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Nefrotoxicidade associado ao uso de Vancomicina com Piperacilina/Tazobactam

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Julho, 2023

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Nefrotoxicidade associado ao uso de Vancomicina com Piperacilina / Tazobactam

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ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☒
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INDEX

Title: Nephrotoxicity associated to the use of Vancomycin with Piperacillin/ Tazobactam

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ABSTRACT

Vancomycin is a first-line drug in the treatment of infections by multi-resistant microorganisms, such as MRSA, coagulase-negative methicillin-resistant Staphylococci and Enterococcus faecium. However, according to several studies, Vancomycin may be associated with significant nephrotoxicity. Several risk factors can increase the occurrence of nephrotoxicity, including high doses, prolonged therapy, combination with other nephrotoxic agents and admission to intensive care units. This study analyzes the relationship between the occurrence of nephrotoxicity in patients without previous chronic kidney disease who were administered Vancomycin with Piperacillin/Tazobactam for at least 48h during hospitalization. A total of 101 patients admitted to the Centro Hospitalar Universitário São João between April and September 2021 were included. Based on the results obtained, no statistically significant association was found between the occurrence of renal dysfunction and the time of concomitant antibiotic therapy (p=0.384), Charlson index (p=0.067), Vancomycin trough levels (p=0.967) or maximum dose intervals of Vancomycin trough (p=0.139). No statistically significant association was also found between the degrees of acute kidney injury and the maximum dose intervals of Vancomycin trough (p=0.363). However, the association between the use of Vancomycin with Piperacillin/Tazobactam and the occurrence of nephrotoxicity cannot be completely ruled out due to missing data in clinical records on the doses administered of these medications. This study has some limitations, as it is a retrospective and observational single-center cohort study, so future research should consider studying larger populations in order to obtain statistically significant results.

KEYWORDS: Nephrotoxicity; Piperacilin; Tazobactam; Vancomycin.

INTRODUCTION

According to the scientific literature, in the face of an infection by multi-resistant microorganisms, such as *Methicillin-resistant Staphylococcus Aureus* (MRSA)[1], *Coagulase-negative methicillin-resistant Staphylococci* and *Enterococcus faecium*, the first-line drug is Vancomycin, which has been associated with significant nephrotoxicity.[2-4]

The recommended dose of intravenous (IV) Vancomycin administration, according to the guidelines of the American Society of Infectious Diseases in patients with normal renal function, is 15-20 mg/kg/dose every 8-12 hours, not exceeding 2g per dose.[5]

Although cases of nephrotoxicity are often reversible, with discontinuation or dose adjustment of the drug, several risk factors contribute to the occurrence of this phenomenon.[6,7] Among these, high doses (especially >20mg/l) or a daily dose exceeding 2 g/day stand out[8,9], prolonged therapy (>7 days) in combination with other potentially nephrotoxic agents and admission to intensive care units with long stays.[10] The bactericidal activity of vancomycin is considered to be mainly time-dependent, rather than concentration-dependent. Increased doses of this drug increase its nephrotoxic risk.[11,12]

The combined antibiotic treatment of Vancomycin with Piperacillin/Tazobactam (VPT) is associated with an increased risk of incidence of nephrotoxicity, which may manifest as Acute Kidney Injury (AKI)[13-15], when compared to other pharmacological combinations. This nephrotoxic effect, accepted as a clinical entity, can, however, be minimized through monitoring of renal function and dose adjustment.[16]

Vancomycin is often used in combination with various antibiotic formulations, including Piperacillin/Tazobactam (PT)[17], both in initial empirical therapy and in

moderate to severe infections. Unlike vancomycin, PT is rarely associated with nephrotoxicity when administered alone.[18]

The results of several studies suggest that the likelihood of acute kidney injury is greater when using Vancomycin with Piperacillin/Tazobactam compared to therapy with Vancomycin alone or combined with Cefepime or Meropenem.[19]

Despite the fact that cases of nephrotoxicity caused by vancomycin are infrequent and often reversible, several possible predisposing factors have been established.[20,21]

Age, prolonged therapies with vancomycin or combination with other nephrotoxic agents, therapeutic regimens with increased doses of vancomycin, critically ill patients and patients with compromised renal function are all factors or conditions that increase the risk of occurrence of vancomycin-induced nephrotoxicity.[22,23]

This dissertation aims to study a possible relationship between the occurrence of nephrotoxicity in patients without prior chronic kidney disease, grouped in a database of the Nephrology Service of the Centro Hospitalar Universitário São João, E.P.E. (CHUSJ), to whom Vancomycin with Piperacillin/Tazobactam was administered for at least 48 hours.

SUBJECTS AND METHODS

This is a single-center retrospective cohort study (see Annex C), which aims to investigate the prevalence of nephrotoxicity in patients who underwent antibiotic therapy with the combination of Vancomycin and Piperacillin/Tazobactam. Additionally, it is intended to understand if supratherapeutic levels are associated with a higher risk of nephrotoxicity.

In the data collection, the digital hospital clinical processes present on the SClínico® platform were retrospectively consulted for all patients included in the study. Subsequently, the data was processed using *IBM SPSS Statistics software version 29.0.0.0 (241)*. The following variables were considered as follows:

1. Place of hospitalization (Medical Ward, Surgical Ward, Intermediate Care Unit, Intensive Care Unit)
2. Hospitalization Time
3. Age
4. Outcome (discharge, death)
5. Gender
6. Charlson Index (Acute myocardial infarction, Heart failure, Peripheral vascular disease, Dementia, Chronic pulmonary disease, Rheumatologic disease, Peptic ulcer disease, Moderate liver disease, Diabetes without complications, Diabetes with complications, Hemiplegia or paraplegia, Renal disease, Solid tumor, Leukemia, Lymphoma, Moderate or severe liver disease , HIV , Metastatic solid tumor); Previous CKD (Acute kidney injury , Acute chronic kidney disease , No kidney injury)
7. Baseline Creatinine
8. Creatinine at the date of discharge
9. Duration of concomitant therapy
10. Maximum dose of Vancomycin in the trough
11. Renal dysfunction
12. Degree of acute kidney injury (KDIGO1, KDIGO2, KDIGO3)
13. Vancomycin dosing intervals in the trough

From a total of 400 patients registered in the Nephrology Service database admitted to CHUSJ between April 2021 and September 2021 who were administered Vancomycin with Piperacillin/Tazobactam for at least 48 hours during hospitalization, 299 were excluded, of which 58 presented AKI/acute CKD, 9 previous AKI, 221 did not receive concomitant vancomycin with Piperacillin/Tazobactam or for at least 48 hours, and 11 patients were not hospitalized during the study period.

Given the defined variables, the following criteria were established:

Inclusion Criteria:

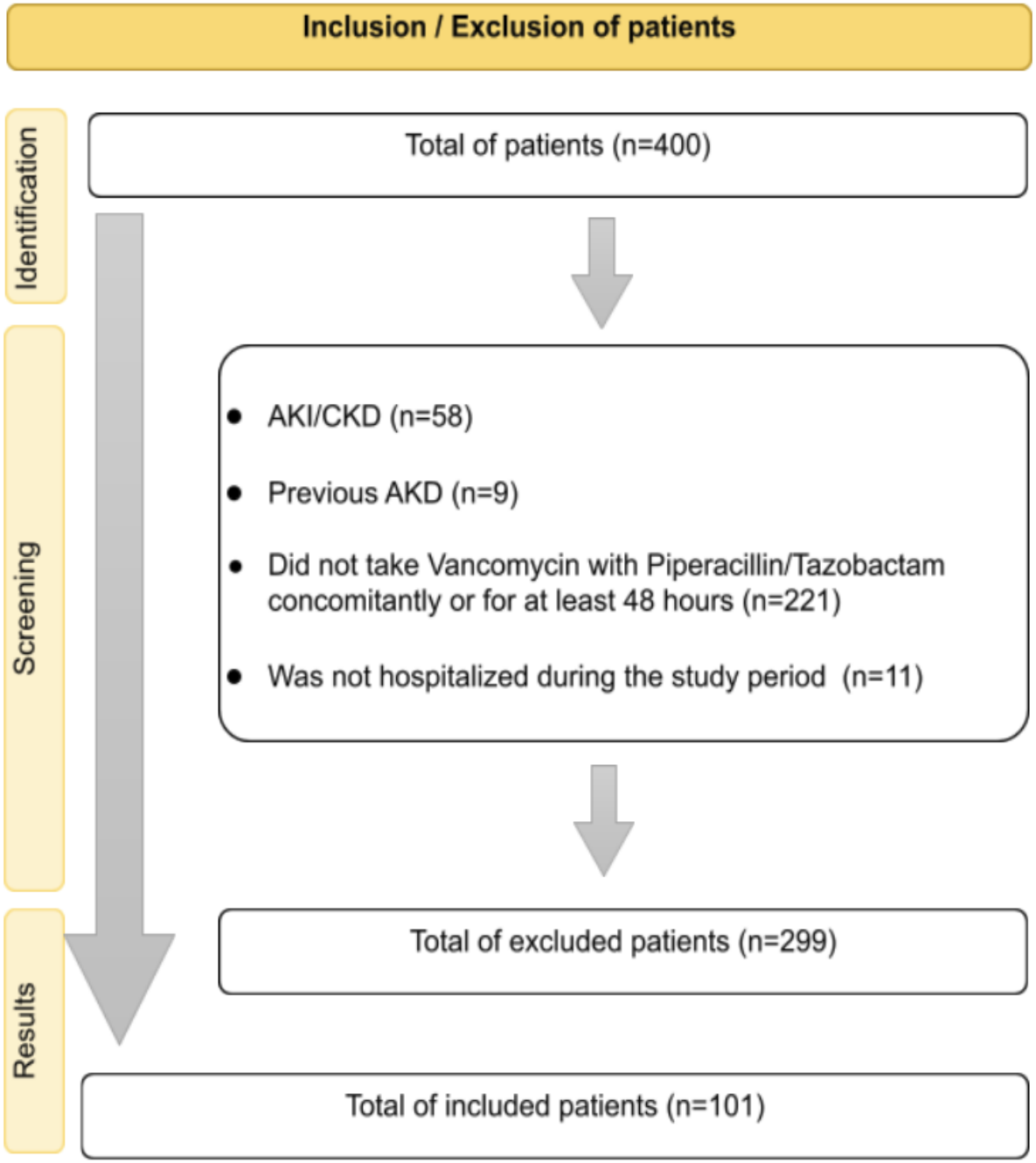
- All patients admitted to CHUSJ between April and September 2021, who underwent antibiotic therapy with Vancomycin in combination with Piperacillin/Tazobactam for at least 48 hours;
- Over 18 years old without previous chronic kidney disease.

