AUC of 0.806 (IC 95% 0.624–0.987, *p* = 0.011), as shown in Figure 2. AKI occurred on average on the sixth day of vancomycin use, and the founded value preceded the diagnosis of AKI by two days.

Based on the values of cutoff obtained by the ROC curve at 2 to 4 days, the free time curve for AKI was constructed. 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 concentrations between 17.5 and 20 mg/L, which also presented shorter free time compared to the group with a serum concentration <17.5 mg/L, log-rank <0.001 (Figure 3).

Table 4 shows the clinical and laboratory variables, and Table 5 shows the characteristics related to vancomycin, distinguishing patients who died or survived.

When the two groups were analyzed using 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 C-protein reactive value (HR 1.26, *p* = 0.011) were identified as risk factors for death, as shown in Table 6.

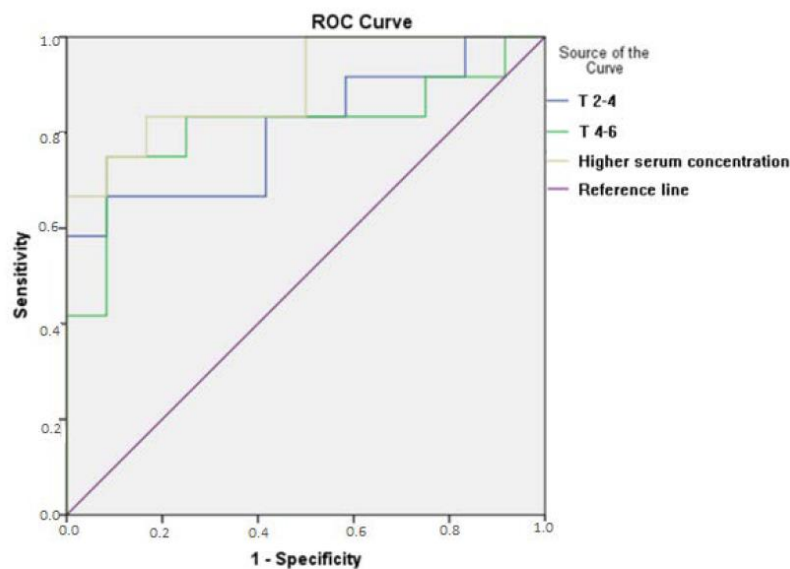


Figure 2. ROC curve for the AKI outcome in the population of septic patients using vancomycin admitted to the ICU. T2-4: Serum concentration between the second and fourth day of use of vancomycin (48–96 h); T4-6: Serum concentration between the fourth and sixth day of use of vancomycin (96–144 h).

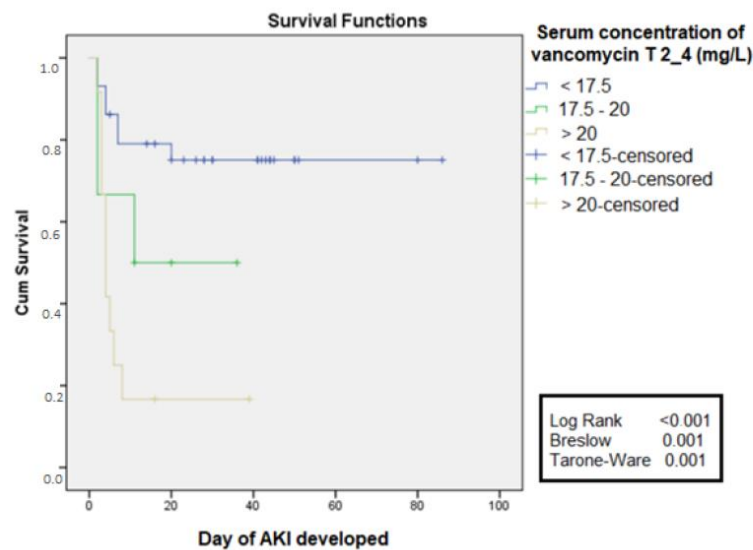


Figure 3. Free time for acute kidney injury according to the values of serum concentration between T2-4 days (48–96 h) use of vancomycin in septic patients in ICUs.

