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# INSUFICIÊNCIA RENAL E AJUSTE DE DOSE DE MEDICAMENTOS EM PACIENTES DE UNIDADE DE TERAPIA INTENSIVA

**DISSERTAÇÃO DE MESTRADO**

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# INSUFICIÊNCIA RENAL E AJUSTE DE DOSE DE MEDICAMENTOS EM PACIENTES DE UNIDADE DE TERAPIA INTENSIVA

Dissertação apresentada ao Programa de Pós-graduação em Medicina e Saúde, da Faculdade de Medicina da Bahia, Universidade Federal da Bahia, como requisito para obtenção do grau de Mestre em Medicina e Saúde.

Orientador: Profº. Drº Luiz Carlos Santana Passos

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**MARIANNE SILVEIRA CAMARGO**

# INSUFICIÊNCIA RENAL E AJUSTE DE DOSE DE MEDICAMENTOS EM PACIENTES DE UNIDADE DE TERAPIA INTENSIVA

Dissertação de autoria de Marianne Silveira Camargo, intitulada Insuficiência renal e ajuste de dose de medicamento em uma unidade de terapia intensiva, apresentada a Universidade Federal da Bahia, como requisito parcial para a obtenção do título de Mestre em Medicina e Saúde.

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**DEDICATÓRIA**

Dedico este trabalho àqueles a quem devo a oportunidade de ter chegado aqui. Meus pais, minha irmã e meu esposo.

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"*A felicidade consiste em ações perfeitamente conformes à virtude, e entendemos por virtude não a virtude relativa, mas a virtude absoluta. Entendemos por virtude relativa a que diz respeito às coisas necessárias e por virtude absoluta a que tem por finalidade a beleza e a honestidade*"

Aristóteles

**SUMÁRIO**

## LISTA DE ILUSTRAÇÕES E TABELAS

### ARTIGO 1



### ARTIGO 2

## LISTA DE ABRAVIATURAS E SIGLAS

| | |
|---|---|
| **AKI** | *Acute kidney injury* |
| **BLI** | *Beta lactamase inhibitor* |
| **BSA** | *Body Surface Area* |
| **BUN** | *Blood Urea Nitrogen* |
| **CG** | *Cockcroft-Gault* |
| **eGFR** | Estimativa da Taxa de Filtração Glomerular |
| **FDA** | *Food and Drug Administration* |
| **GFR** | *Glomerular Filtration Rate* |
| **IBW** | *Ideal Body Weight* |
| **ICU** | *Intensive Care Unit* |
| **IMC** | Índice de Massa Corpórea |
| **IR** | Insuficiência Renal |
| **IRA** | Insuficiência Renal Aguda |
| **IRC** | Insuficiência Renal Crônica |
| **MDRD** | *Modification of Diet in Renal Disease* |
| **RI** | *Renal Impairment* |
| **SAPS** | *Simplified Acute Physiology Score* |
| **TBW** | *Total Body Weight* |
| **TFG** | *Taxa de Filtração Glomerular* |
| **UFBA** | Universidade Federal da Bahia |
| **UTI** | Unidade de Terapia Intensiva |

## ABSTRACT

Renal failure (RF) is one of the most common comorbidities in hospitalized patients. It affects about 10% of patients and is the twelfth cause of worldwide mortality. The presence of this comorbidity favors the development of adverse drug events, as it causes important pharmacokinetic and pharmacodynamic changes that require special care in medication administration. Dose adjustment of medications during renal failure contributes to reduced treatment costs, mortality and length of hospital stay, as more than half of the adverse events produced by drugs are related to dose prescriptions that should have been adjusted. However, disagreements in the literature, the equations for estimating GFR, and the lack of a database containing all drugs that require changes in renal failure, have generated uncertainties about the best way to perform the adjustment. However, despite the risks, the need for dosage adjustment or not and the use of contraindicated drugs are underestimated in clinical practice. In view of the uncertainties and risks associated with failure to use drugs during renal failure, several studies have addressed the issue. However, even in view of the higher incidence of renal dysfunction and the lack of standards in dose adjustments during ICU admission, there are few data that have evaluated the appropriateness of equations and drug doses in the renal insufficiency of patients under intensive care.



**Keywords**: Intensive Care Unit, Drug Dose Adjustment, Glomerular Filtration Rate

## RESUMO

A insuficiência renal (IR) é uma das comorbidades mais comuns nos pacientes hospitalizados. Atinge cerca de 10% dos pacientes e é a décima segunda causa de mortalidade mundial. A presença dessa comorbidade favorece o desenvolvimento de eventos adversos a medicamentos, pois ocasiona mudanças farmacocinéticas e farmacodinâmicas importantes que exigem cuidados especiais na administração de medicamentos. O ajuste de dose dos medicamentos durante o quadro de insuficiência renal contribui com a diminuição dos custos do tratamento, mortalidade e tempo de internação, visto que mais da metade dos eventos adversos produzidos por medicamentos estão relacionados a prescrições em doses que deveriam ter sido ajustadas. Contudo, discordâncias na literatura, nas equações para estimativa da TFG e a falta de uma base de dados que contemple todos os medicamentos que necessitam de alterações no quadro de insuficiência renal, têm gerado incertezas a respeito da melhor forma de realizar o ajuste. Ainda assim, a despeito dos riscos, a necessidade de ajuste de dose ou a não e a utilização de medicamentos contraindicados são subestimados na prática clínica. Diante das incertezas e dos riscos associados às falhas no uso de medicamentos durante a insuficiência renal, diversos estudos têm tratado do tema. Entretanto, mesmo diante da maior incidência de disfunção renal e da falta de padrões nos ajustes de dose durante a internação em UTIs, são escassos os dados que tenham avaliado a adequação das equações e doses de medicamentos na insuficiência renal de pacientes sob cuidados intensivos.



**Palavras-chave:** Unidade de Terapia Intensiva, Ajuste de Dose de Medicamentos, Taxa de Filtração Glomerular.

## 1 INTRODUÇÃO

A doença renal acomete aproximadamente 850 mil pessoas no mundo, anualmente, e representa a 12ª causa de mortalidade em geral. Em situações como sepse grave, insuficiência cardíaca, hipotensão e uso de medicamentos nefrotóxicos ela se torna mais frequente e, por esse motivo, é observada em maior incidência nas Unidades de Terapia Intensiva (UTI's). Os pacientes com insuficiência renal apresentam um elevado risco de apresentar evento adversos a medicamentos (EAM's), especialmente diante das alterações que a perda da função renal produz na excreção de inúmeras substâncias, o que leva à necessidade de ajustes a fim de administrar a dose ideal e diminuir os riscos de toxicidade.

Inúmeros medicamentos podem ter sua farmacocinética alterada por mudanças na filtração, secreção, reabsorção ou metabolismo, observadas durante o quadro de insuficiência renal. Dessa forma, prescrição de medicamento em sobredose, tem sido frequentemente associada à presença de insuficiência renal, uma vez que muitos medicamentos são contraindicados ou necessitam de cuidados especiais nesses casos. Fármacos que utilizam a via renal para sua excreção, como alguns anti-hipertensivos, antimicrobianos e analgésicos, são amplamente utilizados nas UTI's (8) e requerem ajustes de dose com o objetivo de evitar eventos adversos sérios, dentre os quais destacam-se a convulsão, toxicidade neuromuscular, hipertensão, insuficiência cardíaca e até mesmo o coma.

A taxa de filtração glomerular (TFG) é considerada o melhor marcador para diagnóstico, estadiamento e progressão da insuficiência renal. Ela pode ser medida de forma precisa através de marcadores como ioexol, inulina, iotalamato-$I^{125}$, ácido etilenodiaminotetraacético-$Cr^{51}$ (EDTA-$Cr^{51}$) e ácido dietilenotriaminopenta-acético-$Tc^{99}$m (DTPA-$Tc^{99}$m). No entanto, esses testes apresentam desvantagens como alto custo, laboriosidade e geralmente não estão

disponíveis na rotina hospitalar. Além desses testes mais precisos, exames laboratoriais, como a dosagem da creatinina sérica, também são utilizados para estimativa da TFG, mas sofrem influência de diversos fatores como a massa muscular, sexo e regime alimentar. Diante de todos esses inconvenientes, equações como a Modification of Diet in Renal Disease (MDRD), que estima a TFG, e a de Cockcroft-Gault (CG), que produzem uma estimativa do clearence de creatinina, foram criadas e têm sido amplamente utilizadas para tal finalidade.

A fórmula de CG foi criada em 1973, a partir de um estudo que envolveu 236 pacientes com idade entre 18 e 92 anos, com peso médio de 72 kg, dos quais 10 eram do sexo feminino. As variáveis utilizadas na equação de CG são idade, sexo, peso corporal total e creatinina sérica, e o valor obtido através da fórmula deve ser multiplicado por 0,85 quando o paciente for do sexo feminino. Diferentemente, a fórmula para estimativa da TFG conhecida como MDRD (Modification of Diet in Renal Disease), é baseada no clearence de iotalamato-$I^{125}$ e utiliza como variáveis: idade, sexo, raça e creatinina sérica na sua fórmula simplificada, e mais duas variáveis (albumina sérica e ureia nitrogenada) na sua fórmula completa. Apesar de amplamente utilizadas, as duas fórmulas apresentam limitações em relação ao seu uso. A equação de CG apresenta variações em pacientes diabéticos, portadores de insuficiência cardíaca crônica, artrite reumatoide, hipertensos afro-americanos, receptores de transplante cardíaco e obesos. A equação MDRD não é indicada para pacientes com doença hepática em estágio avançado, indivíduos com creatinina sérica normal, idosos, crianças e gestantes. Nenhuma das equações é indicada para pacientes com baixo índice de massa corpórea (IMC).