Exclusion Criteria:

- Patients with previous chronic kidney disease and in need of renal function replacement therapy (hemodialysis or peritoneal dialysis);
- Acute kidney injury present prior to antibiotic therapy defined as an elevation of plasma creatinine value greater than 1.5x the known baseline creatinine value of the patient or >0.3 mg/dl.

This information is systematized in the following flowchart.

Figure 1 - Flowchart with sample selection criteria



RESULTS

From a total of 101 patients included in the study, 41 (40.6%) are women and 60 (59.4%) are men, with an average age of 64.94 years, a median of 66 years, with a standard deviation of 13.9. According to the data collected (see Table I: Characterization of Renal Dysfunction cases according to the degree of Acute Kidney

Injury - Annex B), it can be seen that the total number of patients who developed renal dysfunction during hospitalization was 38, of which 18 patients (47.4%) were classified with acute kidney injury degree KDIGO 1, 11 patients (28.9%) were classified with acute kidney injury degree KDIGO 2 and 9 patients (23.7%) were classified with acute kidney injury degree KDIGO 3.

Regarding Table II: Characterization of Renal Dysfunction cases according to the Vancomycin dosing intervals in the trough (Annex B), of the 36 patients who did not develop renal dysfunction, 3 (8.3%) presented a subtherapeutic dose of Vancomycin in the trough in the range <10mg/l, 5 (13.9%) presented a therapeutic dose of Vancomycin in the trough in the range 10-15mg/l, 8 patients (22.2%) presented a supratherapeutic dose due to infection by multiresistant microorganisms of Vancomycin in the trough in the range 15-20mg/l and 20 (55.6%) presented a supratherapeutic dose of Vancomycin in the trough in the range >20 mg/l.

In relation to patients who developed renal dysfunction, 3 (5.9%) had a subtherapeutic Vancomycin trough dose within the range <10mg/l, 1 (6.7%) had a therapeutic Vancomycin trough dose within the range of 10-15 mg/l, 8 patients (53.3%) had a supratherapeutic dose for infection by multiresistant microorganisms of Vancomycin trough within the range of 15-20mg/l and 6 (40.0%) had a supratherapeutic dose of Vancomycin trough within the range >20mg/l.

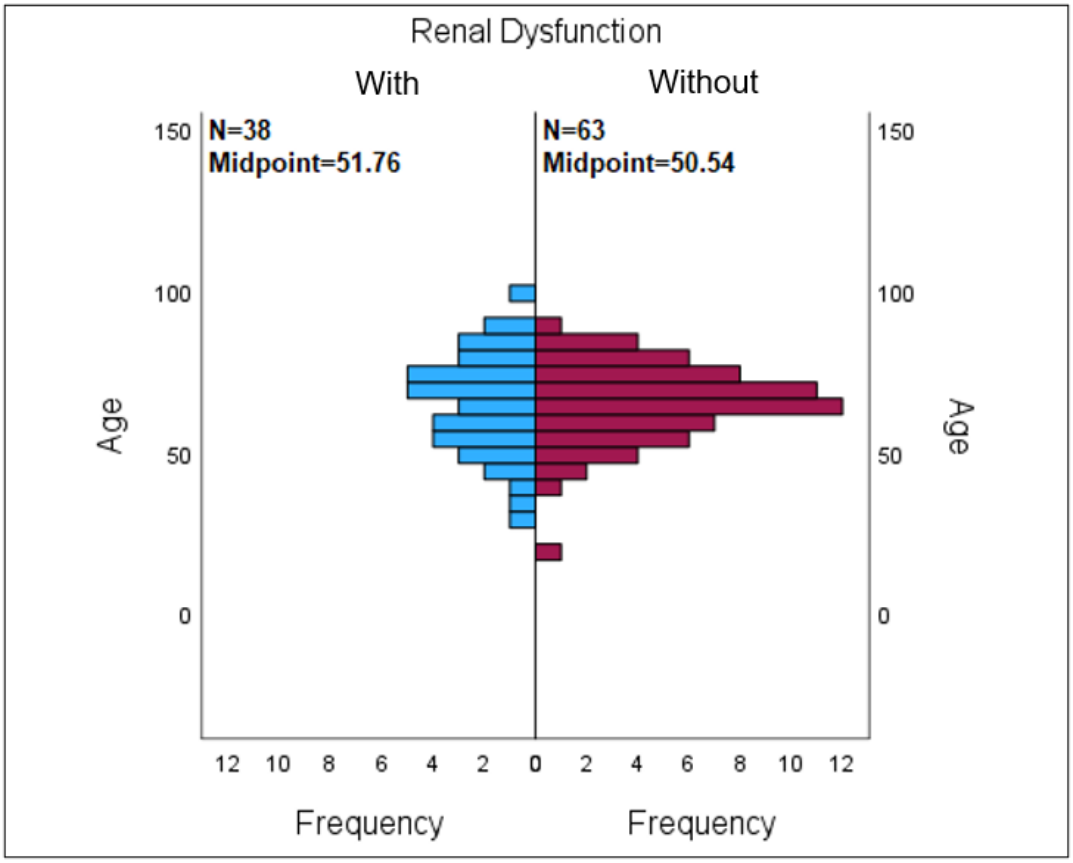
Analyzing Table III: Characterization of Acute Kidney Injury cases according to the intervals of maximum Vancomycin trough doses (Annex B), it can be observed that, out of a total of 15 patients who developed kidney injury, there is no data for the subtherapeutic dose interval of Vancomycin trough <10 mg/l; only 1 patient (6.7%) with KDIGO 3 Renal Injury (33.3%) presented a therapeutic dose of Vancomycin trough, in the range between 10 to 15 mg/l; 8 patients (53.3%), of which 4 patients (57.1%) with

KDIGO 1 Renal Injury, 3 patients (60.0%) with KDIGO 2 Renal Injury and 1 patient (33.3%) with KDIGO 3 Renal Injury presented a supratherapeutic dose for infection by multiresistant microorganisms of Vancomycin trough, within the range between 15 to 20mg/l; and 6 patients (40.0%), 3 (42.9%) with KDIGO 1 Renal Injury, 2 patients (40%) with KDIGO 2 Renal Injury and 1 patient (33.3%) presented a supratherapeutic dose of Vancomycin trough with a value greater than 20mg/l.

To answer the study question, the prevalence of nephrotoxicity associated with the use of Vancomycin with Piperacillin/Tazobactam in patients without previous kidney injury for at least 48h, the Mann-Whitney Test was used, obtaining the results expressed in Table IV: Summarization of Hypothesis Tests (Annex B).