Table 4. Patients' clinical and laboratory characteristics in the use of vancomycin hospitalized in an intensive care unit, compared to its outcome.

Variables	General	Death	No Death	p-Value
	(N = 63)	(N = 29)	(N = 34)	
Age (years) *	54.6 ± 18.7	64.5 ± 17.04	46.2 ± 15.9	0.0001
Male sex (%)	42 (66.7)	19 (65.5)	23 (67.6)	1
Weight (kg) *	72.6 ± 18.6	69.1 ± 15.5	75.5 ± 20.6	0.17
GFR baseline—CKD-EPI (mL/min) *	108.9 ± 28.9	96.08 ± 31.7	119.9 ± 21.3	0.001
Diuresis mL/kg/h *	1.1 ± 0.5	1.04 ± 0.5	1.2 ± 0.5	0.17
CPR (mg/dL) *	16.4 ± 9.8	20.6 ± 10.8	12.8 ± 7.3	0.002
Mean arterial pressure (mmHg) *	105.9 ± 11.9	103.6 ± 12.3	107.8 ± 11.4	0.16
Albumin (g/dL) *	2.25 ± 0.38	2.19 ± 0.32	2.31 ± 0.43	0.19
SOFA	8.5 ± 5.95	8.88 ± 6.68	7.0 ± 0.00	0.008
Hospitalization days *	36.1 ± 21.1	30.28 ± 23.6	41.09 ± 17.6	0.04
Arterial hypertension (%)	32 (50.8)	17 (58.6)	15 (44.1)	0.37
Diabetes mellitus (%)	18 (28.6)	9 (31)	9 (26.5)	0.90
Chronic kidney disease (%)	3 (4.8)	3 (10.3)	0 (0)	0.18
Cardiovascular disease (%)	7 (11.1)	4 (13.8)	3 (8.8)	0.82
Mechanical ventilation (%)	51 (81)	24 (82.8)	27 (79.4)	0.98
Vasoactive drug (%)	35 (55.6)	17 (58.6)	18 (52.9)	0.84
Contrast (%)	7 (11.1)	4 (13.8)	3 (8.8)	0.82
Diuretic use (%)	24 (38.1)	16 (55.2)	8 (23.5)	0.02
Other nephrotoxic drugs (%)#	5 (7.9)	1 (3.4)	4 (11.8)	0.45
Hospitalization Diagnosis:				
Infection (%)	22 (34.9)	13 (44.8)	9 (26.4)	0.21
Cardiovascular (%)	4 (6.3)	3 (10.3)	1 (2.9)	0.32
Infection Focus (%)				
Urinary + bloodstream	4 (13.79)	4 (13.79)	0 (0)	0.04
Pulmonary	32 (50.8)	12 (41.38)	21 (61.76)	0.17
AKI (%)	28 (44.4)	15 (51.7)	13 (38.12)	0.34
KDIGO (%)				
1	5 (17.8)	3 (20)	2 (15)	0.99
2	10 (35.7)	6 (40)	4 (30)	0.76
3	13 (46.4)	6 (40)	7 (53)	0.72

KDIGO: Clinical Practice Guideline for Acute Kidney Injury; AKI: Acute kidney injury; CPR: C- protein reactive; TFG: glomerular filtration rate estimated by CKD-EPI; * Average and standard deviation; # anti-inflammatory non-hormonal, amphotericin B, Acyclovir, amikacin.

Table 5. Features related to vancomycin in patients hospitalized in an intensive care unit, compared to its outcome.