O ajuste de dose dos medicamentos durante o quadro de insuficiência renal contribui com a diminuição dos custos do tratamento, mortalidade e tempo de internação, visto que mais da metade dos eventos adversos produzidos por medicamentos estão relacionados a prescrições

em doses que deveriam ter sido ajustadas. Contudo, discordâncias na literatura, nas equações para estimativa da TFG e a falta de uma base de dados que contemple todos os medicamentos que necessitam de alterações no quadro de insuficiência renal, têm gerado incertezas a respeito da melhor forma de realizar o ajuste. Ainda assim, a despeito dos riscos, a necessidade de ajuste de dose ou a não e a utilização de medicamentos contraindicados são subestimados na prática clínica. Há relatos de que aproximadamente 19% da injúria iatrogênica ocorrem devido eventos adversos a medicamentos e uma revisão que avaliou o nível de adesão a guias de ajuste de dose mostrou que a prevalência de não conformidade de doses prescritas com o recomendado pela literatura variou de 19 a 67%.

Diante das incertezas e dos riscos associados às falhas no uso de medicamentos durante a insuficiência renal, diversos estudos têm tratado do tema. Entretanto, mesmo diante da maior incidência de disfunção renal e da falta de padrões nos ajustes de dose durante a internação em UTI's, são escassos os dados que tenham avaliado a adequação das doses na insuficiência renal de pacientes sob cuidados intensivos e que tenham avaliado esses ajustes através de uma comparação entre as duas equações (MDRD e CG).

## 2 OBJETIVO DO PROJETO DE DISSERTAÇÃO

O objetivo deste trabalho foi avaliar o ajuste de dose de medicamentos baseado na estimativa da taxa de filtração glomerular obtida através das equações de Cockcroft-Gault e MDRD, em pacientes com insuficiência renal internados em uma unidade de terapia intensiva.

## 3 ARTIGO DE REVISÃO

# MÉTODOS E EQUAÇÕES PARA ESTIMAR A TAXA DE FILTRAÇÃO GLOMERULAR E REALIZAR O AJUSTE DE DOSE DE MEDICAMENTOS

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## INTRODUÇÃO

A insuficiência renal é uma das comorbidades mais associadas à mortalidade no mundo e os pacientes por ela acometidos apresentam maior risco de desenvolver eventos adversos a medicamentos[1-2]. Isso ocorre porque as alterações na taxa de filtração glomerular (TFG) influencia na farmacocinética de vários medicamentos, principalmente na eliminação dos fármacos e seus metabólitos. Portanto, em pacientes com insuficiência renal, frequentemente é necessário realizar o ajuste, com o objetivo de administrar a dose ideal do medicamento a esses pacientes e evitar toxicidade por sobredose[2-3].

Para realizar o ajuste da dose é necessário conhecer a TFG, a qual pode ser medida diretamente por diversos métodos. No entanto, todos esses métodos apresentam um alto custo e são muito laboriosos para a prática clínica diária. Assim, em vez da medida direta, a TFG é comumente estimada a partir do nível sérico de marcadores endógenos, como a creatinina[4]. Várias equações que estimam a TFG foram criadas e são amplamente utilizadas em todo o mundo. Contudo, não existe consenso na literatura sobre qual a melhor equação a ser utilizada e todas apresentam limitações no seu uso[5].

Diante das dificuldades enfrentadas com as equações atualmente disponíveis, novas fórmulas e métodos para estimar a TFG têm sido desenvolvidas. Alguns apresentam menos limitações e são mais fidedignos quando comparados aos métodos considerados padrão – ouro, mas ainda são inviáveis de serem realizados rotineiramente[6-7]. Outros, apesar de menos custosos, não se apresentam mais efetivos do que as fórmulas comumente utilizadas[8].

**Insuficiência Renal Aguda (IRA)**

A IRA é uma síndrome frequente, com altos índices de mortalidade, assim como custos elevados para os pacientes e para os sistemas de saúde. Muitas são as causas e fatores de risco para o desenvolvimento da IRA e, apesar de ser uma condição conhecida há muitos anos, ainda não existe uma definição clínica consensual da mesma. Ela pode ser definida com base nos seguintes critérios: aumento da creatinina sérica igual ou superior a 0,3 mg/dL (26,5 μmol/l) dentro de 48 horas; ou aumento da creatinina sérica em 1,5 vezes da linha de base; ou volume urinário de 0,5 ml/kg /h por 6 horas[9].

O risco de IRA é maior quando o indivíduo é exposto a fatores que tornam os rins mais susceptíveis à lesão como desidratação, predisposição genética, comorbidades, uso de medicamentos nefrotóxicos, entre outros. Sempre que possível, a causa e da IRA deve ser definida e o risco de cada paciente, de acordo com suas comorbidades, fatores genéticos e exposições devem ser gerenciados[10].

**Insuficiência Renal Crônica (IRC)**

A IRC é definida como uma alteração na estrutura ou função renal presente por três ou mais meses e que apresenta implicações para a saúde do indivíduo acometido. Como critérios para

caracterizar a IRC podem ser citados albuminúria; alterações do sedimento urinário; alterações eletrolíticas e outras causadas por distúrbios tubulares; alterações estruturais mostradas nos exames de imagem; histórico de transplante renal[11-12].

Os estágios da IRC são categorizados de acordo com a taxa de filtração glomerular e são divididos em 6 categorias (G1, G2, G3a, G3b, G4 e G5), onde na primeira categoria estão aqueles que apresentam TFG igual ou maior que 90 e G5 os que apresentam uma TFG menor que 15 e já estão em falência renal[11].

**Equação de Cockcroft-Gault (CG)**

A equação de CG foi criada em 1973, a partir de um estudo que avaliou o prontuário de 534 pacientes. Desses, apenas 236 pacientes foram incluídos no estudo e apenas 10 eram do sexo feminino. Nessa fórmula, as variáveis utilizadas são idade, peso creatinina sérica. Uma redução de 15% é recomendada caso o paciente seja do sexo feminino. A equação de CG calcula o *clearance* de creatinina dos pacientes[13].

Apesar de amplamente utilizada essa fórmula apresenta algumas limitações. Dentre elas, podemos citar a subestimação da TFG em pacientes magros e superestimação em pacientes obesos e a imprecisão em determinados grupos de pacientes, como aqueles com IRC, insuficiência cardíaca congestiva, artrite reumatoide, dentre outros. Esta equação geralmente superestima a TFG, porque não considera a secreção tubular da creatinina, o aumento do peso em pessoas obesas e a sobrecarga de fluidos[5].

**Equação Modification of Diet in Renal Disease (MDRD)**

Em contraste à equação de CG, a MDRD de 4 variáveis resultou de dados provenientes de um estudo prospectivo, controlado, randomizado, realizado em 15 centros clínicos. Nesse estudo foram incluídos 1628 pacientes com doença renal crônica, em que foram avaliados os efeitos da restrição proteica da dieta e controle rigoroso da pressão arterial. A MDRD é baseada no clearence de iotalamato-I125 e utiliza como variáveis: idade, sexo, raça e creatinina sérica[14-15].

Neste estudo, a acurácia e precisão da TFG estimada por MDRD de 4 variáveis foi semelhante à estimada por MDRD com 6 variáveis e superior à estimada por CG[15]. Entre os problemas relacionados a este estudo estão o fato do mesmo não ter incluído pacientes com eTFG superior a 90 mL/min e as equações não terem sido comparadas em uma amostra separada do estudo. Além disso, essa equação não apresenta boa aplicabilidade em pacientes com Diabetes Mellitus, concentração da creatinina sérica dentro dos limites normais, indivíduos idosos, portadores de doença hepática avançada, dentre outros[5].

**Alterações farmacocinéticas dos medicamentos em pacientes com IR**

A farmacocinética abrange os processos de absorção, distribuição, metabolismo e excreção de um fármaco no organismo. Inúmeras dessas substâncias são excretadas e/ou metabolizadas pelos rins. Como consequência, a redução na capacidade renal pode ter efeitos pronunciados na farmacocinética de muitos medicamentos como resultado de alterações na filtração glomerular, secreção tubular, reabsorção ou metabolismo renal[16].

Após sua entrada no organismo, um medicamento pode ser eliminado por inúmeras vias e de formas diversas. Entre elas, as mais comuns são a eliminação do fármaco pelos rins na sua forma inalterada, pelo metabolismo hepático e/ou intestinal e a eliminação renal dos metabólitos. No caso dos fármacos ou subprodutos eliminados pela via renal, a perda de capacidade dos rins comumente resulta em alterações farmacocinéticas que podem levar à

necessidade de alteração na dose administrada, a fim de prevenir a ocorrência de eventos adversos a medicamentos que surgem com aumento das concentrações séricas e/ou teciduais[17-18].

Além da excreção, a presença de IR pode afetar também o metabolismo, a absorção, a ligação a proteínas plasmáticas, o transporte e distribuição tecidual dos medicamentos. Essas alterações ocorrem de forma particularmente proeminente em pacientes com IR grave e são observadas mesmo quando a via renal não é a principal via de eliminação do medicamento. Assim, um estudo farmacocinético deve ser realizado para a grande maioria dos medicamentos de uso crônico ou mesmo para medicamentos que não serão utilizados por período prolongado, a fim de definir a dose ótima em cada situação. Além disso, para pacientes submetidos à terapia de substituição renal, a farmacocinética deve ser estudada tanto na diálise quanto em condições de não-diálise, para cada tipo de método dialítico comumente utilizado, de forma a determinar até que ponto a diálise contribui para a eliminação dos medicamentos e metabolitos[19-20].