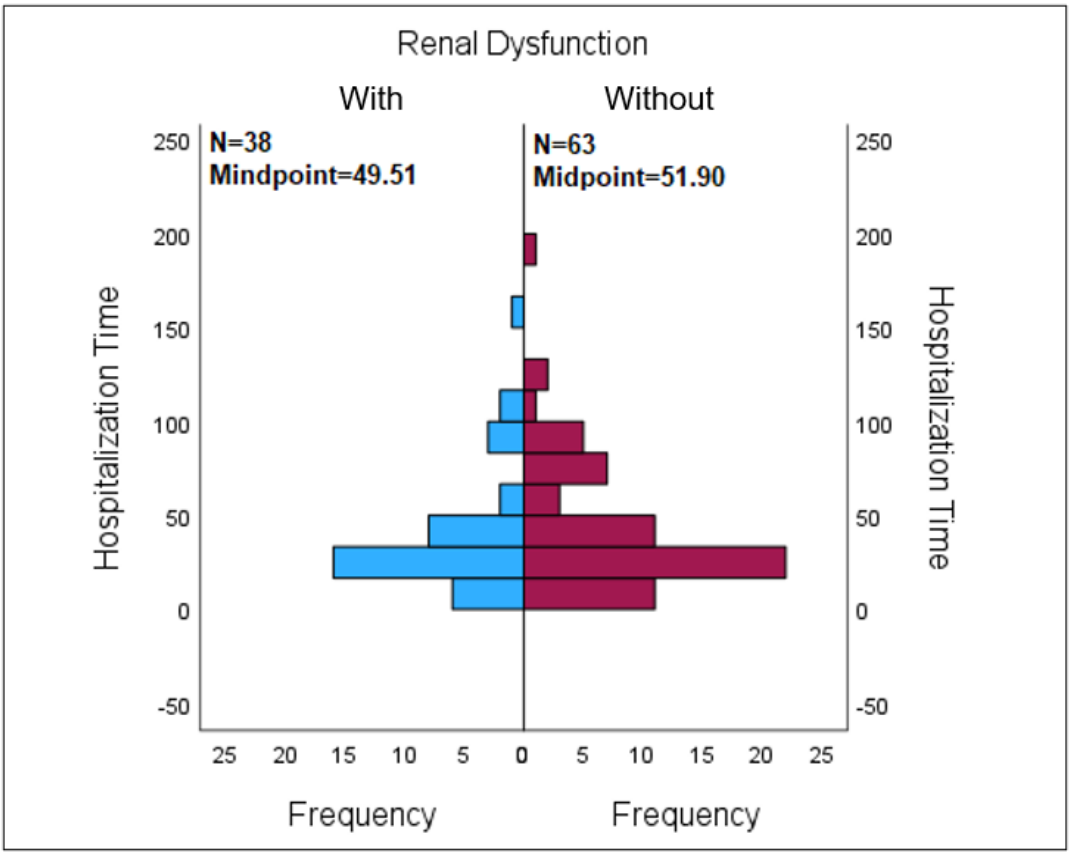
Groups of patients with and without renal dysfunction were compared and the distribution of ages was p=0.839; the distribution of hospitalization time was p=0.692; the distribution of the Charlson index was p=0.067; the distribution of concomitant therapy time was p=0.0384; and the distribution of the maximum Vancomycin trough dose, with a value of p=0.967.

Figure 2 - Graph of the Age



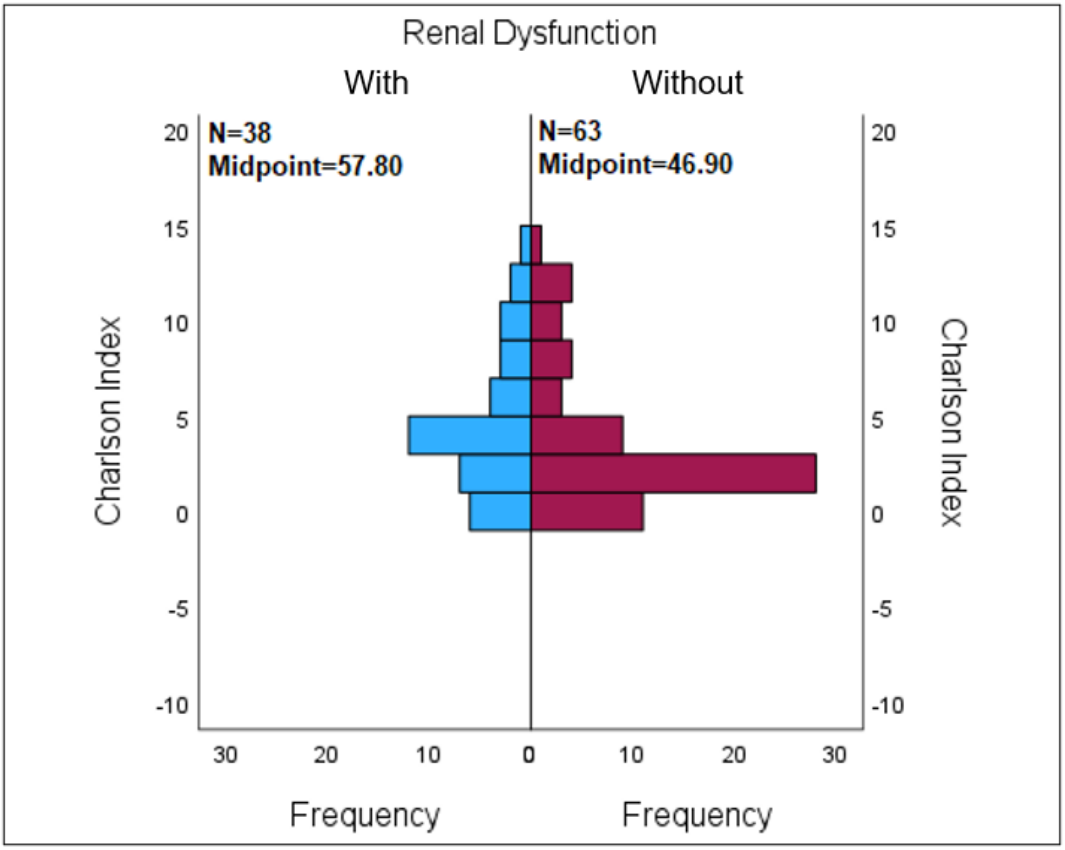
Upon closer observation of the data related to age, it is possible through the analysis of Figure 2, to realize that the median of the distribution of ages of patients with renal dysfunction (n=38) and without renal dysfunction (n=63) does not present a statistically significant difference, whose p-value is p=0.839.

Figure 3 - Graph of the Hospitalization Time



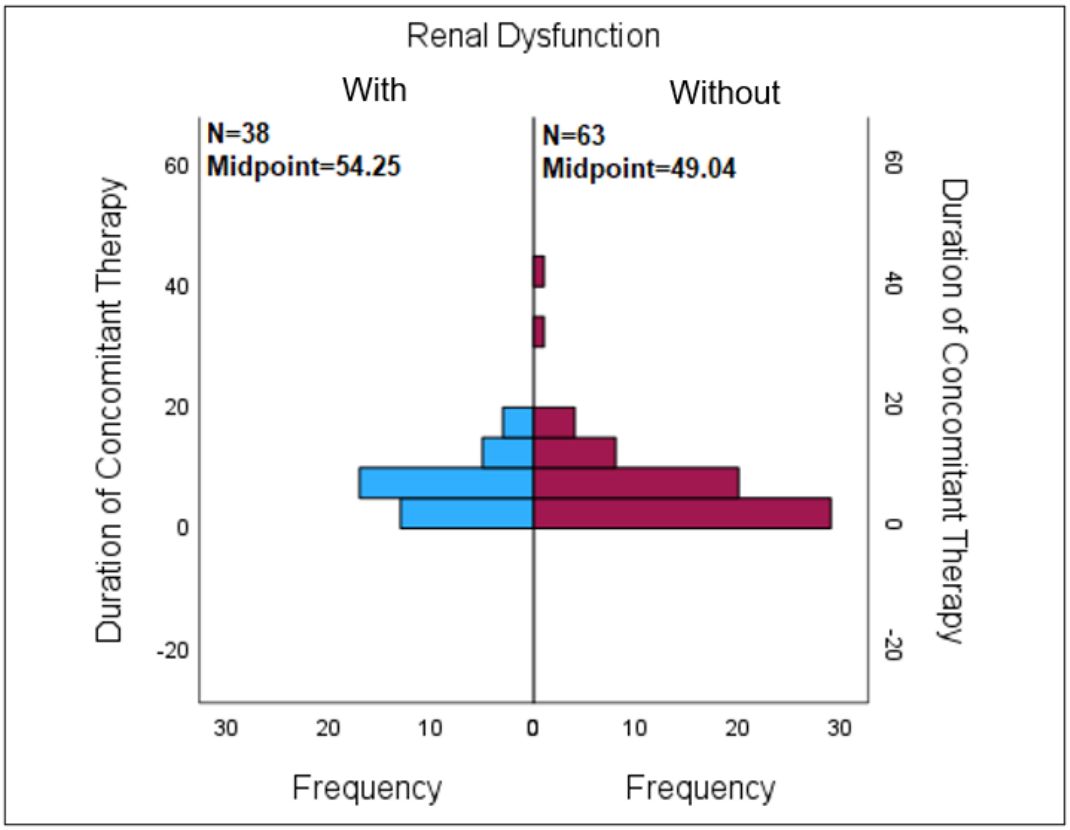
By analyzing Figure 3, it can be observed that the distribution of the medians of the hospitalization time of patients with renal dysfunction (n=38) and without renal dysfunction (n=63) does not present a statistically significant difference, whose p-value is p=0.692.