Variables	General	Death	No Death	p-Value
	(N = 63)	(N = 29)	(N = 34)	
Vancomycin use time (days) *	11.4 ± 7.3	9.4 ± 5.9	13.1 ± 8.05	0.04
Attack dose mg/kg *	24.8 ± 5	24.9 ± 4.4	24.7 ± 5.5	0.33
Vancomycin dose (First) mg/kg *	15.3 ± 3.5	14.8 ± 2.6	18.1 ± 4.1	0.90
Number of doses adjustments **	1.84 (1.8)	1.07 (1.2)	2.50 (2.07)	0.002
Toxic serum level (%)	34 (54)	16 (55.2)	18 (52.9)	1.00
Subtherapeutic level (%)	39 (61.9)	14 (48.3)	25 (73.5)	0.07
Vancomycin T0-T2 (mg/L) *	16.08 ± 8.3	17.91 ± 11.02	14.2 ± 6.5	0.65
Vancomycin T2-T4 (mg/L) *	17.6 ± 9.5	20.0 ± 9.76	11.3 ± 7.81	0.02
Vancomycin T4-T6 (mg/L) *	17.1 ± 8.9	20 ± 9.07	14.08 ± 8.05	0.07

T0-T2: Serum concentration between the beginning and the second day of use of vancomycin (0–48 h); T2-T4: Serum concentration between the second and fourth day of use of vancomycin (48–96 h); T4-T6: Serum concentration between the fourth and sixth day of use of vancomycin (96–144 h); * Average and standard deviation; ** Median and quartiles.

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 doses adjustments	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 use	0.153	0.005–4.25	0.26
CPR (mg/dL)	1.26	1.05–1.51	0.011

ICU: intensive care unit; CPR: C-Protein Reactive; GFR: glomerular filtration rate estimated by CKD-EPI; T2-T4: Serum concentration between the second and fourth day of use of vancomycin (48–96 h).

Based on the values of cutoff obtained by the ROC curve at 2 to 4 days, the free time curve for death was constructed. 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 concentrations between 17.5 and 20 mg/L, which also presented a lower free time compared to the group with a serum level <17.5 mg/L and log-rank 0.018, as shown in Figure 4.

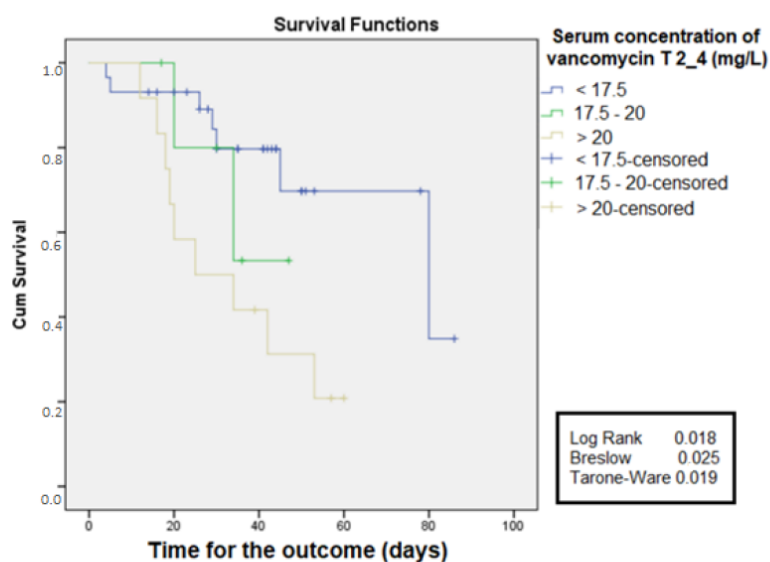


Figure 4. Free time for the outcome of death according to values of serum concentration between T2-4 days (48–96 h) of vancomycin use in ICU patients.

4. Discussion

Due to the pharmacokinetic changes of the critical patient related to the drug distribution, elimination, and metabolization, two concerns still permeate vancomycin use, related to its efficacy and safety. There is an increased risk of subtherapeutic concentrations, which may compromise the treatment and induce bacterial resistance. On the other hand, it is a drug whose main side effect is nephrotoxicity, with AKI risk and short- and long-term problems.

This study assessed the impact of therapeutic monitoring of vancomycin on clinical outcomes. It is known that the serum concentration of vancomycin in the trough between

15 and 20 mg/L corresponds to an area under the curve over the minimum inhibitory concentration (AUC/MIC) equal or greater than 400, determining the optimum activity of the antimicrobial [10,11]. However, the association between serum vancomycin concentration and clinical outcomes is poorly studied.