**Insuficiência Renal e Eventos Adversos a Medicamentos (EAM)**

A IR é uma das comorbidades mais comuns nos pacientes hospitalizados. Atinge cerca de 10% dos pacientes e é a décima segunda causa de mortalidade nos hospitais em todo o mundo[1]. Na Unidade de Terapia Intensiva (UTI) esses números são mais alarmantes, visto que a presença dessa condição se torna mais comum em situações clínicas como sepse grave, hipotensão e complicações cardiovasculares, que são quadros comuns aos pacientes críticos[4]. Além do risco aumentado de óbito, a presença de IR favorece ainda o desenvolvimento de EAM, como consequência das mudanças farmacocinéticas e farmacodinâmicas importantes observadas, que exigem cuidados especiais na administração de medicamentos[22-23]. Nos EUA cerca de 220 mil pessoas morrem anualmente devido aos EAM, os quais estão entre as sete maiores causas de

mortalidade e representam um dos grandes responsáveis pelos custos relacionados ao uso dos medicamentos, com cifras de cerca de US$ 2 bilhões por ano naquele país[24].

A prevenção de EAM em pacientes com IR demanda dois cuidados essenciais: selecionar o medicamento mais adequado e individualizar a dose. Para determinar a dose do medicamento a ser utilizada é importante que tanto os fatores farmacocinéticos quanto os clínicos sejam observados. No entanto, as indicações de doses ajustadas para IR, disponíveis na literatura, podem gerar dúvidas e dificultar a decisão sobre qual é a dose mais adequada para o paciente, uma vez que a sugestão é, frequentemente, descrita para uma ampla faixa de TFG e a dose é reduzida em faixas de percentuais igualmente alargados, ou são sugeridas ampliações nos intervalos entre as doses. Essas mudanças são sugeridas de forma genérica, sem considerar as peculiaridades clínicas, como a gravidade do quadro de base ou mesmo da insuficiência renal. Essa indicação de ajuste é grosseira e pode levar tanto à administração de sobredoses quanto de subdoses dos medicamentos, favorecendo o aparecimento de EAM ou mesmo de falha terapêutica[25-27]. Esses eventos podem ser ainda mais relevantes em pacientes que utilizam medicamentos com índice terapêutico estreito.

**Ajuste de dose de medicamentos em pacientes com IR**

A utilização da estimativa da TFG tem sido a base para a realização do ajuste de dose dos medicamentos excretados pelos rins, no intuito de prevenir a ocorrência de EAM[28]. Contudo, esse cuidado muitas vezes é negligenciado, o que expõe os pacientes a riscos ainda não totalmente estimados. Estudos de diferentes lugares do mundo apontam uma grande taxa de erros de medicação relacionado à dose dos medicamentos nos pacientes com IR, que ocorrem principalmente devido à subestimação dos eventos adversos e à falta de conhecimento da equipe sobre os medicamentos com depuração renal[2,26-29].

Várias estratégias foram avaliadas e se mostraram efetivas na melhoria do cuidado em saúde e, consequentemente, em reduzir o índice de sobredoses de medicamentos em populações acometidas pela IR. Entre essas estratégias, o acompanhamento dos pacientes pelo farmacêutico clínico, a sensibilização da equipe sobre a importância da individualização da dose e a implementação de um programa que alerte sobre a necessidade do ajuste de dose podem ser citadas[30-32]. Porém, apesar de inúmeros estudos que abordam a importância do ajuste de dose de medicamentos em pacientes com insuficiência renal, para a prevenção de eventos adversos a medicamentos, são escassos os estudos que avaliaram o impacto do ajuste de dose de medicamentos em pacientes com IR sobre a mortalidade, tempo de internamento ou mesmo sobre a diminuição dos eventos adversos a medicamentos.

**Comentários dos autores**

A IR é uma das maiores causas de mortalidade do mundo. A presença dessa comorbidade favorece o desenvolvimento de EAM pois ocasiona mudanças farmacocinéticas e farmacodinâmicas importantes que exigem cuidados especiais na administração de medicamentos. Esses eventos estão associados a um maior custo de internamento e aumento no número de hospitalizações, morbidades e mortalidade.

A subestimação desses eventos, as incertezas em relação ao uso de fórmulas para estimar as taxas de filtração glomerular, as discrepâncias das fontes em relação à dose que deve ser utilizada, a falta de conhecimento dos prescritores sobre os medicamentos que necessitam de ajuste de dose e a negligência em relação a insuficiência renal contribuem para o não ajuste de dose dos medicamentos.

Várias estratégias foram avaliadas e se mostraram efetivas na melhoria do cuidado em saúde e consequentemente um menor índice de sobredose de medicamentos em populações acometidas

pela IR. Dentre elas o acompanhamento dos pacientes pelo farmacêutico clínico, a sensibilização da equipe sobre a importância da individualização da dose e a implementação de um programa que alerte sobre a necessidade do ajuste de dose podem ser citadas.

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# 4 ARTIGOS ORIGINAIS

Artigo nº 1

**ESTIMATED GLOMERULAR FILTRATION RATE AND DRUG DOSE ADJUSTMENT IN PATIENTS IN AN INTENSIVE CARE UNIT IN BRAZIL**

Brazilian Journal of Pharmaceutical Sciences

Ressubmetido após solicitação de revisão

Artigo nº 2

**ASSOCIATION BETWEEN INCREASED MORTALITY RATE AND ANTIBIOTIC DOSE ADJUSTMENT IN INTENSIVE CARE UNIT PATIENTS WITH RENAL IMPAIRMENT.**

European Journal of Clinical Pharmacology

Aceito

## 4.1 ARTIGO 1

# ESTIMATED GLOMERULAR FILTRATION RATE AND DRUG DOSE ADJUSTMENT IN PATIENTS IN AN INTENSIVE CARE UNIT IN BRAZIL

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## ABSTRACT

Objectives. This study sought to compare the estimated glomerular filtration rate and the indication of dose adjustment of antimicrobials when using Cockcroft-Gault or Modification of Diet in Renal Disease. Methods. A cross-sectional study was performed with patients admitted to the intensive care unit of a Brazilian general hospital. The glomerular filtration rate was calculated for patients on all days using the Cockcroft-Gault and Modification of Diet in Renal Disease equations. The difference in estimated glomerular filtration and the dose adjustment indication of antimicrobials were assessed. Results. A total of 631 patients were included in this study. The median estimated glomerular filtration was significantly higher when estimated using Modification of Diet in Renal Disease (100.3 mL/min/1.73 m²) than the estimation by Cockcroft-Gault (83.2 mL/min) [$p<0.001$]. Greater differences in estimations produced by the two formulae were observed in patients at extremes of weight and age, and a different dose

adjustment was indicated for all antimicrobials assessed. Conclusions. These results demonstrate a significant difference in estimated glomerular filtration rate values when calculated using either Cockcroft-Gault or Modification of Diet in Renal Disease as well as in the indication of dose adjustment in an intensive care unit.

**Keywords**: Intensive Care Units; Glomerular Filtration Rate; Anti-infective Agents; Renal Insufficiency.

## INTRODUCTION

Kidney disease affects approximately 850,000 people annually around the world and represents the 12$^{th}$ leading cause of mortality in the general population (WHO). Patients affected by loss of renal function present with a high risk of adverse drug events, particularly due to the changes in the pharmacokinetics of numerous renally excreted substances. This results in a need to adjust dosages with the aim of administering an optimal dose and reducing the risk of toxicity. In addition, drug overdose prescriptions have often been associated with the loss of renal function since many medications, including antihypertensive drugs, antimicrobials and analgesics, are contraindicated or require special care in cases such as these (Karsch-Volk, Schmid, Wagenpfeil *et al.*, 2013; Nielsen, Henriksen, Marinakis *et al.*, 2014). These drugs are widely used in the intensive care unit, where loss of renal function occurs in higher incidence (Cardinal, Matos, Resende, *et al.*, 2012; Uchino, Kellum, Bellomo *et al.*, 2005).

Acute kidney injury (AKI) is a very common condition in ICU patients and is associated with mortality rates of 50-60%, despite the advances of medical care (Tejera, Varela, Acosta *et al.*, 2017). Therefore, accurately assessing the kidney function in critically ill patients is pivotal to reduce the severity of complications by supportive therapy as stabilization of the hemodynamic status, prompt treatment of any underlying disease and carefully assessment of nephrotoxic drugs use (Bragadottir, Redfors, Ricksten, 2013; Macedo, Mehta, 2013). In addition, it is essential for the appropriate dosing of drugs aiming to avoid toxicity caused by overdose (Pazhayattil, Shirali, 2014).

The glomerular filtration rate (GFR) is considered the best marker for monitoring renal function throughout its diagnosis, staging, and progression (Katsube, Wajima, Ishibashi *et al.*, 2017). It can be precisely measured by markers such as iohexol, inulin, iodine-125 iothalamate, Cr-51 ethylenediaminetetraacetic acid (Cr-51 EDTA), and Tc-99m diethylenetriaminepenta-acetic

acid (Tc-99m DTPA). However, these tests are expensive, laboriousness, and generally unavailable in routine hospital settings (Martin, Fay, Udy *et al.*, 2011). Given these drawbacks to calculating GFR, equations such as the Modification of Diet in Renal Disease (MDRD) and Cockcroft-Gault (CG), which estimate GFR and creatinine clearance level, respectively, have been developed and used for this purpose (Cockcroft, Gault, 1976; Levey, Coresh, Greene *et al.*, 2006). However, although widely employed, these two equations are limited in their use (Helou, 2010).