Figure 4 - Graph of the Charlson Index



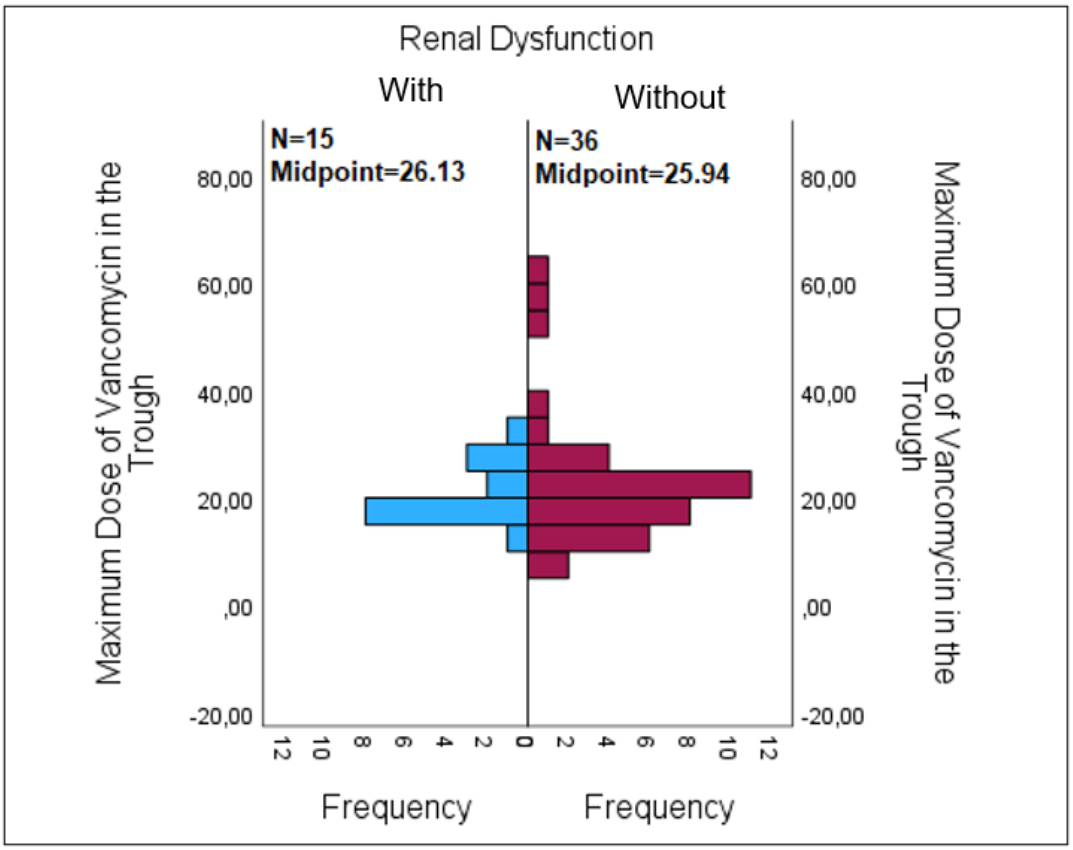
The distribution of the medians of the Charlson Index of patients with renal dysfunction (n=38) and without renal dysfunction (n=63) does not present a statistically significant difference, whose p-value is p=0.067, as shown by Figure 4.

Figure 5 - Graph of the Concomitant Antibiotic Therapy Time



The graph in Figure 5 shows that the distribution of the medians of the concomitant antibiotic therapy time of patients with renal dysfunction (n=38) and without renal dysfunction (n=63) does not present a statistically significant difference, whose p-value is p=0.0384.

Figure 6 - Graph of Maximum Dose of Vancomycin in the Trough



The data in Figure6 suggest that the distribution of the medians of the maximum Vancomycin trough dose of patients with renal dysfunction (n=15) and without renal dysfunction (n=36) does not present a statistically significant difference, whose p-value is p=0.967.

In Table V: Chi-square test between the variables Renal Dysfunction and Maximum Vancomycin trough dose intervals (Annex B), through its analysis, it is observed that with a p-value of p=0.139, the variables Renal Dysfunction and Maximum Vancomycin trough dose intervals do not present a statistically significant difference.

In Table VI: Chi-square test between the variables AKI degree and Maximum Vancomycin trough dose intervals (Annex B), through its analysis, it is understood that with a p-value of p=0.363, the variables AKI and Maximum Vancomycin trough dose intervals do not present a statistically significant difference.

DISCUSSION

In this study, it is understood that among hospitalized patients treated with Vancomycin associated with Piperacillin/Tazobactam against infections by multi-resistant microorganisms, some may develop renal dysfunction, as corroborated by scientific evidence.[2-4]

Regarding to the guidelines of the American Society of Infectious Diseases, in patients with normal renal function, which refer to the recommended daily dose for intravenous administration of Vancomycin, pointing to a value that should not exceed 2g daily[5], which is also suggested in this study. However, the lack of information on Vancomycin and Piperacillin/Tazobactam doses in the available clinical records did not allow access to this information for all patients.

In relation to the cases of nephrotoxicity, although it is known that they can often be reversible, it is also known that there are risk factors.[6,7] that can enhance this occurrence. In this study, it is understood that the combination with other potentially nephrotoxic agents and admission to intensive care units with long stays can be also be risk factors for the development of nephrotoxicity.[10] Similarly, it is also understood that increased doses of Vancomycin enhance the nephrotoxic risk, as suggested by other studies.[8,9,11,12]

With reference to nephrotoxic effect resulting from the combined antibiotic treatment of VPT, which can result in cases of AKI, some studies point to the possibility of it being minimized through monitoring of renal function and dose adjustment[16], something that can be confirmed based on the results of Table V (Annex B).

In terms of the occurrence of acute kidney injury, there is evidence that indicates a higher probability of AKI occurrence with the use of Vancomycin associated with Piperacillin/Tazobactam, compared to Vancomycin therapy alone or combined with

Cefepime or Meropenem.[19] Such evidence could not be confirmed in this study, due to the fact that the other pharmacological formulations were not the subject of study in this document.

Taking into account the predisposing factors for cases where nephrotoxicity caused by Vancomycin is recorded, although infrequent and often reversible, pointed out in some studies, there are several factors that can increase the risk of developing nephrotoxicity. These may include age, pre-existing kidney disease, concomitant use of other nephrotoxic drugs, and high doses or prolonged use of Vancomycin.[20,21] In this study, several factors were analyzed to determine their potential impact on the development of nephrotoxicity caused by Vancomycin. These factors included age, hospitalization time, Charlson index, concomitant antibiotic therapy time, and maximum Vancomycin dose.

Several studies[22,23] point out the following factors or conditions increase the risk of Vancomycin-induced nephrotoxicity: age, prolonged Vancomycin therapy or combination with other nephrotoxic agents, increased dose Vancomycin therapeutic regimens, critically ill patients and patients with compromised renal function. This is also suggested by this investigation.

Based on the analysis, the results of this study do not suggest a statistically significant association between the occurrence of “renal dysfunction” with “concomitant antibiotic therapy time” ($p=0.384$), “Charlson index” ($p=0.067$), “Vancomycin trough levels” ($p=0.967$), nor with “maximum Vancomycin trough dose intervals” ($p=0.139$). Additionally, no statistical significance was found between the variable “degrees of AKI” in patients who developed renal dysfunction and the variable “maximum Vancomycin trough dose intervals” ($p=0.363$).

Although the results do not confirm the association between taking Vancomycin

with Piperacillin/Tazobactam and the occurrence of nephrotoxicity, this cannot be completely ruled out due to the omission of data in clinical records on the doses administered of these drugs. The latter were only available in 50% of the patients in the sample. This fact may have had an impact on the results obtained, they were not statistically significant, as well as due to the small size of the sample.

In addition to this limitation, in this study it can also be pointed out that it is a retrospective and observational unicentric cohort study.

According to what is pointed out here, in terms of implications for clinical practice, this study reinforces the importance of establishing and/or reinforcing pharmacovigilance protocols for monitoring and adjusting Vancomycin doses, particularly in high-risk patients. The need for more systematic records with all relevant information for each patient at each moment is also reaffirmed in this report.

Taking into consideration the above, some aspects should be considered in future investigations, namely the study of populations from which larger samples can be taken, as with a larger sample, statistically significant results could probably be obtained.

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- PEVFF: Literature researching; data collection; analysis and writing of the manuscript
- LPCF: Conception of the work; revision of the article;

- PCLM: Revision of the article;

- VMSF: Revision of the article.