Were evaluated 182 critically ill patients using vancomycin, and 63 patients were included in the study. This difficulty of studying vancomycin nephrotoxicity arises from the following problem: high serum levels are a consequence or cause of AKI due to the accumulation of the drug, which is caused by a reduction in its renal whitening due to septic AKI, as approached by Álvarez et al. [12] and by American guideline [11]. Therefore, the presence of AKI already installed or started before 48 h of vancomycin use was an exclusion criteria for this study.

Most critically ill patients (92%) had performed the serum vancomycin measurement, and the mean measurements of serum concentrations and dose adjustments were 3.87 and 1.84, respectively. Considering that the average time of use was 11.43 days, and according to the protocol already established in the literature, there is an indication that it is not always serum concentrations determined and adjusted by the ICU team, which can contribute to subtherapeutic concentrations of the antimicrobial. Iwamoto et al. [13] found an increased risk of AKI and nephrotoxicity in patients who were not submitted to the monitoring of serum concentrations of vancomycin (OR = 0.25 and $p < 0.05$).

A study conducted by Davis et al. [14] assessed adherence to the guidelines established by the American consensus [11] and showed that only 19% of the institutions questioned used a standard definition to identify nephrotoxicity associated with vancomycin. The most current 2020 guidelines recommend using Bayesian-derived AUC monitoring rather than trough concentrations [14].

Despite the availability of therapeutic drug monitoring, there is a difficulty in achieving and maintaining adequate serum concentrations, especially in the intensive care environment, due to the collection, the patient, and the pharmacokinetic variation of the drugs [8]. In our study, this difficulty also occurred, with high rates of toxic and subtherapeutic concentration.

AKI occurred in 44.4% of patients, with a mortality rate of 46%. On average, the development of AKI occurred on the sixth day of vancomycin use, compatible with data from the literature in which nephrotoxic AKI generally occurs from 4 to 8 days after the initiation of treatment [15,16]. Such data indicate that it was possible to evaluate the role of the nephrotoxicity of vancomycin as the cause of AKI in septic patients in ICUs. Since the role of sepsis was more critical than that of nephrotoxicity, the incidence of AKI (close to 60%), as well as mortality (higher than 70%), would be higher.

The only variable that showed an association with AKI by Cox regression analysis was the highest level of serum vancomycin between the second and fourth days. It differs from previous studies that identified other variables (use of vasoactive drugs, basal creatinine, and age) as predictors of AKI in ICU patients [17,18]. In our study, we evaluated a specific population using vancomycin after ICU admission, and patients with AKI were excluded before introducing the antimicrobial agent, which could justify the different risk factors identified in other studies.

Serum concentrations above 17.53 mg/L between the second and fourth day of use were an excellent predictor of AKI in the critical population, with AUC higher than 0.8 and sensitivity and specificity close to 80%, preceding the diagnosis of AKI in at least 48 h. However, this value is within the range considered therapeutic for severe infections (15–20 mg/L), suggesting that therapeutic concentrations should be less in the critical population due to the presence of other risk factors for AKI: advanced age, previously diminished renal function, dehydration, and the duration of sepsis; the concomitant administration with other nephrotoxic drugs, such as amphotericin B, aminoglycosides, intravenous contrast way, and loop diuretics; and the need for vasopressors due to hemodynamic instability [19,20]. A free time curve was built for AKI, stratifying the serum concentration levels in less than 17.5 mg/L, between 17.5 mg/L and 20 mg/L, and higher

than 20 mg/L, showing the shorter free time and higher serum levels, with a significant difference between curves.

Bosso et al. [15] evaluated 288 patients in a prospective multicentric study and found AKI in 29.6% of patients with serum concentrations levels higher than 15 mg/L and in 8.9% of the patients with vancomycin concentrations lower than 15 mg/L. Gupta et al. [19] identified AKI incidence in 27% of patients, with vancomycin concentrations higher than 15 mg/L as a predictor of nephrotoxicity. Thus, it is questionable whether the ideal therapeutic concentrations aim to prevent AKI.