The CG equation is based in data from a study conducted in 1973 that included 236 patients aging from18 to 92 years, with mean weight of 72 Kg. From that total, only 10 patients were females. The CG equation includes age, sex, total body weight and serum creatinine (Cockcroft, Gault, 1976). On the other hand, MDRD is based on a study including patients with chronic renal disease, which assessed the clearance of iotalamato-$I^{125}$. The brief form of MDRD includes the variables age, sex, ethnicity and serum creatinine and in the complete form, two other variables are included: serum albumin and blood urea nitrogen (BUN) (Levey, Bosch, Lewis *et al.*, 1999; Levey, Coresh, Greene *et al.*, 2006).

Using the creatinine as a marker of renal function have some limitation since it is influenced by several factors as muscle mass, protein intake, physical activity or the use of medicines. In addition, the creatinine is excreted at a variable rate that increases as the renal failure progresses. Therefore, the clearance of creatinine overestimates the real value of the glomerular filtration rate (Kumar, Mohan, 2017).

Given the potential complications and risks associated with the avoidance of drugs during reduced GFR, several studies have addressed this subject. However, despite the higher incidence of renal dysfunction and the lack of standards in dose adjustments during ICU admission, there are few studies that have assessed the appropriateness of the equations and

drug doses in patients with RF under intensive care.

This study sought to compare the estimated GFR (eGFR) and the recommendations for dose adjustment of broad-spectrum antimicrobials using CG and 4-Variable MDRD as well as the differences according to age and weight.

**METHODS**

This was a cross-sectional study, performed in a general hospital located in state of Bahia, in Brazilian Northeast. This institution is classified as a medium- and high-complexity urgent and emergency hospital that serves 134 municipalities with a total of 254 beds (Bahia., 2015). Data were collected from medical records using a form developed in the KoBoToolbox for Android (available at: www.kobotoolbox.org).

All patients admitted between January 2014 and December 2015 who were older than 18 years of age were included in this study. Patients who stayed in the ICU for less than 24 hours, who underwent dialysis or another renal replacement therapy, or whose missing data did not allow for the calculation of eGFR were excluded from this study.

All information contained in the medical records of patients was monitored and analysed from the day before ICU admission to the last day of hospitalization in ICU. The following data were collected from patients records: cause of admission, previous location of the patient before UCI admission (source), weight, height and serum creatinine. Then, these data were transferred to a database for further analysis.

The eGFR was calculated for each day of hospitalization in the ICU, using online calculators from the Brazilian Nephrology Society website (available at: https://sbn.org.br/utilidades/calculadoras/) and double checked using the following formulae:

CG: [(140 - age) x weight / (72 x serum creatinine)] x 0.72 (if female)(Cockcroft, Gault, 1976).

MDRD: (186 x serum creatinine)$^{-1.154}$ x age$^{-0.203}$) x 0.742 (if female) x 1.21 (if African American) (Levey, Coresh, Greene *et al.*, 2006).

Additionally to the comparison between the GFR estimated by CG and MDRD-4, we assessed the difference for dose adjustment recommendations when using the CG or MDRD-4 equations. Therefore, we choose the top five intravenous broad-spectrum antimicrobials requiring dose adjustments in patients with reduced glomerular filtration rate, used in our institution: vancomycin, meropenem, piperacillin/tazobactam, cefepime, and fluconazole. The need for dose adjustment was assessed based on the following sources of information: Micromedex Healthcare Series® and AHFS – Drug Information Handbook 2015 (Micromedex, 2016; APhA, 2015).

Data were analysed with SPSS 23.0. Continuous variables are presented as the median and corresponding measure of dispersion. Proportions were compared using Pearson's chi-squared test. We compared median values between groups using the Wilcoxon signed-rank test, with a significance of 5%.

**Ethical:** The study was approved by the Research Ethics Committee at Multidisciplinary Institute of Health, Federal University of Bahia, Vitória da Conquista, Brazil, with number: 1.460.914

**RESULTS**

The study included 631 patients. Table I describes the clinical and demographic characteristics of the population.

**Table I.** Demographic characteristics of the study population

| Characteristics | (N=631) |
|---|---|
| | **Median (IQR*)** |
| **Age (years)** | 50 (32 - 67) |
| **Weight (kg)** | 70 (60 - 75) |
| **Baseline serum creatinine** | 1 (0.7 - 1.9) |
| **Length of stay in Intensive Care Unit** | 6 (3 - 12) |

*Interquartile range

Most patients were male (64.2%) with a median weight of 69.3 kg. Admissions were most frequently due to neurological (34.6%) and surgical (32.3%) causes.

Median eGFR was 100.3 mL/min/1.73 m² for MDRD-4 and 83.2 mL/min for CG (p<0.001).

Due to differences in eGFR results calculated using the CG or MDRD, there may be differences in the indication of drug dose adjustment. In table II, for each chosen antimicrobial, is compared the number of times the dose adjustment should be conducted according to the respective eGFR range, following the recommended dose adjustment, when the GFR is estimated by CG and MDRD-4 equations.

**Table II.** Frequency of dose adjustment according to recommended for each estimated glomerular filtration range calculated using CG or MDRD for broad-spectrum antimicrobials (N=5,528).

| Drug | Creatinine clearance range | eGFR calculated using CG (%) | eGFR calculated using MDRD (%) | p-value* |
|---|---|---|---|---|
| **Cefepime** | 30 - 60 | 1062 (19.2) | 854 (15.4) | p<0.001 |
| | 11 - 30 | 832 (15) | 729 (13.2) | |
| | <11 | 88 (1.6) | 103 (1.9) | |
| **Piperacillin/ Tazobactam** | 20- 40 | 849 (15.4) | 741 (13.4) | p<0.001 |
| | < 20 | 473 (8.6) | 408 (7.4) | |
| **Fluconazole** | <50 | 1652 (19.9) | 1455 (26.3) | p<0.001 |

*Chi-squared test
eGFR: estimated glomerular filtration rate; CG: Cockcroft -Gault; MDRD: Modification of Diet in Renal Disease

The study showed a greater difference in eGFR between equations in patients at extremes of weight and age. Figures 1 and 2 show the relationship between median eGFR, as determined using CG and MDRD-4 versus weight and age, respectively.