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ANNEXES

SÃO JOÃO

DELIBERAÇÃO DO CONSELHO DE ADMINISTRAÇÃO

Após apreciação e pareceres favoráveis da Comissão de Ética e do Centro de Epidemiologia Hospitalar, considerando que se encontram reunidos os requisitos e demais trâmites previstos no circuito para submissão de projetos de investigação no Centro Hospitalar Universitário de S. João e em conformidade com as disposições legais em vigor, o Conselho de Administração – ao abrigo das competências previstas no Artigo 71.º dos Estatutos dos hospitais, centros hospitalares, institutos portugueses de oncologia e unidades locais de saúde, aprovados pelo Decreto-Lei n.º 52/2022, de 4 de agosto – delibera:

1. Aprovar a realização do projeto de investigação:
   - "Nefrotoxicidade do uso de Vancomicina com Piperacilina/Tazobactam".
   - Serviço(s) onde decorrerá o projeto de investigação: Unidade de Farmacologia Clínica.
   - Investigador(a) principal: Pedro Eliseu Vicente Frutuoso Fernandes
2. Remeta-se à Comissão de Ética para os procedimentos adequados e demais trâmites convenientes.

CONSELHO DE ADMINISTRAÇÃO DO CENTRO HOSPITALAR UNIVERSITÁRIO DE S. JOÃO, EPE • REUNIÃO DE 3 DE AGOSTO DE 2023

Presidente do Conselho de Administração

Prof.ª Doutora Maria João Baptista

Diretor Clínico	Enfermeiro Diretor	Vogal Executiva	Vogal Executiva
– AUSENTE –			
Prof.º Doutor Roberto Roncon	Enfermeiro Pedro Emílio Mota	Dra. Sofia Leal	Dra. Fernanda Oliveira

› Comissão de Ética
› Centro de Epidemiologia Hospitalar
› Direção Clínica

CES 191/2023

Centro de Epidemiologia Hospitalar

Tomei conhecimento. Nada a opor. À DC.

30 de Julho de 2023

A Diretora do Centro de Epidemiologia Hospitalar

(Prof.ª Doutora Ana Azevedo)

n.º 491 / 2023

DIRECÇÃO CLÍNICA
31 JUL. 2023

SÃO JOÃO

PEDIDO DE AUTORIZAÇÃO

Realização de Investigação

Exmo. Senhor Presidente do Conselho de Administração
do Centro Hospitalar Universitário de São João

Nome do Investigador Principal:

Pedro Eliseu Vicente Frutuoso Fernandes

Título da Investigação:

Nefrotoxicidade do uso de Vancomicina com Piperacilina/Tazobactam

Pretendendo realizar no(s) Serviço(s) de:

Farmacologia Clínica

a investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efetivação.

Para o efeito, anexo toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar Universitário de São João/ Faculdade de Medicina da Universidade do Porto respeitante à investigação, à qual enderecei pedido de apreciação e parecer.

Com os melhores cumprimentos.

O Investigador/ Promotor

Porto, 05 *de* Maio *de* 2023 . Pedro Eliseu Vicente Frutuoso Fernandes
assinatura

SÃO JOÃO | Encarregado de Proteção de Dados / Data Protection Officer
Entrada 29/06/2023

Centro Hospitalar São João
Centro de Epidemiologia Hospitalar
20/7/2023

CES-IM005-1

Parecer da Comissão de Ética do

Centro Hospitalar Universitário de São João / Faculdade de Medicina da Universidade do Porto

Título do Projeto: Nefrotoxicidade do uso de Vancomicina com Piperacilina/Tazobactam

Nome do Investigador Principal: Pedro Eliseu Vicente Frutuoso Fernandes, estudante da FMUP (que com os profissionais de ligação indicados, dispõem de competências científicas para a realização do estudo

Onde decorre o Estudo: Na Unidade de Farmacologia Clínica. Apresentou declaração do Coordenador da Unidade Farmacologia Clínica, Prof. Doutor Fernando Magro. *Deverá incluir declaração da direção do Serviço de Nefrologia.*

Objetivos do Estudo:

Investigar a prevalência de nefrotoxicidade em doentes que realizaram antibioterapia com associação de vancomicina e Piperacilina/Tazobactam.

Contribuição para a vigilância e monitorização de reações adversas decorrentes da utilização destes fármacos.

Sensibilização para a importância da farmacovigilância.

Estudo realizado no âmbito do Mestrado Integrado em Medicina da FMUP, sob orientação do Prof. Doutor Luís Figueira, da Dra. Paula Moreira e do Dr. Vítor Fernandes (que serão os profissionais de ligação).

Conceção e Pertinência do estudo:

O tratamento antibiótico combinado de Vancomicina com Piperacilina/Tazobactam (VPT) está associado a um aumento de duas vezes o risco de incidência de nefrotoxicidade, podendo esta manifestar-se como Lesão Renal Aguda (LRA), quando comparada com outra combinações farmacológicas. Este efeito nefrotóxico, aceite como entidade clínica, pode, no entanto, ser minimizado através da monitorização da função renal e do ajuste da dose. A vancomicina é frequentemente usada combinada com diversas formulações antibióticas, incluindo a (PT), tanto em terapia empírica inicial como em infeções moderadas a severas. Ao contrário da vancomicina, a (PT) raramente se associam a nefrotoxicidade quando administrada isoladamente. Os resultados de diversos estudos sugerem que a probabilidade de ocorrência de lesão renal aguda é maior aquando do uso de vancomicina com piperacilina/tazobactam comparando com a terapêutica com vancomicina isolada ou combinada com cefepima ou meropenem.

Esta dissertação pretende estudar uma possível relação entre a ocorrência de nefrotoxicidade em doentes sem doença renal crônica prévia, agrupados numa base de dados do Serviço de Nefrologia do Centro Hospitalar Universitário São João, E.P.E. (CHUSJ), a quem foi administrada Vancomicina com Piperacilina / Tazobactam durante pelo menos 48h.

Estudo observacional de coorte retrospetivo, de todos os doentes admitidos no CHUSJ durante o período de abril a setembro de 2021, que realizaram antibioterapia com vancomicina em associação com piperacilina-tazobactam durante pelo menos 48h. Recolha de forma anonimizada a partir de registos clínicos digitais (401 doentes).

Benefício/risco: Não aplicável

Confidencialidade dos dados:
Todos os dados dos participantes serão codificados.
Apresentou um pedido de reutilização de registos clínicos para Investigação e Desenvolvimento ao RAI, e uma 'avaliação sobre o impacto da proteção de dados' para o EPD.

Respeito pela liberdade e autonomia do sujeito de ensaio: Não aplicável

***Curriculum* do investigador**: Adequado à investigação.

Data previsível da conclusão do estudo: julho de 2023

Conclusão: Proponho um parecer favorável à realização do estudo, após a entrega da declaração em falta.

Porto, 19 de maio de 2023

O Relator da CE, Prof. Doutor Manuel Vaz da Silva

21/06/2023
Entregou a declaração em falta.
Pedro Brito

Questionário eletrónico

n.º 191 / 2023

SÃO JOÃO

SUBMISSÃO DE PROJETO DE INVESTIGAÇÃO PARA PARECER E AUTORIZAÇÃO

Preenchimento em formato digital obrigatório

Caro/a Investigador/a

Este questionário vai ser objeto de apreciação pela Comissão de Ética (CE), que emitirá o competente parecer; pelo Responsável de Acesso à Informação (RAI), que emitirá um despacho de autorização ou indeferimento, relativamente à reutilização da informação a que pretende ter acesso; pelo Encarregado de Proteção de Dados (EPD), que emitirá um parecer, mediante a 'avaliação do impacto sobre a proteção de dados' (que deve anexar a este pedido); pelo Centro de Epidemiologia Hospitalar; sendo enviado, num último momento, para decisão institucional do Conselho de Administração do CHUSJ. Os respetivos despachos de parecer e autorização serão exarados no final deste documento, e enviados posteriormente, de modo a poder iniciar, nesse momento, a investigação a que se propõe.

IDENTIFICAÇÃO DO ESTUDO

Título do projeto:

Nefrotoxicidade do uso de Vancomicina com Piperacilina/Tazobactam

Data prevista para início: 14 / 09 / 2023 Data prevista para o término: 03 / 07 / 2023

EQUIPA DE INVESTIGAÇÃO

1. Investigador principal

Nome: Pedro Eliseu Vicente Frutuoso Fernandes

Afiliação institucional: ☐ CHUSJ ☒ FMUP Outro: _____

Serviço/ Departamento: _____

Grupo profissional: Estudante do 6º ano do Mestrado Integrado e Cédula Profissional n.º: _____

Contacto telefónico: 914109495 Endereço eletrónico institucional: up199901205@edu.med.up.pt

Formação em Boas Práticas Clínicas (GCP): ☒ Não ☐ Sim

2. Co-investigadores

Nome: _____

Afiliação institucional: _____

Grupo profissional: _____ Cédula Profissional n.º: _____

Contacto telefónico: _____ Endereço eletrónico institucional: _____

Nome: _____

Afiliação institucional: _____

Grupo profissional: _____ Cédula Profissional n.º: _____

Contacto telefónico: _____ Endereço eletrónico institucional: _____

(acrescentar nº de investigadores, se apropriado ao projeto de investigação)

3. Promotor *(se aplicável)*: _____

CARACTERIZAÇÃO DA INVESTIGAÇÃO

1. Metodologia da investigação

☐ Qualitativa ☐ Mista (qualitativa+quantitativa) ☐ Outra. Qual? _____

Se quantitativa:

☐ Experimental ☒ Observacional ☐ Sem intervenção ☐ Com intervenção

Se experimental ou observacional com intervenção, qual o tipo de intervenção?