Age, mean PCR value, the serum concentration of vancomycin between the second and fourth days, and estimated glomerular filtration rate were associated with mortality. Chertow et al. [20] showed that small increases in serum creatinine were significantly associated with the increase in AKI patients' mortality. Liangos et al. [21] found that chronic diseases such as diabetes mellitus (DM) were associated with a higher risk of development of AKI, with a consequent increase in mortality. CPR concentration indicating systemic inflammation was shown in the literature associated with mortality, as presented by Villacorta et al. [22] in patients with heart failure, in which CPR > 3 mg/dL was associated with a higher mortality in comparison to individuals with lower values ($p = 0.018$).

This study presents some limitations: the obtained sample was small due to the difficulty of studying nephrotoxicity in critically ill patients, since there are many exclusion variables; the data were obtained in a single center; the agents' resistance to vancomycin was not studied; and the serum concentration levels were not studied as a prognostic predictor of AKI (severity and need for acute renal support). Despite these limitations, this was the first study of the therapeutic monitoring of vancomycin to present cutoff values to refine the management in the population of septic patients in an intensive care scenario, when AUC cannot be used.

5. Conclusions

The current 2020 guidelines [23] recommend using Bayesian-derived AUC monitoring rather than trough concentrations. However, due to a higher number of laboratory analyses and the need for an application to calculate the AUC, many centers still use therapeutic trough levels between 15 and 20 mg/L. The results of this study suggest that a narrower range of serum concentration of vancomycin was a predictor of AKI in critically ill septic patients, preceding the diagnosis of AKI in at least 48 h, and can be a useful monitoring tool when AUC cannot be used.

When the early identification of serum vancomycin levels is performed, it is possible to make dose adjustments essential to prevent AKI or modify its natural history.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by Research Ethics Committee of Botucatu School of Medicine with number CAAE 6582/117.4.0000.5411. This study was registered in the Brazilian Registry of clinical trials (ReBEC) under Number RBR-4zrwzt.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: All Research Data is found in this manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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Capítulo III: Apresentação de trabalhos e palestras na temática



CERTIFICAMOS QUE

WELDER ZAMONER

Participou do **XX CONGRESSO PAULISTA DE NEFROLOGIA**, realizado no Bourbon Atibaia Convention Center, Atibaia - SP, de 25 a 28 de setembro de 2019, na qualidade de **Palestrante** na atividade **Lesão Renal Aguda - Diálise com tema Terapia renal substitutiva e farmacocinética de antibióticos**.

Atibaia, 28 de setembro de 2019

Prof^ª Dra. Maria Almerinda Ribeiro Alves
Presidente do XX Congresso Paulista de Nefrologia

Prof. Dr. Lúcio Requião-Moura
Coordenador da Comissão Científica

Prof. Dr. Rodrigo Bueno
Tesoureiro



CERTIFICAMOS QUE

WELDER ZAMONER

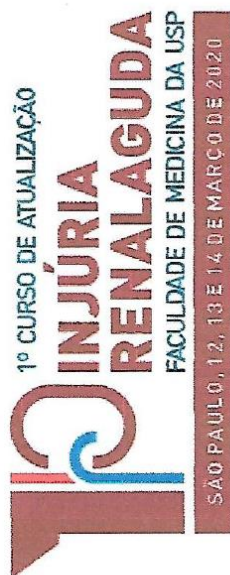
Participou do XX CONGRESSO PAULISTA DE NEFROLOGIA, realizado no Bourbon Atibaia Convention Center, Atibaia - SP, de 25 a 28 de setembro de 2019, na qualidade de Palestrante na atividade Curso de Lesão Renal Aguda com tema Nefrotoxicidade de novas drogas utilizadas na prática clínica.

Atibaia, 28 de setembro de 2019

Prof^a Dra. Maria Almerinda Ribeiro Alves
Presidente do XX Congresso Paulista de Nefrologia

Prof. Dr. Lúcio Requião-Moura
Coordenador da Comissão Científica

Prof. Dr. Rodrigo Bueno
Tesoureiro



CERTIFICAMOS QUE

WELDER ZAMONER

Participou como Palestrante do Módulo Teórico do 1º Curso de Atualização Injúria Renal Aguda realizado pela Disciplina de Nefrologia da Faculdade de Medicina da Universidade de São Paulo - São Paulo/ SP, nos dias 12 e 13 de Março de 2020, com carga - horária de 20 horas.