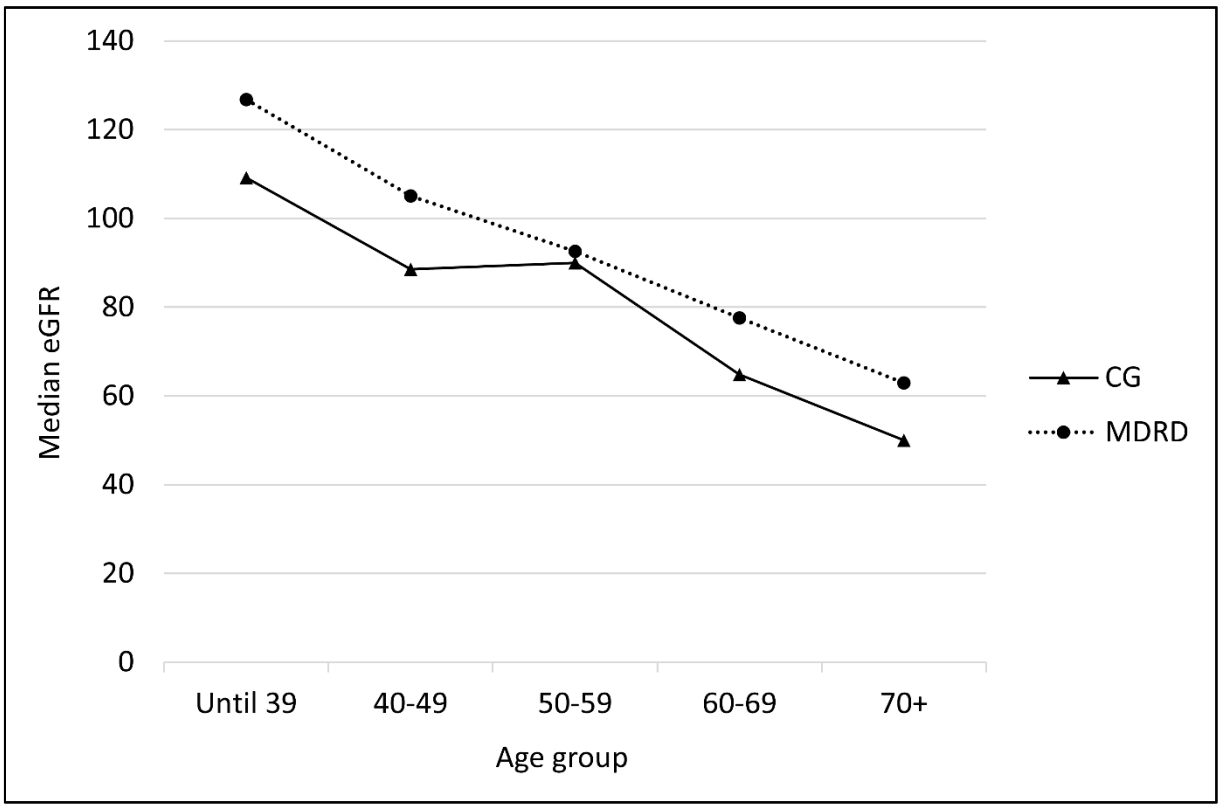


**Figure 1.** Median estimated glomerular filtration rate calculated using MDRD-4 or Cockcroft-Gault versus age group.

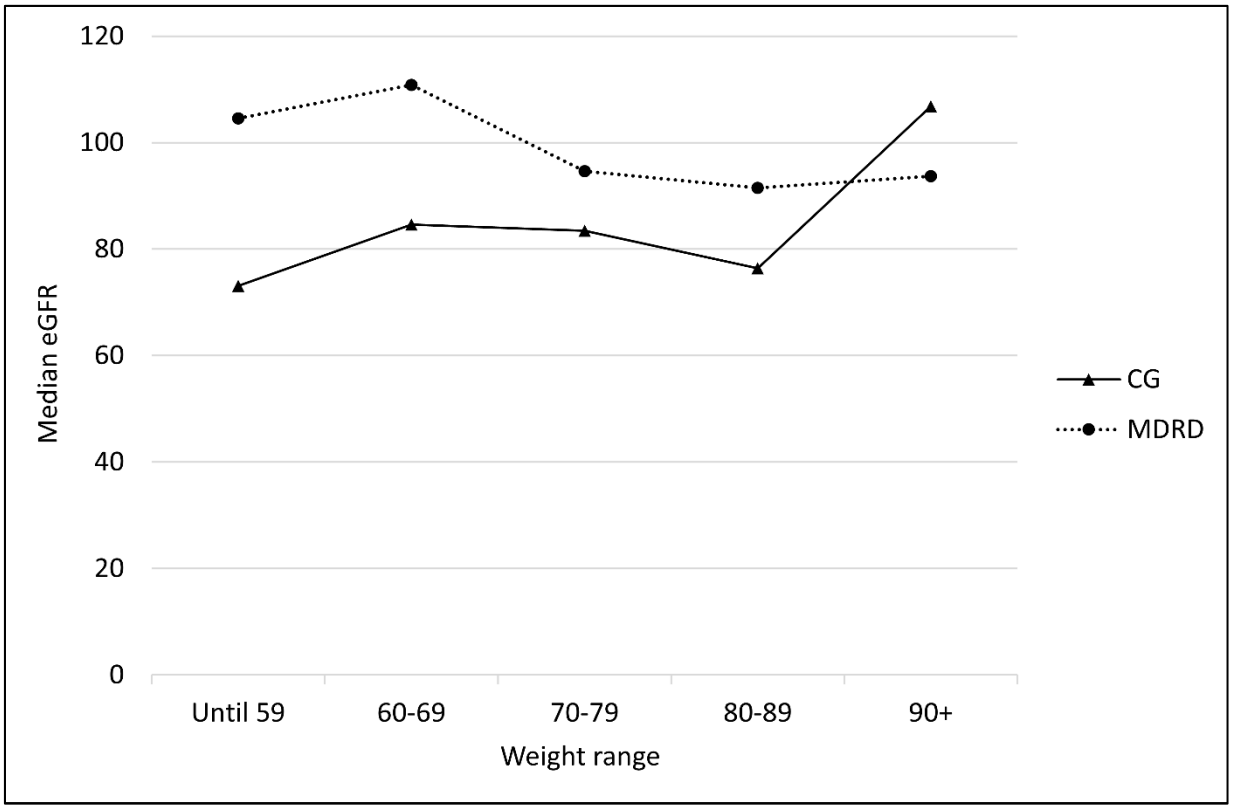


**Figure 2.** Median estimated glomerular filtration rate calculated using MDRD-4 or Cockcroft-Gault versus weight range.

## DISCUSSION

This study demonstrated a significant difference in eGFR in ICU patients when calculated using MDRD-4 and CG. Disagreements between the equations raise doubts about how the dose adjustment should be performed, which can lead to serious errors, including medication errors. To reduce this difference between the equations, eGFR can be calculated using the body surface area (BSA), although this data is difficult to obtain in medical records. Furthermore, in many cases, its measurement is imprecise. In addition, the impact of BSA correction seems to be limited (Roblin, Sobarnitsky, Basselin *et al.*, 2009).

As observed in Figure 1, in the age group of 50 to 59 years, eGFR values are similar, although the difference becomes more significant with advanced age. This difference between eGFR, as calculated by either CG or MDRD-4, in elderly patients has been previously observed. It was

found that GFR, when compared to the gold standard, was underestimated when calculated using CG and overestimated when calculated using MDRD (Saha, Bhattarai, Batra *et al.*, 2015). Similarly, a study showed a difference in dose adjustment between the equations for drugs, such as amantadine and digoxin, which are commonly used in elderly patients (Gill, Malyuk, Djurdjev *et al.*, 2007). In this population, it is common to find patients with reduced muscle mass and, consequently, very low serum creatinine levels. Some studies suggest rounding these creatinine levels to 1 mg/dL, although this practice may lead to an underestimation of creatinine clearance levels. Thus, some studies continue to suggest using CG as a safer option for these patients since use of MDRD-4 results in a higher estimation of GFR, which may result in higher adjusted doses.

In this study, the difference observed between eGFR calculated using either CG or MDRD-4 was also significantly increased at extremes of weight, as seen in Figure 1. As expected, up to the weight range of 70-79 kg, eGFR as calculated using CG is lower than that calculated using MDRD-4. This is because only the CG equation considers weight, which is a positive factor in this equation. Conversely, GFR tends to be higher in obese patients than in the rest of the population, which causes a greater discrepancy in GFR and more dramatically affects the adjustment of drug dosage (Jesudason, Clifton, 2012; Nyman, Dowling, Hudson *et al.*, 2011).

In our study, we used the total body weight (TBW) of the patients, since this is the recommended weight used in the original study that defined the CG equation (Cockcroft, Gault, 1976). Some authors state that the use of ideal body weight (IBW) is indicated for patients at the extremes of weight, although, in these cases, an underestimation of GFR may occur (Hudson, Mason, Huch, 2011). Other authors indicate the use of a cofactor to increase the reliability of the CG equation (Wilhelm, Kale-Pradhan, 2011). Therefore, prior to drug dose adjustment, it is important to seek guidance from the pharmaceutical company that produces the drug to determine whether the recommendation for dose adjustment is made based on TBW or IBW. In

some cases, this information can be found in the package leaflet (Nyman, Dowling, Hudson *et al.*, 2011).

In patients at extremes of weight and age, who showed higher eGFR difference between the equations, the results suggest a need for greater care in the application of the equations. Many studies have been conducted with specific groups and have compared them with the gold standard, although there is no clear answer as to the best form and equation to calculate eGFR.

A feature similar to both equations used to calculate eGFR is the dependence on serum creatinine. Both serum creatinine and BUN are often excreted by kidneys in a constant way and therefore are commonly used as markers to assess renal function. Although, since several factors such as muscle mass, diet, hydration, analytical variations or even ethnicity can influence the excretion of these two markers, their use in some groups may be not safe for eGFR (Kumar, Mohan, 2017). The Brazilian population is the result of an intense process of miscegenation between several different ethnicities, including Europeans, black Africans, and indigenous people, which resulted from colonization and the intense immigration that occurred in recent centuries (Brasil, 2009). Thus, unlike previous data from groups with low ethnic variability, the results of this study were obtained from a widely multiracial population. Likewise, this study included ICU patients who are frequently affected by hemodynamic instability, which other studies have found to be an uncommon condition (Potes, Conroy, Xu-Wilson *et al.*, 2017).

In order to assess the patient throughout the hospitalization period and to consider all variability that occurs during that period, such as weight changes, diet, and use of medications, the GFR was estimated daily using both equations and all test results were classified according to the creatinine clearance range used to indicate the dose adjustment (Table II). In agreement with previous data (Golik, Lawrence, 2008; Kumar, Mohan, 2017), this study demonstrated that

different suggestions of dose adjustment could occur according to the equation used for eGFR. For all creatinine clearance ranges, significant differences were found between test results. These results indicate that deciding which dose should be prescribed, according to eGFR alone, can be harmful to the patient, since both a sub-dose and overdose of medications can be harmful (Brown, Masselink, Lalla, 2013).

Several broad-spectrum antibiotics, commonly used in ICU, are potentially nephrotoxic while are mainly excreted by the kidneys. Vancomycin, for example, is widely used for the treatment of infections caused by resistant strains of gram-positive bacteria but presents high nephrotoxicity rates (Luque, Mesnard, 2018; Park, Lim, Park *et al.*, 2018). Other agents as piperacillin/tazobactam, meropenem, imipenem and cefepime, active against gram-negative bacteria, are associated with lower nephrotoxic rates but may cause central nervous toxicity in overdose or can to potentiate the toxicity of other antibiotics such as vancomycin. Hence, using those broad-spectrum antibiotics require close attention in renal function aiming to avoid its depletion as well as to prevent kidneys or other organ injury caused by overdoses of these drugs resulting from loss of glomerular filtration (Cook, Gillon, Grisso *et al.*, 2018).

Given the risks inherent to dose adjustment of certain drugs, it is necessary to consider which decision would carry reduced risk to the patient when there is a difference in the indication of dose adjustment. For example, in addition to higher costs, a higher than necessary dose carries a risk of adverse reactions, such as convulsion and myoclonus. Conversely, if the dose is lower than necessary, therapeutic failure may occur, thereby leading to an increased length of stay, a worsening of clinical status, and even death (Hudson, Mason, Huch, 2011; Nyman, Dowling, Hudson *et al.*, 2011). Moreover, eGFR is also used to guide nutritional support and the need for renal replacement therapy (Brown, Masselink, Lalla, 2013).

In 1998, the Food and Drug Administration (FDA) published guidelines for the pharmaceutical

industry, which suggests the use of the CG equation to estimate renal function since it was the most commonly used equation for this purpose (FDA, 1998). In 2010, the FDA published new guidelines recommending the use of both the creatinine clearance level and GFR for drug dose adjustment, which makes it possible to use the MDRD-4 equation (FDA, 2010). However, for previously approved drugs, it is unlikely that any changes will be made, since tests have already been performed and these drugs are already on the market. Thus, for some drugs that have dose adjustment instructions based on the CG equation, the use of MDRD-4 may have important implications since this equation usually suggests higher doses than does CG, which results in a greater uncertainty in their implementation (Golik, Lawrence, 2008; Hermsen, Maiefski, Florescu *et al.*, 2009).