☐ Algoritmo de decisão diagnóstica/terapêutica ☐ Comunicação

☐ Outra. Qual? _____

2. Aleatorização dos braços de intervenção: ☒ Não ☐ Sim

3. Se observacional, qual o desenho?

☐ Coorte prospetivo ☒ Coorte retrospetivo ☐ Caso-controlo

☐ Transversal ☐ Ecológico ☐ Outro. Qual? _____

REALIZAÇÃO DA INVESTIGAÇÃO

Local onde se realiza a investigação: ☒ CHUSJ ☐ FMUP ☐ Outro

Serviço/ Departamento: Farmacologia Clínica

Existem outros Centros onde se realizará a investigação? ☒ Não ☐ Sim. Quais? _____

ENTIDADE(S) QUE TUTELA(M) A INVESTIGAÇÃO

1. CHUSJ – Serviço: Farmacologia Clínica

2. FMUP – Departamento: UC Dissertação

3. Outra instituição. Qual? _____

ORIENTADOR *(se aplicável)*

Nome: Luís Pedro Caldas Figueira

Afiliação: CHUSJ Endereço eletrónico institucional: figueira@med.up.pt

PROFISSIONAL DE LIGAÇÃO *(se aplicável - ver anexo)*

Nome: Paula Cristina Leão Moreira Serviço: Farmacologia Clínica

ENQUADRAMENTO DA INVESTIGAÇÃO

Em trabalho académico? ☐ Não ☒ Sim Conferidor de grau? ☐ Não ☒ Sim

Síntese dos objetivos:

Investigar a prevalência de nefrotoxicidade em doentes que realizaram antibioterapia com associação de vancomicina e Piperacilina/Tazobactam;
Contribuição para a vigilância e monitorização de reações adversas decorrentes da utilização destes fármacos.
Sensibilização para a importância da farmacovigilância.

Fundamentação ética *(incluir informação sumária sobre o estado da arte, ganhos em conhecimento/inovação, ponderação geral sobre benefícios/risco)*:

Com base nos resultados deste estudo, que considera a literatura científica neste âmbito, pode-se-á ponderar possíveis recomendações para procedimentos terapêuticos a adotar no uso de de vancomicina com Piperacilina / Tazobactam em especial em doentes cujo risco de
O estudo será conduzido de acordo com o protocolo aprovado e em conformidade com a Declaração de Helsínquia, (GCP-ICH) - boas práticas Clínicas e todas as leis e regulamentos aplicáveis.

PARTICIPANTES PREVISTOS PARA A INVESTIGAÇÃO

Estão definidos critérios de inclusão / de exclusão de doentes? ☐ Não ☒ Sim

Onde e como serão recrutados os participantes no estudo?
Recolha a partir de registos clínicos digitais

Qual é o tamanho amostral? 401 doentes

Está prevista a recolha de material biológico específico para a investigação?

☒ Não ☐ Sim. Identifique e justifique:

BENEFÍCIO/RISCO DECORRENTE DA PARTICIPAÇÃO

Descreva os benefícios previsíveis:

Descreva os riscos/incómodos previsíveis:

CONSENTIMENTO INFORMADO, ESCLARECIDO E LIVRE

Prevê a obtenção de consentimento informado? ☐ Sim ☒ Não

Se não, justifique:

Prevê informação escrita para os participantes? ☐ Sim. **Enviar modelo preenchido.**

☒ Não. Justifique:

O modelo para obtenção de consentimento é o modelo institucional do CHUSJ? ☐ Sim ☐ Não

PROTEÇÃO DE DADOS PESSOAIS

Necessita consultar registos clínicos? ☐ Não ☒ Sim

Está previsto o tratamento de dados pessoais? ☐ Não ☒ Sim

Se sim, de que forma é garantida a pseudonimização dos dados recolhidos? *(codificação, uso de filtros, siglas...)*

Codificação

Descreva o património informacional a que pretende ter acesso *(v.g.: nome, idade, data nascimento, idade, morada, diagnóstico, história clínica, tratamento...)*:

Idade, Sexo, Nº de dias de internamento, Local de Internamento, Índice de Charlson, Nível de Creatinina basal, Nível de Creatinina à data de Alta, Dose de vancomicina inicial, Dose de piperacilina inicial, Valor de Vancomicina em Vale, Diagnóstico de Lesão renal aguda, Grau de lesão Renal Aguda KDIGO, Necessidade de terapêutica de substituição da função renal (TSFR);

Está prevista a criação de um Banco de Dados? ☐ Não ☒ Sim

Está previsto o registo de som ou de imagem dos participantes? ☒ Não ☐ Sim

O estudo envolve investigação genética? ☒ Não ☐ Sim

PROPRIEDADE INTELECTUAL

De quem será a propriedade intelectual da investigação e seus resultados?

☒ Investigador ☐ Promotor ☒ Serviço/CHUSJ ☐ Todos

DIVULGAÇÃO DOS RESULTADOS

Está prevista a divulgação dos resultados da investigação? ☒ Não ☐ Sim

Se sim, estão definidos critérios de publicação? ☐ Não ☐ Sim. Quais? _____

CONTRAPARTIDAS PARA OS PARTICIPANTES

Estão previstas contrapartidas para os participantes? ☒ Não ☐ Sim

Pela participação? ☒ Não ☐ Sim

Pelas deslocações? ☒ Não ☐ Sim

Pelas perdas salariais? ☒ Não ☐ Sim

Por outras perdas e/ou danos? ☒ Não ☐ Sim

EXAMES COMPLEMENTARES DE DIAGNÓSTICO

Estão previstos exames complementares de diagnóstico, para além dos inerentes à rotina assistencial?

☒ Não ☐ Sim. Quais? _____

Por quem serão suportados estes custos?

PROTOCOLO FINANCEIRO

Existe protocolo financeiro com o CHUSJ? ☒ Não ☐ Sim

SEGURO

Este estudo prevê intervenção clínica que implique a existência de um seguro para os participantes?

☒ Não ☐ Sim *(se sim, junte cópia da respetiva Apólice)*

Data previsível para fim das credenciais de acesso: 03 /07 /2023

DOCUMENTOS ANEXOS *(em suporte digital)*

- [x] Pedido de autorização ao Presidente do Conselho de Administração do CHUSJ
- [x] Protocolo do estudo
- [ ] Caderno de recolha de dados (CRF)
- [x] Declaração Diretor(es) Serviço(s)
- [x] Informação Orientador
- [x] Profissional de ligação
- [ ] Informação aos participantes
- [ ] Modelo de consentimento a utilizar
- [ ] Instrumentos de avaliação *(escalas, inquéritos)* _____
- [x] Curriculum/a vitae *(investigador/es)*
- [ ] Questionário para Encarregado de Proteção de Dados (EPD)
- [x] Termo de Responsabilidade do Centro Académico Clínico *(para investigadores da FMUP que não pertençam ao CHUSJ)*
- [ ] Protocolo financeiro
- [ ] Outros: _____

TERMO DE RESPONSABILIDADE

Aceitação dos termos e condições de reutilização

Cumulativamente com as obrigações decorrentes da *Lei n.º 26/2016, de 22 de agosto*, maxime dos *n.º 2 e 3 do artigo 21 e o n.º 1 e 2 do artigo 12*, ao submeter o presente pedido, concordo e fico ainda juridicamente vinculado aos seguintes termos e condições:

- Comprometo-me a manter confidencial toda a informação à qual vou ter acesso;
- Após explicação do RAI do CHUSJ, embora a Lei 26/2016, de 22 de agosto, imponha como requisito a anonimização sem possibilidades de reversão, tal desiderato, é não só uma impossibilidade matemática já comprovada, como ainda resulta num prejuízo para a investigação, face à quantidade e à qualidade da informação a retirar à fonte, razão pela qual, concordando com o RAI, assumimos como compromisso a pseudonimização, o que impõe uma avaliação e gestão do risco, num quadro ético-jurídico que aceitamos e nos comprometemos a colaborar e respeitar;
- Não vou elaborar registos, suscetíveis de identificar ou tornar identificável a identidade das pessoas a quem os mesmos dizem respeito;
- Comprometo-me a consultar os processos clínicos nos termos e locais que me forem indicados para o efeito;
- Tomei conhecimento, que a violação de qualquer dos compromissos aqui assumidos, poderá resultar no apuramento de responsabilidades disciplinares, civis e penais, e ainda, à impossibilidade futura de aceder a informação de saúde para fins de investigação.
- Independentemente de requerer a Certidão de Reutilização, DAta REuse Certificate for Research (DARE), comprometo-me a citar as fontes, sempre que publicitar, no todo ou em parte, resultados da presente investigação.