São Paulo, 14 de Março de 2020.

Profª. Dra. Lúcia Andrade

Professora Associada - Disciplina de Nefrologia
Faculdade de Medicina - Universidade de São Paulo



Prezado Dr. Welder Zamoner

De 12 a 14 de março de 2020 acontecerá o 1º Simpósio de Atualização em Injúria Renal Aguda da Faculdade de Medicina da Universidade de São Paulo (IRA USP), que será um evento de extensão da disciplina de Nefrologia da Faculdade de Medicina da USP, e será voltado para contribuir com a educação continuada de profissionais de saúde atuantes em Nefrologia e em Terapia Intensiva.

Gostaríamos de convidá-lo a participar do evento como **palestrante**, para a administração de uma aula intitulada **Antibiótico na IRA e na Terapia Renal Substitutiva** com duração de **25 minutos** (com 5 minutos de discussão ao final de cada apresentação). Esta programação está prevista para o horário das **15:30 às 16:00 horas do dia 12 de março de 2020** na Faculdade de Medicina da USP, em São Paulo.

O programa completo poderá ser consultado no site <http://irausp.com.br/>.

Desde já agradecemos a sua colaboração e esperamos que o IRA USP 2020 cumpra com sua finalidade de oferecer um curso de excelência para a atualização em Nefrologia.

Atenciosamente,

Comissão Organizadora

CERTIFICADO

Certificamos que o trabalho

**REMOÇÃO DOS ANTIMICROBIANOS VANCOMICINA E
MEROPENEM PELA HEMODIÁLISE EM PACIENTES COM
LESÃO RENAL AGUDA ASSOCIADA A SEPSE: ESTUDO
PILOTO**

foi apresentado na modalidade Aprovado para a Sessão Pôster
Comentado, por Welder Zamoner, no evento XXVIII Congresso
Brasileiro de Nefrologia ocorrido de 14 a 17 de setembro de 2016 no
Centro Cultural e de Exposições Ruth Cardoso em Maceió/AL.

Maceió, 17 de setembro de 2016



CBN 2016 XXVIII CONGRESSO
BRASILEIRO 14 a 17 / 9
Maceió / AL **DE NEFROLOGIA**
VIII CONGRESSO LUSO BRASILEIRO DE NEFROLOGIA
ENCONTRO BRASILEIRO DE ENFERMAGEM EM NEFROLOGIA
Centro Cultural e de Exposições Ruth Cardoso
NEFROLOGIA INTEGRATIVA

CARMEN TZANNIO BRANCO MARTINS
Presidente da SBN - Gestão 2015/2016

MARCELO MAZZA DO NASCIMENTO
Diretor Científico da SBN - Gestão 2015/2016

MARIA ELIETE PINHEIRO
Presidente do XXVIII CBN

REALIZAÇÃO



GERENCIAMENTO



CCM



CERTIFICADO

Certificamos que

WELDER ZAMONER

participou do XIX Congresso Paulista de Nefrologia, realizado no Bourbon Atibaia Convention - Atibaia/SP de 5 a 7 de Outubro de 2017, na qualidade de Apresentador(a) de TL

TERAPIA RENAL SUBSTITUTIVA - TLD 5399 - Remoção de Vancomicina por Hemodiálise em Pacientes com Lesão Renal Aguda

São Paulo, 7 de Outubro de 2017


Lúcio R. Requião Moura

Presidente do XIX Congresso Paulista de Nefrologia


Maria Almerinda Ribeiro Alves
Coordenadora da Comissão Científica


Patrícia Ferreira Abreu
Tesoureira



CERTIFICADO

Certificamos que

O trabalho: LESÃO RENAL AGUDA POR VANCOMICINA: ESTUDO PILOTO SOBRE A INCIDÊNCIA E FATORES DE RISCO EM PACIENTES SEPTICOS

participou do XIX Congresso Paulista de Nefrologia, realizado no Bourbon Atibaia Convention - Atibaia/SP de 5 a 7 de Outubro de 2017, na qualidade de Tema Livre