The difficulty in estimating GFR in ICU patients is associated with several factors, such as sudden changes in renal volume and haemodynamic activity, which are common in this population. In individuals with frequent changes in serum creatinine concentration or with acute kidney injury, the use of equations should be performed with caution since none are considered safe in these cases and have not been completely validated for this purpose (Cockcroft, Gault, 1976; Levey, Coresh, Greene *et al.*, 2006; Sunder, Jayaraman, Mahapatra *et al.*, 2014). Clinicians often suggest assessing urine for various markers over a period of 24 hours to estimate GFR. However, this method is not precise and requires additional resources and time to obtain results (El-Minshawy, Saber, Osman, 2010).

Choosing one over another between CG and MDRD may lead to the prescription of a medication overdose or to the treatment switch, based on the eGFR result. Various formulae were created after CG and considered better than it. However, there is no consensus on which one is better to estimate the GFR. Thus, the choice must take into consideration patients' individual characteristics and the drug therapy aim, regarding risks and benefits (Cartet-Farnier, Goutelle-Audibert, Maire *et al.*, 2017; Delanaye, Guerber, Scheen *et al.*, 2017).

We did not include in the comparison other equations to estimate GFR as the CKD-EPI Creatinine Equation. However, our results cover the majority of GFR estimations conducted in our settings, especially for doses adjustments, since CG and MDRD are most frequently applied. Moreover, we did not compare the eGFR by CG and MDRD with the creatinine clearance rate measured by gold-standards markers as iohexol or inulin because there are not often used in a routine basis.

This study demonstrated a significant difference in eGFR values when calculated using either CG or MDRD-4 as well as in the indication of dose adjustment of broad-spectrum antimicrobials administered to patients admitted in an ICU. In the analysis, weight and age have influenced for higher divergence between the eGFR obtained by the two equations.

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## 4.2 ARTIGO 2

# ASSOCIATION BETWEEN INCREASED MORTALITY RATE AND ANTIBIOTIC DOSE ADJUSTMENT IN INTENSIVE CARE UNIT PATIENTS WITH RENAL IMPAIRMENT.

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## ABSTRACT

**Purpose:** Adjusting the antibiotic dose based on estimation of glomerular filtration rate (eGFR) may result in subdose use and may be significantly more problematic for intensive care unit (ICU) patients. This study aimed to assess the outcomes of antibiotic dose adjustment in ICU patients with renal impairment. **Methods**: A retrospective cohort study was conducted in adult patients admitted from January 2014 to December 2015 in an ICU of a Brazilian hospital. The eGFR was determined using Cockcroft–Gault and Modified Diet in Renal Disease equations for each day of hospitalization. Treatment failure was defined based on the clinical, laboratory, and radiological criteria. **Results**: After the initial assessment, 126 (19.9%) met the inclusion criteria. From the 168 opportunities for dose adjustment, 99 (58.9%) were performed. Mean eGFR in the group with dose adjustment was 38.5 mL/min/1.73m$^2$ vs 40.7mL/min/1.73m$^2$ in the group without dose adjustments. The treatment failure rate among patients with dose

adjustment was 59.3% vs 38.9% in the group treated with usual dose ($p$ = 0.023), and their mortality rates were 74.1% and 55.5%, respectively ($p$ = 0.033). In the multivariate analysis including the prognostic score, the association between dose adjustment and treatment failure/mortality rates was also observed. **Conclusions:** In ICU patients with renal impairment, the antibiotic dosage adjustments, based on eGFR, significantly increased the risk of treatment failure and death.

**keywords:** Anti-Infective Agents; Renal Insufficiency; Intensive Care Units; Mortality.

## INTRODUCTION

Infections are the leading cause of death in intensive care units (ICU) worldwide. Despite the development of new drugs, diagnostic tests, and monitoring tests, the rate of mortality associated with infections has increased in the last few years[1,2]. This increase is primarily associated with the rapid emergence of antibiotic-resistant bacteria, delays in starting treatment, and prescription of incorrect antimicrobial drugs or incorrect dose[1,3,4].

Prescribing the wrong dose of antibiotic is a common error in some groups of patients, including those with extreme age, those with multiple comorbidities, or critically ill patients admitted in the ICU[5], since these conditions produce physiological disturbances, resulting in important pharmacokinetic changes. However, data on antibiotic dose adequacy in these special patient populations are limited[6,7]. Patients with renal impairment (RI) are commonly exposed to incorrect medication dosing. Hence, they are at higher risk of adverse drug events caused by drug overdose or subdose[8].

Many drugs are excreted by the kidneys. When the glomerular filtration barrier is compromised, some substances may accumulate in the body producing toxicity. Thus, in several situations, it is necessary to reduce the dose to avoid harming the patients[9,10]. This dose adjustment is usually conducted based on the glomerular filtration rate (GFR), which can be estimated using equations composed of patient data and some constants. However, these equations can present several limitations in their use[11]. Moreover, the dose indicated for patients with RI differs between databases, which raises doubts during the dose adjustment. Consequently, suboptimal doses are frequently used, resulting in treatment failure[12,13].

Most of the studies that defined the doses and adjustments of antimicrobials in RI were performed in healthy patients, noncritical patients, or even in patients with restricted clinical profiles, such as adults without other associated comorbidities[3]. Regardless of the increased

risk of treatment failure or adverse drug reactions, data on the clinical impact of antimicrobial dose adjustment in patients with RI remain unclear. Hence, many doubts still persist about the risks and benefits of dose adjustment for different groups of patients such as those in the ICU, the elderly, newborns, or those with multiple conditions[14-16]. The choice is between adjust the dose and risking negative outcomes for the patients, such as treatment failure or death, and not adjusting the dose and exposing the patients to the risk of severe adverse drug reactions.

This is the frequent question faced by the ICU healthcare team when defining the treatment of infections[17]. Thus, this study aimed to assess the outcomes of antimicrobial dose adjustment in ICU patients with renal impairment.

## METHODS

This cohort study was conducted with retrospective data from ICU patients admitted in a tertiary hospital in the northeast region of Brazil. The hospital primarily handles urgent and emergency cases and covers 134 municipalities.

Data were collected from patients' medical records using a digital form developed in the KoBoToolbox for Android (KoBoToolbox, Harvard Humanitarian Initiative, Cambridge, USA, available at: https://www.kobotoolbox.org/). The data extracted from the patients' medical records were analyzed, beginning on the day before ICU admission until the last day in the unit. The following data were obtained: cause of admission, comorbidities, medications, laboratory test results, infection sites, cultures, weight, height, daily urine output, relevant medical history, and clinical outcomes. Moreover, the severity of patient's clinical status upon admission was measured according to the Simplified Acute Physiology Score (SAPS 3).

All patients admitted between January 2014 and December 2015, aged ≥18 years, and who stayed in the ICU for >24 hours were considered for this study. Patients whose missing data did

not allow the calculation of eGFR or the evaluation of treatment results (success/failure) or those patients whose the prescribed dose did not match the recommendations of the used guidelines were excluded from the study.

For the eGFR, CG and MDRD-4 equations were used[18,19]. The eGFR was calculated daily, and the need for dose adjustment was assessed based on the following sources of information: Micromedex Healthcare Series® and AHFS Drug Information Handbook 2015[20,21]. Therapeutic drug monitoring through measurement of the serum drug levels was not performed in the studied ICU. Thus, the dose adjustment of antibiotics is usually performed as follows: for the first 24 hours, the usual dose is prescribed for individuals with normal renal function. From the second day onwards, an adjusted dose is prescribed according to the daily updated eGFR.

After inclusion, patients were divided into two groups. First group consisted of patients with eGFR range indicating dose adjustment but that have used usual dose of the antibiotic (not adjusted) for the whole treatment; second group consisted of patients with eGFR range indicating dose adjustment whose dose was reduced according to the eGFR range (adjusted).

Two outcomes were compared between the groups: treatment failure and death. Treatment failure was analyzed by physical examination, organic dysfunction, comorbidities, broadening antimicrobial spectrum, laboratory tests, and image exams. Successful treatment was defined by an improvement in the signs and symptoms of infection, while failure was defined by the persistence of infection, clinical deterioration or death. [22,23].

In the statistical analyses, continuous variables are reported as mean (Standard Deviation, SD) for variables with normal distribution or median (Interquartile Range, IQR) for variables that did not present normal distribution and the comparisons were performed using Student’s t-test or Mann-Whitney U test, respectively. Proportions were compared using Pearson’s chi-squared

test. The bivariate analysis was conducted to examine the association between the outcomes and antibiotic dose adjustment and clinical features including sex, age, admission diagnosis in ICU. SAPS 3, admission source and antibiotic class. The SAPS 3 was categorized in ≤ 57 or > 57. This cut off point was previously defined as a better prediction of higher mortality in ICU patients in another Brazilian study[24]. All significant factors in the bivariate analysis were included in the multiple regression model (Poisson with robust variance). Data were analyzed using STATA 14.2 (Stata/IC, Stata Corp., College Station, Texas, USA).

**RESULTS**

During the period of this study, a total of 632 patients were admitted in the ICU. Among the total ICU patients, 279 (46.9%) presented with RI, of which 126 (45.2%) used at least one antimicrobial agent needing dose adjustment and met inclusion criteria. General characteristics of the study population are described in Table 1.

