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# Fluid stewardship in intensive care: clinical pharmacist's actions analysis

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## Abstract

**Objective:** To describe and analyze the pharmaceutical interventions performed by clinical intensivist pharmacists in the management of fluid therapy**. Methods:** This is an observational, retrospective, descriptive study conducted in a clinical ICU of a tertiary teaching hospital from January 2018 to December 2022. The study evaluated the classification according to the "four rights of fluid therapy" adapted from Hawkins[14] (right drug, right dose, right route, and right patient); the acceptability of pharmaceutical interventions; the classification of interventions involving hidden fluids, and the medications involved in this classification. **Results:** The study included 415 patients, the majority of whom were male, 51% (213). The mean age was 57.4 ± 17.2 years. A total of 993 pharmaceutical interventions related to fluids were performed, comprising 12.2% of the interventions during the study period and corresponding to 2.4 per patient. The acceptability rate was 90% (894). Of the cited interventions, the majority (591) were related to the "right dose" (59.4%). The other interventions were: 167 (16.9%) related to the "right drug," 163 (16.4%) to the "right route," and 72 (7.2%) to the "right patient." The management of hidden fluids was present in 722 (72.7%) interventions, with a focus on antimicrobials, totaling 256 (35.4%); followed by electrolytes and vitamins with 229 (31.7%), and antiulcer agents with 124 (17.2%). **Conclusion:** The pharmaceutical interventions analyzed were related to the "four rights of fluid therapy" and had high acceptability from the team. There was significant demand for pharmaceutical intervention in fluid management. The findings indicate the potential role of the clinical intensivist pharmacist as a key player in the fluid therapy management of critically ill patients.

**Keywords:** fluid therapy; critical care; clinical pharmacy

## Stewardship de fluidos na terapia intensiva: análise das ações do farmacêutico clínico

## Resumo

**Objetivo:** descrever e analisar as intervenções farmacêuticas realizadas pelos farmacêuticos clínicos intensivistas no manejo da fluidoterapia. **Métodos:** estudo observacional, retrospectivo, descritivo, realizado em uma UTI clínica de um hospital de ensino terciário, de janeiro de 2018 a dezembro de 2022. Foram avaliados: a classificação quanto aos "quatro certos da fluidoterapia" adaptado de Hawkins[14] (medicamento certo, dose certa, via certa e paciente certo); a aceitabilidade das intervenções farmacêuticas; a classificação quanto a pertencer ao grupo dos *hidden fluids* e os medicamentos envolvidos nessa classificação. **Resultados:** foram incluídos no estudo 415 pacientes, a maioria do gênero masculino, 51% (213). A idade média foi de 57,4 ± 17,2 anos. No total, foram realizadas 993 intervenções farmacêuticas relacionadas a fluidos, compreendendo 12,2% das intervenções do período estudado e correspondendo a 2,4 por paciente. A aceitabilidade foi 90% (894). Das intervenções citadas, a maioria (591) foram relacionadas à "dose certa" (59,4%). As demais intervenções foram: 167 (16,9%), relacionadas ao "medicamento certo", 163 (16,4%) à "via certa" e 72 (7,2%) ao "paciente certo". O manejo dos *hidden fluids* esteve presente em 722 (72,7%) intervenções, com destaque para os antimicrobianos, com um total de 256 (35,4%); seguido dos eletrólitos e vitaminas, com 229 (31,7%) e dos antiulcerosos com 124 (17,2%). **Conclusão:** as intervenções farmacêuticas analisadas relacionaram-se aos "quatro certos da fluidoterapia" e tiveram alta aceitabilidade da equipe. