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Evaluation of Pharmaceutical Interventions for Dose Adjustment in Critically Ill Patients with Renal Dysfunction

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Abstract

Objective: To evaluate pharmaceutical interventions for dose adjustments in renal failure patients in intensive care units (ICUs), considering acceptance by prescribers and the distribution of medications by therapeutic class. **Methods:** This prospective cross-sectional study was conducted from November 1, 2024, to January 31, 2025, involving critically ill patients with acute or chronic renal insufficiency. Prescriptions from patients in the hospital's four ICUs (Adult General ICU, Neonatal ICU, Pediatric ICU, and Cardiac ICU) requiring dose adjustments based on renal function (GFR < 60 mL/min/1.73 m² or on dialysis) were included. Prescriptions of patients with normal renal function (GFR > 60 mL/min/1.73 m²) or those with correct dose adjustments by the prescriber were excluded. Interventions were recorded in the Soul MV system, based on UpToDate, Micromedex, and Sanford Guide, and were performed through rounds, direct, or telephone contact. Medications were classified using the Anatomical Therapeutic Chemical Classification System (ATC). **Results:** A total of 2,616 prescriptions were analyzed, of which 96.9% did not require dose adjustment. In 80 prescriptions (3.1%), the adjustment was needed but not performed. Clinical pharmacists made 109 interventions in 41 patients with renal injury. Most interventions (71.6%) were based on GFR, and 28.4% were based on dialysis modality. The acceptance rate of interventions was 68.8%. The adjusted medications were primarily anti-infectives (78%), followed by hematological agents (14%), cardiovascular (4%), nervous system (3%), and gastrointestinal (1%). **Conclusion:** The study highlights the importance of clinical pharmacists in dose adjustment management for critically ill patients with renal dysfunction, emphasizing their role in improving treatment safety and efficacy.

Keywords: renal elimination; hospital pharmacy service; evidence-based pharmaceutical practice.

Avaliação das Intervenções Farmacêuticas para Ajuste de Dose em Pacientes Críticos com Disfunção Renal

Resumo

Objetivo: Avaliar as intervenções farmacêuticas no ajuste de doses em pacientes com lesão renal nas unidades de terapia intensiva (UTIs), considerando a aceitação pelos prescritores e a distribuição dos medicamentos por classe terapêutica. **Métodos:** Estudo transversal prospectivo realizado entre 1º de novembro de 2024 e 31 de janeiro de 2025, com pacientes críticos com insuficiência renal, aguda ou crônica. Foram incluídas prescrições de pacientes das UTIs do hospital (CTI Geral Adulto, UTI Neonatal, UTI Pediátrica e CTI Cardíaco) que necessitavam de ajustes de dose com base na função renal (TFG < 60 mL/min/1,73 m² ou em diálise). As intervenções foram registradas no sistema Soul MV e fundamentadas em UpToDate, Micromedex e Sanford Guide, realizadas via rounds, contato direto ou telefônico. Os medicamentos foram classificados pelo sistema de Classificação Anatômico-Terapêutica-Química (ATC). **Resultados:** Foram analisadas 2.616 prescrições, das quais 96,9% não necessitaram de ajuste. Em 80 prescrições (3,1%), o ajuste era necessário, mas não realizado. Farmacêuticos clínicos realizaram 109 intervenções em 41 pacientes com injúria renal. A maioria das intervenções (71,6%) foi baseada na TFG, e 28,4% na modalidade dialítica. A taxa de aceitação das intervenções foi de 68,8%. Os medicamentos ajustados foram predominantemente anti-infecciosos (78%), seguidos por agentes hematológicos (14%), cardiovasculares (4%), do sistema nervoso (3%) e do trato alimentar (1%). **Conclusão:** O estudo enfatiza a importância da atuação do farmacêutico clínico no ajuste de doses em pacientes críticos com disfunção renal, destacando o impacto positivo na segurança e eficácia do tratamento.

Palavras-chave: eliminação renal; serviço de farmácia hospitalar; prática farmacêutica baseada em evidências.

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Journal of Hospital Pharmacy and Health Services

Introduction

The kidneys play a fundamental role in eliminating many drugs and their metabolites from the body through blood filtration and urinary excretion. In renal failure, the kidneys' filtration function is impaired, which can lead to the accumulation of substances, including medications. Some drugs may further impair renal function, worsening the condition of renal insufficiency.[1] The accumulation of drugs and their metabolites can result in adverse drug reactions (ADRs), ranging from mild responses to severe adverse events such as seizures, organ damage, or even death.[2]

Renal insufficiency is a common condition among patients admitted to intensive care units (ICUs), with approximately 20% to 40% of cases progressing to acute kidney injury, representing a major clinical challenge, particularly in relation to medication dose adjustments.[3] As critically ill patients often present with both acute and chronic renal dysfunctions, inadequate dose adjustments can lead to serious adverse effects, such as toxicity or therapeutic failure, compromising patient safety and recovery.[4-5]

Drug-induced nephrotoxicity due to acute kidney injury, especially among hospitalized patients, is estimated to occur in 19% of cases. This high incidence highlights the need for more cautious approaches to prevent or minimize such events.[6]

The participation of pharmacists in the care of ICU patients is an effective strategy for preventing medication errors and adverse drug events (ADEs), as pharmacists provide essential information and contribute significantly to patient safety.[7-8] Dose adjustment based on renal function is undoubtedly one of the most relevant interventions that clinical pharmacists can perform.[9]

A study conducted in Thailand demonstrated that trained clinical pharmacists were able to provide high-quality dosage adjustment recommendations for these patients, following standard dosing guidelines. Moreover, dosage adjustment resulted in significant savings in direct costs and the prevention of expenses related to adverse drug reactions.[10]

A Brazilian study identified a high frequency of dose adjustments for antimicrobials based on renal function in prescriptions for adult ICU patients. The rates were higher than those observed in non-critical patients. The joint efforts of physicians and pharmacists were crucial to this outcome. This practice contributed to the optimization of therapy and a reduction in both the duration of antimicrobial use and ICU stay.[11]

In Brazil, there are few studies evaluating dose adjustments in ICU patients with renal insufficiency, with most research focusing on non-critical patients.[5] Renal failure in critically ill patients requires precise dose adjustments, but frequent prescribing errors, limitations in electronic systems, variability in recommendations, and insufficient specific training of the medical team highlight the need for pharmaceutical interventions to ensure treatment safety and efficacy.[2]

The objective of this study was to evaluate pharmaceutical interventions related to dose adjustments in patients with renal injury admitted to intensive care units, considering the acceptance rate by prescribers and the distribution of medications by therapeutic class.

Methods

This prospective cross-sectional study was conducted between November 1, 2024, and January 31, 2025, and analyzed pharmaceutical interventions related to dose adjustments in critically ill patients with renal insufficiency, both acute and chronic.

For statistical analysis, Microsoft Excel (Redmond, WA) was used. Data were presented as absolute and relative frequencies for categorical variables. Numerical variables were described using means and standard deviations. The project was reviewed and approved by the institution's Research Ethics Committee on October 22, 2024, under opinion number 7.175.924 (CAAE: 83646024.0.0000.5259).

The Brazilian Consensus on Pharmaceutical Care defines a pharmaceutical intervention or recommendation as a "planned, documented act carried out with the patient and healthcare professionals, aimed at resolving or preventing problems that interfere or may interfere with pharmacotherapy, as an integral part of the pharmacotherapeutic follow-up process".[12]

The study included prescriptions for patients admitted to four intensive care units (Adult General ICU, Neonatal ICU, Pediatric ICU, and Cardiac ICU) who required dose adjustment based on renal function—that is, patients undergoing dialysis or with a glomerular filtration rate (GFR) below 60 mL/min/1.73 m². Prescriptions were excluded if the patient did not require dose adjustment (GFR > 60 mL/min/1.73 m²) or if the dose adjustment had already been correctly made by the prescriber. It is worth noting that a single patient could be included in the study more than once if more than one medication required dose adjustment.

Patients in the four ICUs were monitored by three clinical pharmacists working daily at the bedside, who assessed prescriptions using an electronic prescribing system.

The units included in the study comprised a total of 46 beds: 10 in the Adult General ICU, 18 in the Neonatal ICU, 6 in the Pediatric ICU, and 12 in the Cardiac ICU. These units consistently have an occupancy rate equal to or close to 100%.

During the review of medical prescriptions, the clinical pharmacist assessed the need for medication dose adjustment in cases where the patient presented any degree of renal injury. This assessment involved verifying whether the patient was on dialysis or calculating the glomerular filtration rate (GFR) using creatinine clearance. It is important to note that dose adjustment was only suggested after 24 hours of initiating the medication.

In patients with renal injury, the clinical pharmacist analyzed the prescribed medications requiring adjustment and provided guidance for dose optimization. For patients undergoing dialysis, the adjustment was proposed according to the dialysis modality. For those not on dialysis but presenting with renal insufficiency, the pharmacist's dose adjustment recommendations were based on the glomerular filtration rate (GFR). The need for dose adjustment based on GFR varied depending on the pharmacological characteristics of each medication. The Uptodate, Micromedex, and Sanford databases were used as references for suggesting dose adjustments.

The study used the CKD-EPI equation to calculate GFR in adult patients, as it is more accurate than the MDRD equation, particularly at normal or near-normal values. CKD-EPI is recommended by the KDIGO guidelines (2012) and provides more reliable estimates, with higher accuracy in patients with GFR above 60 mL/min/1.73 m². It is also less biased and applicable across a broader range of values.[13,14]

JHPHS
Journal of Hospital Pharmacy and Health Services

To calculate GFR in children, the Schwartz equation was used, known for its simplicity, ease of use, broad validation, and accuracy in pediatric populations, especially in young children and adolescents.[15,16]

Pharmaceutical interventions were carried out during multidisciplinary rounds, via telephone, or through direct contact with the involved healthcare professionals. All activities were electronically recorded in the Soul MV software, adapted for the hospital institution. These interventions were documented by completing a digital form linked to the patient's electronic medical record. The intervention form is integrated into the indicator dashboard, with data automatically generated after the pharmacist's input. Furthermore, the system allows for the creation of reports containing sociodemographic information of the study participants.

In the intervention form, pharmacists had a specific section to document interventions related to dose adjustments based on renal function. This section included information on the patient, the hospital unit, the medication involved in the dose adjustment, the reason for adjustment (based on dialysis modality or GFR), and whether the intervention was accepted.

Additionally, pharmacists recorded information regarding pharmacotherapeutic follow-up and recommendations made to the multidisciplinary team using the electronic document called "pharmaceutical progress note."

The interventions performed were classified based on their acceptability and categorized as accepted or not accepted. An intervention was considered accepted when, after pharmacist contact with the prescriber, the prescription was modified to include the suggested dose adjustment; it was considered not accepted when the dose was not adjusted.

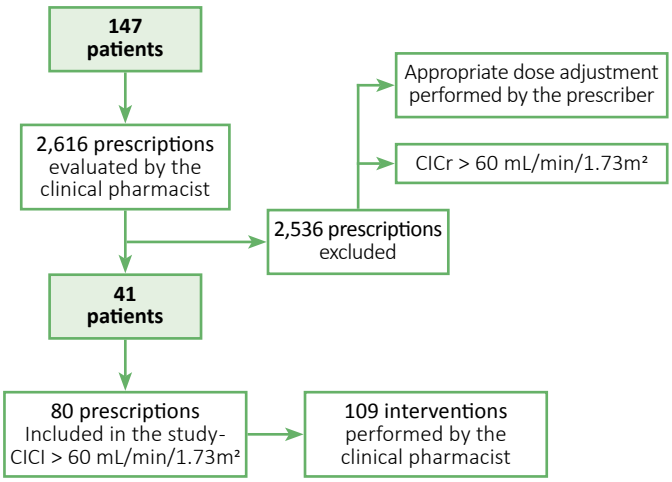
Furthermore, the medications involved in the dose adjustment interventions were categorized using the Anatomical Therapeutic Chemical (ATC) Classification System, which standardizes medications based on the organ or system they act upon, and their therapeutic, pharmacological, and chemical properties (https://www.whocc.no/atc_ddd_index).

Sociodemographic variables (sex and age) were also collected, along with the reason for ICU admission (classified according to the primary anatomical system based on the International Classification of Diseases and Related Health Problems – ICD), and length of hospital stay.

Results

During the study, a total of 2,616 medical prescriptions from patients admitted to the four ICUs included in the research were evaluated. Of these, 2,536 prescriptions (96.9%) were excluded either because they did not require dose adjustment (GFR > 60 mL/min/1.73 m²) or because the appropriate adjustment had already been made by the prescriber. The remaining 80 prescriptions (3.1%) required dose adjustment based on renal function for at least one medication, but the adjustment had not been made. In these cases, the clinical pharmacist performed 109 pharmaceutical interventions in 41 patients with renal injury, resulting in an average of 2.7 interventions per patient (Figure 1).

Figure 1. Sample Inclusion Flowchart



It was observed that among the patients who required medication dose adjustments, there was a predominance of males (N=23; 56.1%). The mean age was 49.4 ± 27.1 years. Regarding age group distribution, the study included 6 neonates (14.6%), 6 children and adolescents (14.6%), and 29 adults (70.7%). The main cause of ICU admission was cardiovascular disease, with a notable number of patients undergoing coronary artery bypass graft surgery due to coronary artery disease (12 patients). The average length of hospital stay was 39.8 ± 29.1 days. The descriptive variables of the sample are presented in Table 1.

Table 1. Sociodemographic and clinical characteristics of patients for whom dose adjustment was recommended by the clinical pharmacist in four ICUs of a university hospital in Rio de Janeiro, from November 2024 to January 2025.

Variables	N=41
Age (years) – mean ± SD	49.4 ± 27.1
Sex – n (%)	
Male	23 (56.1)
Female	18 (43.9)
Length of hospital stay (days) – mean ± SD	39.8 ± 29.1
Reason for ICU admission – n (%)	
Diseases of the heart and blood vessels	23 (56.1)
Perinatal conditions	6 (14.6)
Diseases of the genitourinary system	3 (7.3)
Neoplasms (tumors)	3 (7.3)
Diseases of the endocrine system	2 (4.9)
Diseases of the immune system	2 (4.9)
Diseases of the respiratory system	1 (2.4)
Calcium carbonate poisoning	1 (2.4)

SD: standard deviation

Among the suggested dose adjustments, 78 (71.6%) were based on creatinine clearance and 31 on dialysis modality. Of the latter, 30 cases (27.5%) involved patients on conventional hemodialysis, while 1 patient (0.9%) was undergoing peritoneal dialysis.

JHPHS
Journal of Hospital Pharmacy and Health Services

Regarding the acceptability of dose adjustments recommended by the clinical pharmacist, 68.8% (n=75) were accepted, while 31.2% (n=34) of the suggested adjustments were not implemented by the prescriber. When acceptability was analyzed by age group, acceptance was 20% (2/10) among neonates, 83.3% (10/12) among children and adolescents, and 72.4% (63/87) among adults. Of the 109 medications for which dose adjustment was suggested by the pharmacist, 85 (78.0%) belonged to the group of systemic anti-infectives (ATC group J), followed by drugs acting on the blood and hematopoietic organs (13.8%), and 5 (4.6%) on the cardiovascular system. Table 2 shows the categorization of the medications according to the system or organ they act upon.

Table 2. Categorization of medications according to the system or organ they act upon, based on the Anatomical Therapeutic Chemical (ATC) Classification.

ATC Classification	n (%)
J- Antiinfectives for systemic use	85 (78.0)
B- Blood and blood-forming organs	15 (13.8)
C- Cardiovascular system	5 (4.6)
N- Nervous system	3 (2.8)
A- Alimentary tract and metabolism	1 (0.9)
Total	109 (100)

The medications that received the highest number of interventions were: meropenem (14.7%), enoxaparin (13.8%), piperacillin + tazobactam (11.0%), and teicoplanin (10.1%). Table 3 presents a complete list of medications for which dose adjustments were recommended.

Table 3. Dose adjustments suggested by the clinical pharmacist, categorized by medication

Medication	n (%)
Meropenem	16 (14.7)
Enoxaparin	15 (13.8)
Piperacillin + Tazobactam	12 (11.0)
Teicoplanin	11 (10.1)
Ceftazidime	8 (7.3)
Vancomycin	6 (5.5)
Ampicillin + Sulbactam	5 (4.6)
Sulfamethoxazole + Trimethoprim	5 (4.6)
Amikacin	4 (3.7)
Ampicillin	4 (3.7)
Enalapril	3 (2.8)
Levofloxacin	3 (2.8)
Tramadol	3 (2.8)
Amoxicillin + Clavulanate	2 (1.8)
Cefepime	2 (1.8)
Fluconazole	2 (1.8)
Acyclovir	1 (0.9)
Atenolol	1 (0.9)
Cefuroxime	1 (0.9)
Ciprofloxacin	1 (0.9)
Daptomycin	1 (0.9)
Spironolactone	1 (0.9)
Metoclopramide	1 (0.9)
Oxacillin	1 (0.9)
Total	109 (100)

All 10 adjustments recommended for neonatal patients referred to medications within the antimicrobial class. In the group of children and adolescents, out of the 12 adjustments suggested by the pharmacist, 11 were related to antimicrobials and only 1 to a different class of medication.

Regarding the distribution of dose adjustments suggested by clinical pharmacists across the evaluated units, 59 (54.1%) interventions occurred in the Cardiac ICU, 28 (25.7%) in the General Adult ICU, 12 (11.0%) in the Pediatric ICU, and 10 (9.2%) in the Neonatal ICU.

Discussion

Of the 2,616 prescriptions analyzed, 3.1% required dose adjustments, resulting in 109 pharmaceutical interventions in 41 patients with renal injury. Most of the adjustments were based on creatinine clearance (71.6%), with 28.4% involving patients undergoing dialysis therapy. The acceptance rate of the recommended adjustments was 68.8%, being higher among children/adolescents (83.3%) and adults (72.4%). Systemic anti-infectives were the most frequently adjusted drug class (78%).

Dose adjustment in patients with renal impairment is essential not only to reduce the risk of adverse drug reactions or nephrotoxicity, but also to ensure therapeutic efficacy. In this context, the clinical pharmacist plays a crucial role by ensuring that necessary adjustments are appropriately made. Collaboration between physicians and pharmacists is key to minimizing treatment risks and achieving better patient outcomes.[11] Pharmaceutical interventions for dose adjustments based on renal function are among the most significant interventions carried out by clinical pharmacists.[9]

Dose correction or individualization is a fundamental intervention performed by clinical pharmacists. The main interventions carried out by these professionals involve dose adjustment or modification of dosing frequency.[17–19] In a Brazilian study analyzing pharmaceutical interventions during the review of medical prescriptions in ICUs, out of 933 interventions performed, 436 (46.73%) were related to dose or frequency individualization or correction.[2]

The main causes of ICU admission were heart and vascular diseases (56.1%), followed by perinatal conditions (14.1%). These findings are consistent with the distribution of pharmaceutical interventions observed: 59 (54.1%) occurred in the Cardiac ICU and 10 (9.2%) in neonatal patients.

During the study, 78 (71.6%) dose adjustments were based on creatinine clearance, and 31 were based on dialysis modality. The literature recommends that dose adjustments be made according to dialysis modality in patients undergoing dialysis, whereas for non-dialysis patients, adjustments should be based on creatinine clearance. It is important to emphasize that the databases and scientific literature addressing this topic provide information for dose adjustment based on both dialysis modality (such as peritoneal dialysis, intermittent hemodialysis, and continuous hemodialysis) and creatinine clearance.

In this study, the acceptance rate of dose adjustments recommended by the clinical pharmacist was 68.8% (n=75). In a prospective European study involving hospitalized patients with renal impairment in an internal medicine unit, 123 pharmaceutical interventions were performed, of which 40.6% (n=50) were accepted and 59.4% (n=73) were rejected.[20]

JHPHS
Journal of Hospital Pharmacy and Health Services

Two Spanish studies reported acceptance rates for dose adjustments of 65.6% and 65.5%, respectively.[21,22] These values are similar to those observed in the present study. A Brazilian study conducted in an adult intensive care unit identified a high acceptance rate of dose adjustment recommendations for patients with renal dysfunction: 22 out of 26 interventions (84.6%) were accepted. Despite the small number of interventions, this finding reinforces the importance of the clinical pharmacist's role as part of the multidisciplinary team in the care of critically ill patients.[5]

The present study showed a high acceptance rate (68.8%) by prescribers regarding the dose adjustment recommendations for patients with renal dysfunction, with most interventions occurring during the pharmacist's participation in multidisciplinary rounds. Several studies suggest that this acceptance is directly related to the integration of the pharmacist into the healthcare team, especially through their presence during clinical rounds and direct interaction with patients.[23–25] Brazilian studies have also shown that high acceptance rates indicate that the recommendations are clinically relevant.[26–28]

In our study, the main reason given by prescribers for not implementing dose adjustments based on renal function was the severity of the patients and uncertainty about the ideal serum drug levels. This is partly due to the fact that, in the study setting, serum monitoring is not performed for any of the selected medications, which may raise doubts regarding the appropriate dosing. The clinical severity of the patients and the lack of individualized pharmacokinetic data were also identified by Rojas *et al*. (2023) as possible reasons for the lack of adherence to dose adjustment in critically ill patients with renal impairment. Another common justification for not accepting the pharmacist's recommendation is the improvement in renal function.[21]

Another barrier to physicians' adherence to pharmaceutical recommendations identified in some studies is ineffective communication between professionals. The lack of clinical information on patients, independent and parallel workflows among medical staff, and authority conflicts or professional boundaries during patient care hinder effective communication between clinical pharmacists and physicians.[29,30]

Ten dose adjustments were suggested for neonatal patients, of which only 2 (20%) were accepted. The acceptance rate of dose adjustments in this population was considerably lower compared to the other groups, with 83.3% acceptance among children and adolescents and 72.4% among adults. This lower rate is related to the limitations of serum creatinine as an indicator of renal function in neonates. In the first days of life, creatinine levels may be elevated due to maternal transfer, especially within the first 48 to 72 hours after birth. Furthermore, interpreting renal function in neonates involves various clinical factors, making it difficult to base clinical decisions solely on absolute creatinine values.[32]

In the present study, 85 (78.0%) of the pharmaceutical dose adjustment recommendations were related to systemic anti-infectives (ATC group J), followed by medications acting on blood and blood-forming organs (13.8%). This finding is consistent with several other studies, which also identify antimicrobials as the most prevalent pharmacological group requiring dose adjustments.[5,21,31,33]

In this study, the antimicrobials that most frequently required dose adjustment according to renal function were, respectively, Meropenem and Piperacillin + Tazobactam. Similar results were observed in two Brazilian studies conducted in university hospitals, which also investigated the frequency of dose adjustments based on patients' renal function.[3,11]

In our results, of the 22 adjustments made in the neonatal, pediatric, and adolescent groups, 21 were related to antimicrobials, with only one involving a medication from another therapeutic class. Thus, it was observed that, in these age groups, unlike in adults, the prescription of medications from other therapeutic classes requiring dose adjustment in renal impairment was less common.

The second medication for which the pharmacist most frequently recommended dose adjustment was enoxaparin, with 15 interventions (13.8%). In all these cases, the intervention consisted of recommending dose correction of enoxaparin, without suggesting substitution with unfractionated heparin, which does not require dose adjustment in patients with renal impairment. This approach was appropriate, since, according to UpToDate, substitution with unfractionated heparin is indicated for patients with a glomerular filtration rate (GFR) below 30 mL/min, especially in cases of venous thromboembolism prophylaxis in trauma patients with moderate to high risk of thrombosis—conditions that did not apply to the patients in this study. It is important to emphasize that dose correction is necessary because enoxaparin clearance is reduced by 17% to 44% in patients with mild to moderate renal impairment.[34]

The results highlight the crucial role of the clinical pharmacist in optimizing therapy in patients with renal impairment, with a high acceptance rate of dose adjustment interventions, especially in children/adolescents and adults. Clinically, these interventions contribute to personalized medication therapy and reduction of adverse events. Scientifically, the findings provide important information for future research on pharmaceutical recommendations related to dose adjustment in critically ill patients with renal dysfunction.

Among the limitations of this research are the absence of evaluation of subsequent clinical outcomes and the fact that dose adjustments were not suggested for all medications requiring modification. Furthermore, the data were obtained from prescriptions of patients admitted to critical care units, which are characterized by particular conditions, potentially limiting the generalizability of the results. Therefore, it is important to conduct further studies that also include non-critical patients and investigate the impact of not adjusting medication doses.

Other limitations include the short data collection period (3 months) and potential seasonality bias, which may have affected the results. Additionally, a limitation is that dose adjustment did not consider certain clinical situations frequently observed in critically ill patients where, despite literature support for adjustment, factors such as imminent risk of death and perfusion alterations may justify postponing or even withholding the dose adjustment.

Conclusion

This study highlighted the importance of the clinical pharmacist's role in dose adjustment for ICU patients with renal dysfunction, given the high prevalence of this condition. The results indicated that a significant portion of commonly prescribed medications require adjustments to ensure their safety and therapeutic efficacy. This underscores the fundamental role of clinical pharmacists in identifying and preventing potential risks. The predominance of therapeutic classes such as antimicrobials among medications needing adjustment reinforces the necessity for more precise pharmaceutical interventions in this area.

JHPHS
Journal of Hospital Pharmacy and Health Services

Clinical pharmacy identified several challenges in dose adjustment for patients with renal dysfunction, highlighting opportunities to improve pharmacotherapy by focusing on treatment necessity, efficacy, and safety. The involvement of clinical pharmacists can contribute to increasing the rate of appropriate dose adjustments in patients with renal insufficiency. It is expected that this study will encourage the inclusion of clinical pharmacists as integral members of the multidisciplinary healthcare team.

The implementation of rigorous institutional practices, such as automated protocols or checklists for dose adjustment based on renal function, is essential. Furthermore, future studies evaluating clinical outcomes in patients with adjusted and non-adjusted doses are recommended to demonstrate the clinical benefits of these interventions and enhance patient safety.

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