Mortality rate in the studied population was 69% (87 patients). The most frequent infection sites were pulmonary, abdomen, and skin, which affected 47 (37%), 36 (29%), and 10 (7.9%) patients, respectively. The site of infection was not identified in 22 (17.5%) cases. About 69 patients (54.8%) had sepsis or septic shock and 93 (73.8%) presented higher probabilities of death (SAPS 3 > 57).

From the 126 patients included in this study, we identified a total of 168 opportunities for dose adjustments of antimicrobial agents. In all these cases, antibiotics were used at the standard dose in the first day of treatment. The group of patients with dose adjustment following recommendations according to eGFR had higher rates of treatment failure (table 2) and mortality (table 3) than the group without dose adjustment. From all included patients, 60 (47.6%) showed treatment failure and mortality rate among patients with therapeutic failure was 44 (73%) vs 36 (52%) in the group whose treatment was effective ($p$ = 0.029). When

assessed only in patients with therapeutic failure, mortality rate in dose adjustment group was 7 (43.8%) vs 9 (56.2%) for the group with no adjustment ($p = 0.370$).

**Table 1.** General characteristics of the study population.

| Drug | Dose adjustment conducted | | Total | *p*-value |
|---|---|---|---|---|
| | Yes (N=54) n (%) | No (N=72) n (%) | | |
| **Sex** | | | | |
| Male | 34 (53) | 30 (47) | 64 | 0.018 |
| Female | 20 (32) | 42 (68) | 62 | 0.018 |
| **Source** | | | | |
| Surgical clinic | 5 (71.4) | 2 (28.6) | 7 | 0.116 |
| Medical clinic | 1 (14.3) | 6 (85.7) | 7 | 0.116 |
| Other hospital | 1 (11.1) | 8 (88.9) | 9 | 0.046 |
| Surgery centre | 14 (48.3) | 15 (51.7) | 29 | 0.502 |
| Emergency | 33 (45) | 41 (55) | 74 | 0.638 |
| **Admission diagnosis in UCI (by system)** | | | | |
| Endocrinal | 2 (66.7) | 1 (33.3) | 3 | 0.399 |
| Cardiac | 0 | 5 (100) | 5 | < 0.001 |
| Gastrointestinal | 2 (28.6) | 5 (71.4) | 7 | 0.432 |
| Pulmonary | 4 (40) | 6 (60) | 10 | 0.849 |
| Others | 12 (42.9) | 16 (57.1) | 28 | 1.000 |
| Neurologic | 12 (38.7) | 19 (61.3) | 31 | 0.591 |
| Surgical | 22 (52.4) | 20 (47.6) | 42 | 0.127 |
| **SAPS 3 range**† | | | | |
| < 57 | 18 (54.5) | 15 (45.5) | 33 | 0.114 |
| > 57 | 36 (38.7) | 57 (61.3) | 93 | 0.114 |
| **Antibiotic** | | | | |
| Glycopeptides | 2 (50) | 2 (50) | 4 | 0.769 |
| Miscellaneous | 7 (63,6) | 4 (36,4) | 11 | 0.145 |
| Carbapenems | 9 (42,9) | 12 (57,1) | 21 | 0.247 |
| Quinolones | 15 (51,7) | 14 (48,3) | 29 | 0.477 |
| Cephalosporins | 10 (33,3) | 20 (66,7) | 30 | 0.061 |
| Ureidopenicillins+BLI‡ | 11 (35,5) | 20 (64,5) | 31 | 0.339 |
| **Age (years)** – Mean (SD*) | 56.8 (21.2) | 57.68 (17.3) | - | 0.795 |
| **SAPS 3** – Mean (SD*) | 68.9 (18.5) | 66.7 (17.9) | - | 0.502 |
| **Length of stay in ICU** – Median (IQR**) | 9 (6 - 16) | 8 (3.8 - 15) | - | 0.132 |
| **Baseline eGFR** – Mean (SD*) | 39.52 (31.6) | 40.7 (36.9) | - | 0.851 |

*UCI – Intensive care unit; † Simplified Acute Physiology Score; ‡BLI - Beta lactamase inhibitor; §SD - Standard deviation; ¶IQR - Interquartile Range; **Estimated glomerular filtration range

**Table 2.** Therapeutic failure in patients with renal impairment treated by antibiotics needing dose adjustment in an intensive care unit (bivariate analysis).

| | Therapeutic failure | | RR | 95%IC | *p*-value |
|---|---|---|---|---|---|
| | n/N | % | | | |
| **Dose adjustment** | | | | | |
| Adjusted | 32/54 | (59.3) | 2.23 | 1.11 - 4.70 | 0.023 |
| Not adjusted | 28/72 | (38.9) | | | |
| **SAPS 3 range** | | | | | |
| > 57 | 46/93 | (49.5) | 1.33 | 0.60 - 2.96 | 0.487 |
| ≤ 57 | 14/33 | (42.4) | | | |
| **Sepsis/septic shock** | | | | | |
| Yes | 36/69 | (52.2) | 1.50 | 0.74 - 3.04 | 0.260 |
| No | 24/57 | (42.1) | | | |
| **Sex** | | | | | |
| Female | 27/50 | (54.0) | 1.24 | 0.87 - 1.79 | 0.245 |
| Male | 33/76 | (43.4) | | | |
| **Source** | | | | | |
| Surgical clinic | 4/7 | (57.1) | 1.00 | - | - |
| Medical clinic | 4/7 | (57.1) | 1.00 | 0.40 - 2.49 | 1.00 |
| Other hospital | 3/9 | (33.3) | 0.58 | 0.19 - 1.80 | 0.350 |
| Surgical center | 12/29 | (41.4) | 0.72 | 0.33 - 1.58 | 0.416 |
| Emergency room | 37/74 | (50.0) | 0.88 | 0.44 - 1.73 | 0.702 |
| **Admission diagnosis in UCI (by system)** | | | | | |
| Endocrinal | 2/3 | (66.7) | 1.00 | - | - |
| Cardiac | 0/5 | 0 | 0.90 | 0.31 - 2.64 | 0.848 |
| Gastrointestinal | 2/5 | (40.0) | 0.64 | 0.20 - 2.08 | 0.461 |
| Pulmonary | 4/12 | (33.3) | 0.90 | 0.35 - 2.33 | 0.828 |
| Others | 12/28 | (42.9) | 0.75 | 0.31 - 1.82 | 0.524 |
| Neurologic | 12/31 | (38.7) | 0.58 | 0.23 - 1.45 | 0.246 |
| Surgical | 22/42 | (52.4) | 0.71 | 0.30 - 1.70 | 0.445 |
| **Antibiotic** | | | | | |
| Miscelaneous | 4/11 | (36.4) | 1.00 | - | - |
| Cephalosporins | 10/30 | (33.3) | 0.92 | 0.36 - 2.33 | 0.855 |
| Quinolones | 17/29 | (58.6) | 1.61 | 0.69 - 3.74 | 0.267 |
| Carbapenems | 11/21 | (52.4) | 1.44 | 0.59 - 3.49 | 0.419 |
| Ureidopenicillins+BLI | 14/31 | (45.2) | 1.24 | 0.52 - 2.98 | 0.628 |
| Glycopeptides | 4/4 | (100) | 2.75 | 1.25 - 6.03 | 0.012 |
| **Age - Mean(SD)** | | | | | |
| Failure | 58.2 (19.2) | | - | - | 0.557 |
| Success | 56.2 (20.0) | | | | |

*Simplified Acute Physiology Score; †UCI – Intensive care unit; ‡BLI - Beta lactamase inhibitor; §SD - Standard deviation

**Table 3.** Mortality in patients with renal impairment treated by antibiotics needing dose adjustment in an intensive care unit (bivariate analysis).

| | Death | | RR | 95%IC | *p* |
|---|---|---|---|---|---|
| | n/N | % | | | |
| **Dose adjustment** | | | | | |
| Adjusted | 40/54 | (74.1) | 2.29 | 1.06 - 4.92 | 0.033 |
| Not adjusted | 40/72 | (55.6) | | | |
| **SAPS* 3 range** | | | | | |
| > 57 | 64/93 | (68.8) | 2.35 | 1.04 - 5.23 | 0.037 |
| ≤ 57 | 16/33 | (48.5) | | | |
| **Sepsis/septic shock** | | | | | |
| Yes | 52/69 | (75.4) | 3.17 | 1.49 - 6.74 | 0.002 |
| No | 28/57 | (49.1) | | | |
| **Sex** | | | | | |
| Female | 33/50 | (66.0) | 1.07 | 0.82 - 1.39 | 0.635 |
| Male | 47/76 | (61.8) | | | |
| **Source** | | | | | |
| Surgical clinic | 4/7 | (57.1) | 1.00 | - | - |
| Medical clinic | 7/7 | (100) | 1.75 | 0.92 - 3.33 | 0.089 |
| Other hospital | 8/9 | (88.9) | 1.55 | 0.78 - 3.08 | 0.206 |
| Surgical center | 14/29 | (48.3) | 0.84 | 0.40 - 1.78 | 0.658 |
| Emergency room | 47/74 | (63.5) | 1.11 | 0.57 - 2.17 | 0.756 |
| **Admission diagnosis in UCI† (by system)** | | | | | |
| Endocrinal | 2/3 | (38.7) | 1.00 | - | - |
| Cardiac | 3/5 | (66.7) | 0.90 | 0.31 - 2.64 | 0.848 |
| Gastrointestinal | 4/7 | (60.0) | 0.86 | 0.31 - 2.40 | 0.769 |
| Pulmonary | 8/10 | (42.9) | 1.20 | 0.51 - 2.84 | 0.678 |
| Others | 16/28 | (60.0) | 0.86 | 0.36 - 2.03 | 0.727 |
| Neurologic | 20/31 | (53.6) | 0.97 | 0.42 - 2.25 | 0.939 |
| Surgical | 27/42 | (47.6) | 0.96 | 0.42 - 2.22 | 0.932 |
| **Antibiotic** | | | | | |
| Miscelaneous | 4/11 | (36.4) | 1.00 | - | - |
| Cephalosporins | 13/30 | (34.5) | 0.89 | 0.51 - 1.54 | 0.678 |
| Quinolones | 14/29 | (48.3) | 0.81 | 0.41 - 1.0 | 0.477 |
| Carbapenems | 2/21 | (9.5) | 1.42 | 0.89 - 2.27 | 0.142 |
| Ureidopenicillins+BLI‡ | 11/31 | (35.5) | 1.01 | 0.46 - 1.44 | 0.959 |
| Glycopeptides | 2/4 | (50) | 0.79 | 0.26 - 2.32 | 0.662 |
| **Age - Mean (SD§)** | | | | | |
| Death | 57.3 (18.6) | | - | - | 0.935 |
| Discharge | 56.9 (21.4) | | | | |

*Simplified Acute Physiology Score; †UCI – Intensive care unit; ‡BLI - Beta lactamase inhibitor; §SD - Standard deviation

In figure 1 is presented the multivariate analysis with the variables significantly associated with mortality in the bivariate analysis. With exception of the use of glycopeptides antibiotics, no other variable presented significance in the bivariate analysis for therapeutic failure. Notwithstanding, glycopeptides were not included in the multivariate analysis because only four patients had used glycopeptides and in all cases, their doses were adjusted.

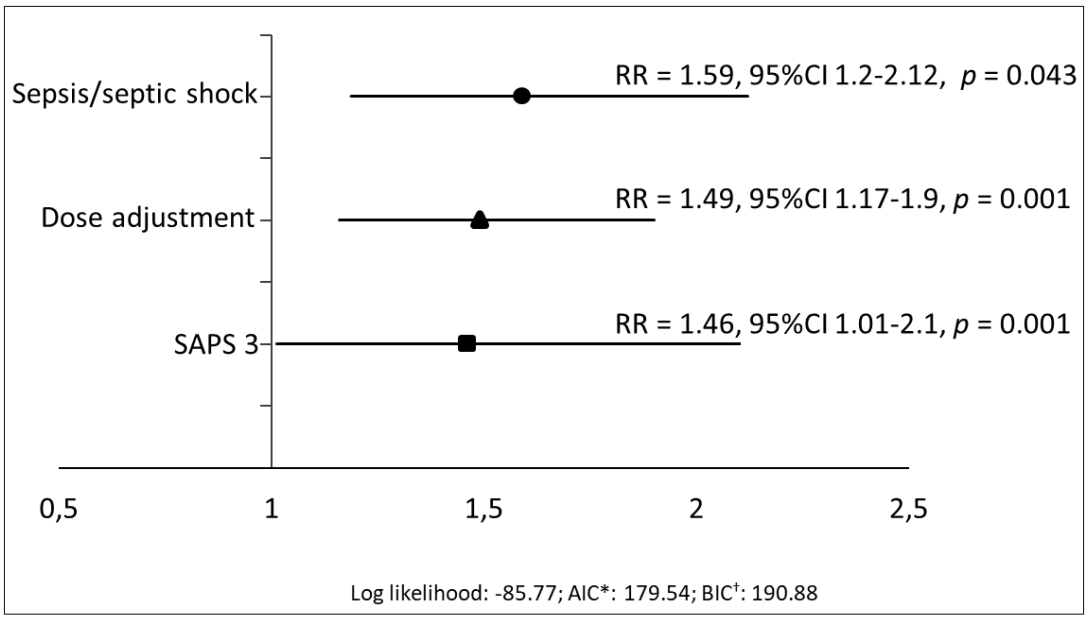


**Figure 1.** Poisson regression analysis for risk of death with predictors significant in the bivariate analysis.

*AIC – akaike's information criterion; BIC – bayesian information criterion

## DISCUSSION

This study demonstrated that continuing the antimicrobial dose adjustment, based on eGFR, may significantly increase therapeutic failure and mortality rates in ICU patients with RI. Moreover, the association with higher mortality remained even when the outcome was pooled in the multivariate analysis with the SAPS 3, categorized as higher or minor risk of death.

The uncertainties around the medication dose adjustment in patients with RI have led to a broad discussion on this issue. Nevertheless, a slight change in the recommendations for adjustments was observed, which are still conducted in a non-individualized manner, independent of the

patient's clinical status. Actually, these recommendations are general for a wide range of GFR, which are often estimated. In several cases, the estimates seemed unreliable, mainly because the patient's serum creatinine concentration was used for all equations, and the dosage may vary with patients' muscle mass, diet, hydration status, ethnic characteristics, and others[13].

Moreover, these equations were obtained from a specific group of individuals, and their use in critically ill patients could be inadequate[14,25]. For these conditions, GFR must be determined directly with laboratory tests instead of using estimation. However, the methods currently available for direct measure are laborious and expensive for hospitals, making them impracticable if performed on a routine basis[13,11].

The inappropriate use of antibiotics has been identified more frequently in ICU patients than in other groups[26]. Errors involving the use of anti-infective agents even include the wrong choice of antimicrobial agents and the administration of inappropriate doses that do not achieve therapeutic levels at the site of infection. Difficulties in establishing correct doses are caused by several factors that produce constant changes in GFR, such as metabolic and physiologic variations, use of nephrotoxic drugs, invasive procedures or devices, and various comorbidities that affect ICU patients[27]. Additionally, the rapid increase in minimal inhibitory concentrations (MICs) that has been observed in the last decades and the unavailability of technologies or knowledge that can support the choice of the correct dose have made the prescription of antimicrobial agents for ICU patients a real challenge.

Most studies suggest that, when possible, the use of agents that are poorly excreted by the kidneys should be considered in patients with RF. However, most often, there are no alternatives that can fulfill this criteria. Hence, the risks and benefits of prescribing the antimicrobial medication without dose adjustment in the first 24 hours must be evaluated[29]. The application of this recommendation was observed in the patients included in this study

when doses were adjusted in the presence of RI. In these cases, the doses were administered without adjustment during the first 24 hours and were only adjusted after this period. However, this intervention was not sufficient to avoid the high rate of therapeutic failure.

During the treatment of an infection, therapeutic failure is strongly associated with death. However, the treatment response is not due solely to the antimicrobial agent, but also to other factors such as age, site and severity of the infection, and comorbidities. Thus, an improvement in patient's clinical and laboratorial condition can be observed in spite of the administration of inaccurate agent's dose. Moreover, in the specific case of infections, underdosing antimicrobials by dose adjustment can result in other problems that are more difficult to be measured, but that can also increase the risk of death. Low antibiotic level in the site of infection, for instance, may retard the patient's response what extend the length of stay and promotes antimicrobial resistance. Consequently, the patient will be exposed to several other risks and if a subsequent infection occurs, it may be caused by a multiresistant strain what significantly increases the risk of death[1].

In view of the lack of studies conducted in specific groups to clearly define the appropriate medication doses, one of the more used measures to avoid negative outcomes is to provide therapeutic drug monitoring by measuring the drug's serum level[4]. Several studies have suggested this practice for the treatment of patients with RI. However, only a few hospitals adopt the use of serum drug measurements, as the tests are expensive. Moreover, these tests are available only for a few antimicrobial drugs[30]. Thus, the use of this tool in clinical practice is limited and has not helped enough in the optimization of antimicrobial use.

There are inherent difficulties with retrospective chart reviews, including the possible absence of relevant information, mainly referring to the prescriber's impression about the patient's clinical status at the time of antimicrobial prescription, which may be a limitation of this study.

Besides that, the unavailability of local data about the MICs could prompt doctors to prescribe amounts that are lower than the recommended dose, increasing the risk of treatment failure. However, this study was performed in an ICU with high rates of infections caused by multiresistant microorganisms, where the vast majority of treatments are started with maximum doses, reducing the risk of possible bias. In the same way, appropriate choice of the antimicrobial agent could have influenced treatment failure and mortality rates. However, with rare exceptions, both groups included in this study were treated in the same ICU by the same healthcare team, what reduces the chance of high differences in decision-making.

Finally, the lack of data or tools supporting the antimicrobial dose adjustment has been a source of insecurity in the care of patients with RI, particularly under clinical conditions that significantly change the pharmacokinetics. Therefore, the prescribers constantly face the following dilemma: not to perform the adjustment and expose the patients to the risk of overdose, which in general are known, monitorable, and controllable or to prescribe the antimicrobial agents with a dose adjustment, perhaps in subdose, and possibly reduce the chance of microbiological cure, which may have a more significant impact on the patient's clinical outcomes, especially in the current scenario with the shortage of therapeutic alternatives. In this way, even if the answer to that doubt is reasonably foreseeable, in daily clinical practice, the conduct of health providers has been conflicting among different settings or even within a same team and the data of our study should reduce the uncertainty surrounding this decision, and reinforce confidence when prescribing an antibiotic for an ICU patient with RI.

## CONCLUSION

In ICU patients with RI, the antibiotic dosage adjustments, based on eGFR, were seen to significantly increase the risk of treatment failure and death. These data suggest that when the

only strategy available for adjustment is based on the eGFR, the use of the full dose of the antibiotic should be considered.

**Conflict of Interest:** The authors declare that they have no conflict of interest.

**Ethical approval:** "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." For this type of study formal consent is not required.

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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