Autores: Welder Zamoner, Karina Eid, Laís Bevaller, Isabela G Pierre, Adriano Santos, Andre Luis Balbi, Daniela Ponce

São Paulo, 7 de Outubro de 2017

Lúcio R. Requião Moura
Lúcio R. Requião Moura

Presidente do XIX Congresso Paulista de Nefrologia

Maria Almerinda Ribeiro Alves
Maria Almerinda Ribeiro Alves
Coordenadora da Comissão Científica

Patrícia Ferreira Abreu
Patrícia Ferreira Abreu
Tesoureira



RIO DE JANEIRO - 2018

XXIX CONGRESSO BRASILEIRO DE NEFROLOGIA

XVII CONGRESSO BRASILEIRO DE ENFERMAGEM EM NEFROLOGIA

CERTIFICADO

Certificamos que o trabalho

**VANCOINEMIA COMO PREDITORA DIAGNÓSTICA E PROGNÓSTICA DE LESÃO RENAL AGUDA
NEFROTÓXICA EM PACIENTES CRÍTICOS**

foi apresentado na modalidade Pôster Comentado, por Welder Zamoner, no evento XXIX Congresso Brasileiro de Nefrologia ocorrido de 19 a 22 de setembro de 2018 no Windsor Oceânico Hotel em Rio de Janeiro/RJ.

Rio de Janeiro, 22 de setembro de 2018


JOCEMIR RONALDO EÜGEN
Presidente do CBN 2018


CARMEN TZANNO BRANCO MARTINS
Presidente da SBN - Gestão 2017/2018


MARCELO MAZZA DO NASCIMENTO
Diretor Científico da SEN - Gestão 2017/2018

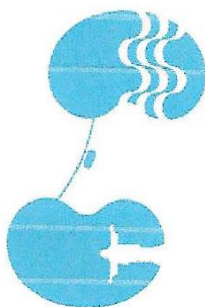
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Sociedade
Brasileira de
Nefrologia

GERENCIAMENTO





RIO DE JANEIRO - 2018

XXIX CONGRESSO BRASILEIRO DE NEFROLOGIA

XVII CONGRESSO BRASILEIRO DE ENFERMAGEM EM NEFROLOGIA

CERTIFICADO

Certificamos que o trabalho

O PAPEL DA VANCOCINEMIA NA POPULAÇÃO NÃO-CRÍTICA COMO PREDITORA DIAGNÓSTICA E PROGNÓSTICA DE LESÃO RENAL AGUDA

foi apresentado na modalidade Apresentação Oral, por Welder Zamoner, no evento XXIX Congresso Brasileiro de Nefrologia ocorrido de 19 a 22 de setembro de 2018 no Windsor Oceânico Hotel em Rio de Janeiro/RJ.

Rio de Janeiro, 22 de setembro de 2018

JOACIMIR RODOLFO EUGON
Presidente do CBN 2018

CARMEN TZANNÔ BRANCO MARTINS
Presidente da SBN - Gestão 2017/2018

MARCELO MAZZA DO NASCIMENTO
Diretor Científico da SBN - Gestão 2017/2018

REALIZAÇÃO



Sociedade
Brasileira de
Nefrologia

COEFICIAMENTO



CCM
CONGRESSES



*The Twenty-Fifth Annual International Conference on
Advances in Critical Care Nephrology
February 24-27, 2020*

AKI & CRRT 2020 Conference San Diego, California

Presents this certificate to
Welder Zamoner

In appreciation for your poster presentation titled:

*Serum Concentration of Vancomycin is a Diagnostic Predictor of
Nephrotoxic Acute Kidney Injury in Critically Ill Patients*

Ravindra L. Mehta, MBBS, MD, DM, FACP, FASN
Chairman, Organizing Committee



*The Twenty-Fifth Annual International Conference on
Advances in Critical Care Nephrology
February 24-27, 2020*

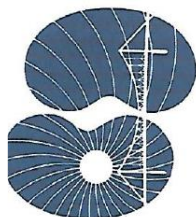
AKI & CRRT 2020 Conference San Diego, California