COMPROMISSO DE HONRA E DECLARAÇÃO DE INTERESSES

Eu, Pedro Eliseu Vicente Frutuoso Fernandes ,

abaixo assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes na Declaração de Helsinquia (1960, e sucessivas emendas), da Organização Mundial de Saúde, da Convenção de Oviedo e das 'Boas Práticas Clínicas' (GCP/ICH) no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CE de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo, nos últimos três meses. Comprometo-me a entregar à CE o relatório final da investigação, assim que concluído.

Data: 05 /05 /2023

Pedro Eliseu Vicente Frutuoso Fernandes
assinatura

COMISSÃO DE ÉTICA CHUSJ/FMUP

Centro Hospitalar **São João**

Parecer da CE, emitido na reunião plenária de 19/05/2023

Aguarda esclarecimentos

CONSIDERADOS QUE FORAM COMO SATISFATÓRIOS OS ESCLARECIMENTOS PRESTADOS PELO(A) INVESTIGADOR(A), A CES APROVA POR UNANIMIDADE O PARECER DO RELATOR, PELO QUE NADA TEM A OPOR À REALIZAÇÃO DESTE PROJETO DE INVESTIGAÇÃO.

21/06/2023

RAI 23008884

RAI - Responsável pelo Acesso à Informação no Centro Hospitalar Universitário de São João (Art. 9º, Lei 26/2016 de 22 de Agosto)

SÃO JOÃO
Gabinete de Apoio ao RAI
Recebido em 22/06/2023
A funcionária

SÃO JOÃO
AUTORIZADO
RAI - Responsável pelo Acesso à Informação do Centro Hospitalar de São João (Art. 9º, Lei 26/2016, de 22/8)
22/06/2023

CENTRO DE EPIDEMIOLOGIA HOSPITALAR

SÃO JOÃO

ENCARREGADO DE PROTEÇÃO DE DADOS (EPD)
CENTRO HOSPITALAR UNIVERSITÁRIO DE S. JOÃO, EPE
Paulo Alexandre Mota da Silva
Encarregado de Proteção de Dados do CHUSJ
epd@chsj.min-saude.pt

Ref.ª CES CHUSJ: **191 / 2023**

Título do Projeto

Nefrotoxicidade do uso de Vancomicina com Piperacilina/Tazobactam

Responsável pelo tratamento	Pedro Eliseu Vicente Frutuoso Fernandes
Instituição	Centro Hospitalar Universitário São João (CHUSJ)
	Faculdade de Medicina da Universidade do Porto (FMUP)
Investigador	Interno **Externo**
Contacto telefónico	914109495 **Endereço Electrónico** up199901205@edu.med.up.pt
Profissional de Ligação	Paula Cristina Leão Moreira (Interna Formação Específica)
Amostra	103

Análise de Risco Tolerável **Baixo** Elevado Muito Elevado

Parecer do EPD: **Data:** 25/07/2023

Finalidade: Investigar a relação entre o uso concomitante de Vancomicina com Piperacilina/Tazobactam e a ocorrência de nefrotoxicidade.

Licitude: fundamento previsto no artigo 9(2)(j), com as garantias do **89(1)** do **RGPD**, e artigo **31(1)** da **LERGPD**.

Categorias de dados pessoais: variáveis identificadas com detalhe na AIPD, datada de 29/06/2023, **ponto 13**, tendo presente o **princípio da minimização dos dados.**

Conservação: os dados serão alvo de **pseudonimização**, armazenados em **local seguro**, em área restrita com acesso limitado ao profissional de ligação e Investigador Principal, com acesso a ficheiros protegido por **palavra-passe**, efetuando-se a conservação até a conclusão da investigação, que se estima ser até **31 de julho de 2023**. Os dados recolhidos **serão destruídos** após a finalização do estudo.

Comunicação de Dados: **não há partilha** de dados pessoais.

Face ao exposto, e observadas as recomendações, entende-se que a presente AIPD apresenta os elementos necessários para assegurar que o **tratamento é realizado em conformidade com o RGPD.**

Recomendações:

1. Garantir medidas de segurança acicionais no transporte dos dados com recurso a dispositivos electrónicos de armazenamento (Laptop, Cloud Institucional), nomeadamente através de medidas de cifragem e autenticação;
2. Em caso de necessidade de extensão de prazo e/ou de qualquer alteração dos pressupostos atinentes ao presente parecer o Investigador Principal deverá solicitar a reapreciação do projeto de investigação junto do EPD.

Revisão AIPD:

☐ Data da próxima revisão: ___/___/_____ ☒ Não carece de revisão.

Anexos:

1. Processo CES n.º 191/2023
2. Parecer CES (21/06/2023)
3. AIPD (29/06/2023)
4. Protocolo de investigação

Encarregado de Proteção de Dados
Assinado por: **PAULO ALEXANDRE MOTA DA SILVA**
Data: 2023.07.25 12:38:27+01'00'
Localização: CHUSJ

CARTÃO DE CIDADÃO

ANNEX B – Tables

Table I: Characterization of Renal Dysfunction cases according to the degree of Acute Kidney Injury[a]

		AKI Degree			
		1	2	3	Total
Renal Dysfunction	Nr. of cases	18	11	9	38
	% Renal Dysfunction	47.4%	28.9%	23.7%	100.0%

a. AKI – Acute Kidney Injury

Table II: Characterization of Renal Dysfunction cases according to the Vancomycin dosing intervals in the trough

			Renal Dysfunction cases according to the Vancomycin dosing intervals in the trough				
			Subtherapeutic [<10mg/l]	Therapeutic [10-15mg/l]	Multiresistant [15-20mg/l]	Suprathera peutic [>20mg/l]	Total
Renal Dysfunction	No	Nr. of cases	3	5	8	20	36
		Percentage	8.3%	13.9%	22.2%	55.6%	100.0%
	Yes	Nr. of cases	0	1	8	6	15
		Percentage	0.0%	6.7%	53.3%	40.0%	100.0%
Total		Nr. of cases	3	6	16	26	51
		Percentage	5.9%	11.8%	31.4%	51.0%	100.0%

Table III: Characterization of Acute Kidney Injury cases according to the intervals of maximum Vancomycin trough doses

			Intervals of maximum Vancomycin trough doses			
			Therapeutic [10-15mg/l]	Multiresistant [15-20mg/l]	Supratherapeutic [>20mg/l]	Total
AKI degree	KDIG0 1	Nr. of cases	0	4	3	7
		Percentage	0.0%	57.1%	42.9%	100.0%
	KDIG0 2	Nr. of cases	0	3	2	5
		Percentage	0.0%	60.0%	40.0%	100.0%
	KDIG0 3	Nr. of cases	1	1	1	3
		Percentage	33.3%	33.3%	33.3%	100.0%
Total		Nr. of cases	1	8	6	15
		Percentage	6.7%	53.3%	40.0%	100.0%

Table IV: Summarization of Hypothesis Tests

Null Hypothesis	Test	Sig. [a.]	Decision
1. Age distribution is equal in the categories of renal dysfunction.	Mann Whitney U Test Independent Samples	.839	Accept null hypothesis
2. Distribution of Hospitalization Time is equal in the categories of Renal Dysfunction.	Mann Whitney U Test Independent Samples	.692	Accept null hypothesis
3. Distribution of Charlson index is equal in the categories of renal dysfunction.	Mann Whitney U Test Independent Samples	.067	Accept null hypothesis
4. Distribution of Time of concomitant antibiotic therapy is equal in the categories of Renal Dysfunction.	Mann Whitney U Test Independent Samples	.384	Accept null hypothesis
5. Distribution of Vancomycin trough is equal in the categories of Renal Dysfunction	Mann Whitney U Test Independent Samples	.967	Accept null hypothesis

a. Significance level is .050.

Table V: Chi-square test between the variables Renal Dysfunction and Maximum Vancomycin trough dose intervals

	Value	Standard Deviation	Assintomatic Significance (Bilateral)
Pearson's chi-square	5.489[a]	3	.139
Likelihood ratio	6.113	3	.106
Nr. of cases	51		

a. 5 cells (62.5%) expected a count less than 5. The minimum expected count is .88.

Table VI: Chi-square test between the variables AKI degree and Maximum Vancomycin trough dose intervals

	Value	Standard Deviation	Assintomatic Significance (Bilateral)
Pearson's chi-square	4.333	4	.363
Likelihood ratio	3.587	4	.465
Nr. of cases	15		

ANNEX C – STROBE Statement—Checklist of items that should be included in reports of cohort studies

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	5,6
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	6
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	8-11
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	NA
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10,11
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	NA
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	NA
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			11-18
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	11
		(c) Consider use of a flow diagram	11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA Annex B NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	19-21
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA

*Give information separately for exposed and unexposed groups.
Note: NA - Not apply

ANNEX D – Standards of the Portuguese Journal of Nephrology and Hypertension

Aims and Scope

Portuguese Journal of Nephrology and Hypertension is the official organ of the Portuguese Society of Nephrology and is published quarterly. Supplementary issues on selected themes may also be published at the discretion of the Editor-in-Chief.