Presents this certificate to
Welder Zamoner

In appreciation for your poster presentation titled:

*The Role of Vancokinemia in the Non-Critical Population as a
Diagnostic and Prognostic Predictor of Acute Kidney Injury*

Ravindra L. Mehta, MBBS, MD, DM, FACP, FASN
Chairman, Organizing Committee



**XXXI CONGRESSO
BRASILEIRO DE NEFROLOGIA**
XIII Congresso Luso-Brasileiro de Nefrologia
XIX Congresso Brasileiro de Enfermagem em Nefrologia
21 A 24 DE SETEMBRO DE 2022 • CENTROSUL • FLORIANÓPOLIS-SC

Certificamos que o trabalho

**COMPARAÇÃO DE DIFERENTES ESQUEMAS DE ADMINISTRAÇÃO DE VANCOMICINA EM
PACIENTES COM INJÚRIA RENAL AGUDA EM HEMODIÁLISE: UM ENSAIO CLÍNICO
RANDOMIZADO**

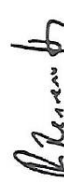
dos autores: WELDER ZAMONER; RICARDO DE SOUZA CAVALCANTE; DANIELA PONCE, foi apresentado na modalidade Apresentação oral - Finalista Prêmio Jovem Pesquisador, no evento XXXI Congresso Brasileiro de Nefrologia, XIII Congresso Luso-Brasileiro de Nefrologia e XIX Congresso Brasileiro de Enfermagem em Nefrologia ocorrido de 21 a 24 de setembro de 2022, no Centro de Convenções de Florianópolis (CentroSul) em Florianópolis/SC.

24 de setembro de 2022

Para validar, acesse <http://www.congressos.com.br/validacao/?cod=68897529>


Dr. Osvaldo Mereghe Vieira Neto
Presidente da
Sociedade Brasileira de Nefrologia


Dr. José H. Rocco Suassuna
Presidente da
Sociedade Brasileira de Nefrologia


Dr. Roberto Benvenuti
Presidente do XXXI Congresso
Brasileiro de Nefrologia


Dr. Marcelo Mazza do Nascimento
Diretor do Departamento de
Ensino Teórico SEN



Capítulo IV: Prêmio Jovem Pesquisador (SBN, 2022)



XXXI CONGRESSO
BRASILEIRO DE NEFROLOGIA
XIII Congresso Luso-Brasileiro de Nefrologia
XIX Congresso Brasileiro de Enfermagem em Nefrologia
21 A 24 DE SETEMBRO DE 2022 • CENTROSUL • FLORIANÓPOLIS-SC

Conferimos ao trabalho

COMPARAÇÃO DE DIFERENTES ESQUEMAS DE ADMINISTRAÇÃO DE VANCOMICINA EM PACIENTES COM INJÚRIA RENAL

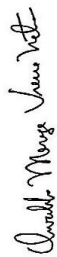
AGUDA EM HEMODIÁLISE: UM ENSAIO CLÍNICO RANDOMIZADO

Dos autores

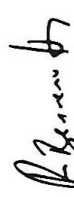
Welder Zamoner; Ricardo de Souza Cavalcante; Daniela Ponce;

O Prêmio Jovem Pesquisador, pelo trabalho apresentado como Tema Livre Oral durante o XXXI Congresso Brasileiro de Nefrologia, XIII Congresso Luso-Brasileiro de Nefrologia e XIX Congresso Brasileiro de Enfermagem em Nefrologia, ocorrido entre os dias 21 e 24 de setembro de 2022, no Centro de Convenções de Florianópolis CentroSul, em Florianópolis.

Florianópolis, 24 de setembro de 2022.


Dr. Osvaldo Merege Vieira Neto
Presidente da
Sociedade Brasileira de Nefrologia


Dr. José H. Rocco Suassuna
Diretor Científico da
Sociedade Brasileira de Nefrologia


Dr. Roberto Benvenuti
Presidente do XXXI Congresso
Brasileiro de Nefrologia


Dr. Marcelo Mazza do Nascimento
Diretor do Departamento de
Enfermagem em Nefrologia SEN