The Journal publishes articles on clinical or laboratory topics of relevance to nephrology, dialysis, transplantation and hypertension. Papers relating to basic immunology, physiology, genetics and epidemiology are accepted when kidney related.

Portuguese Journal of Nephrology and Hypertension publishes Editorials and in-depth Reviews, Original Articles, Short Communications, Technical Notes, Case Reports and Letters. Articles are accepted and published in English. Manuscripts submitted to the Portuguese Journal of Nephrology and Hypertension will be sent for peer review on the understanding that the author(s) have not published the material elsewhere.

The Journal is peer-reviewed and is indexed in Web of Science's SciELO Citation Index and Directory of Open Access Journals, with free online access in our website: https://www.spnefro.pt/rpnh.

Portuguese Journal of Nephrology and Hypertension complies with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals produced by the ICMJE (International Committee of Medical Journal Editors). Please see http://www.icmje.org.

Review and publication speed

All submissions will be subject to an immediate editorial screening process by the Editor-in-Chief after which they will normally be sent to three reviewers. The Editor-in-Chief will make every effort to reach a decision on all submitted papers within 8 weeks of receipt. Papers will normally be published in the next issue to go to press after their acceptance. Papers that do not meet the scientific standards of the journal may be declined by the Editor-in-Chief without further review.

Content types

The Portuguese Journal of Nephrology and Hypertension publishes: 1) Editorials; 2) Review Articles; 3) Original Articles; 4) Case Reports; 5) Letters to the Editor; 6) Nephropathology Quiz; 7) Top article.

Editorials

Editorials are usually invited, but authors may propose a paper for the Editor-in-Chief's consideration. They may have up to 2000 words and a maximum of 2 tables or figures. A maximum of 5 references is generally recommended.

Review Articles

Review articles should provide novel insights and comprehensive analyses of topics on Nephrology, and interpretation of the published literature. They are usually commissioned by the Editors. However, unsolicited reviews will be considered. These articles may have up to 5000 words and an abstract of up to 300 words. The use of 3 tables or figures is acceptable. A maximum of 70 references is generally recommended.

Original Articles

An original article must focus on relevant clinical investigation or basic research, and is limited to 4000 words including an abstract with up to 300 words. The order of the text should be as follows: Introduction, Subjects and Methods (any statistical method must be detailed in this section), Results and Discussion. A maximum of 50 references is generally recommended.

Case Reports

Original and succinct description structured in Introduction, Case Report and Discussion. They should not exceed 2500 words (including an abstract up to 300 words) and should not include more than 4 tables or figures. A maximum of 30 references is generally recommended.

Letters to the Editor

Letters must contain information related to an article published in the Journal or may concern a topic of current interest in Nephrology. Letters (maximum of 3 authors) are limited to 500 words and 1 table or figure. A maximum of 5 references is generally recommended.

Nephropathology Quiz

A case report to educate clinicians on the renal pathology. This section includes a concise clinical history, images of histology and discussion. These articles are usually invited and are limited to 2000 words, 8 figures and 20 references.

Top article

These articles, by invitation of the Editors, must contain a commentary concerning an international paper published in the last 3 months. These manuscripts are limited to 1500 words and 20 references.

Manuscript Submission

Once you have prepared your manuscript according to the Instructions below, submitted you manuscript online through: http://rpnh.spnefro.pt. Please pay particular attention to the Disclosures section.

Manuscript Preparation

Manuscripts must be typed in English and double-spaced with page numbers.

The title page must include:

- manuscript title
- all authors' full names, highest academic degrees, affiliations and e-mail address
- name, affiliation, address and e-mail address of the corresponding author
- all authors must be identified with their ORCID number
- word count for the abstract
- word count for the text, excluding references, figures, and tables

Do not forget to download the Authorship Responsibility Statement/Authorization for Publication and Conflict of Interest. The article can only be submitted with these two documents.

Required documents in submission

Authorship Responsibility Statement and Authorization for Publication

Conflict of Interest file (ICMJE template)

Manuscript Order

Ensure that the manuscript includes all of the following items:

- Abstract
- Key-words
- Introduction
- Materials and Methods
- Results
- Discussion
- Disclosures
- Acknowledgments
- References
- Tables (all cited) with appropriate descriptive titles
- Figures and legends (all cited)

Abstract:

Not more than 300 words. Abbreviations should not be used.

Key-Words:

Not more than 6, in alphabetical order, and the terms used (when possible) should be from the Medical Subject Headings list of the Index Medicus.

Disclosures:

- Conflict of interests: Each manuscript must include a conflict of interest statement before the References section. The disclosure statement will describe the sources of any support for the work in the form of grants, consulting fees or honoraria from industry, equipment, provision of drugs, travel related with the study or any combination thereof. Any relevant financial activities outside the submitted paper but considered stakeholders in the field must be detailed. The corresponding author should provide a Conflict of Interest Declaration describing the possible financial interests of all the authors. The absence of any interest must also be declared.

- Funding: All sources of funding should be declared. Authors should declare the role of study sponsors, if any, in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. If the study sponsors had no such involvement, the authors should so state.

- Consent for publication: Authors must declare their consent for publication and must include the statement: "the results presented in this paper have not been published previously, in whole or in part, except in abstract form".

- Informed Consent and Ethics: Identifying details of patients should not be published in descriptions unless the information is essential for scientific purposes and the patient gives written informed consent for publication. Patients shown in photographs should have their identity obscured or the picture must be accompanied by written permission to use the photograph.

When reporting experiments on human subjects, it is mandatory to indicate whether the procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975 (revised in 2015) and, in the case of renal transplant, the Declaration of Istanbul.

When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

- Author Contribution: With regard to authorship credit, PJNH has adopted the criteria recommended by the International Committee of Medical Journal Editors (ICMJE) in the current update of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: "Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; AND 2) drafting the article or revising it critically for important intellectual content; AND 3) final approval of the version to be published." Those who contributed to the work but do not qualify for authorship should be listed in the acknowledgments. Please specify the contribution of each author to the paper, e.g. study concept or design, data collection, data analysis or interpretation, writing the paper, others, who have contributed in other ways should be listed as contributors.

- Acknowledgements: All contributors who do not meet the criteria for authorship as defined above should be listed in an acknowledgements section.

References:

Authors are responsible for bibliographic accuracy. All the references, including those with only electronic sources, should be cited according to the "Vancouver Citation Style" which can be consulted on the Internet at: https://www.imperial.ac.uk/media/imperial-college/administration-and-support-services/library/public/vancouver.pdf

References must be numbered consecutively in the order in which they are cited in the text. Each reference should give the name and initials of all authors unless they are more than six, when only the first three should be given followed by et al. Authors' names should be followed by the title of the article, journal abbreviations according to the style used in Index Medicus, the year of publication, the volume number and the first and last page numbers. For papers in the course of publication, "in press" replaces the date; the journal name must be given in the references. Manuscripts that are unpublished, in preparation, or submitted, and personal communications should not be cited in the reference list but may appear parenthetically in the text. References to books should contain the author(s) name(s) and initials, the title of the book, followed by place of publication, publisher, year, and relevant pages. Websites must be referenced by the following order: title, URL and access date.

Examples:

1. Journals:

Hogan J, Mohan P, Appel GB. Diagnostic tests and treatment options in glomerular disease: 2014 update. Am J Kidney Dis 2014;63(4):656-666

2. Books:

Morris Peter, Knechtle Stuart. Kidney Transplantation - Principles and Practice. 7th Edition. Saunders, 2014:72

3. Website:

Substitutive Renal Therapy of Chronic Renal Disease in Portugal.

Available at https://www.spnefro.pt/tratamento_da_doenca_renal_terminal/2013
Accessed October 6, 2013.

4. Published Meeting Abstract:

Jorge Silva, Jorge Antunes, Telmo Carvalho, Pedro Ponce. Efficacy of preventing hemodialysis catheter infections with citrate lock (Encontro Renal abstract SE001). Port J Nephrol Hypert 2011; 25(1):56

Tables: Tables should supplement, not duplicate, the information in the main text. References to tables should be made in order of appearance in the text and should be in Roman numerals in brackets, e.g. (Table II). Each table should be typed on a separate sheet and have a brief heading describing its contents.

Figures: All illustrations (transparencies, photographs, diagrams, graphs, etc.) should be labelled consecutively in Arabic numerals (Fig. 1, 2...), according to their relative positions in the text. If a figure has been published before, the original source must be acknowledged and written permission from the copyright holder must be submitted with the material.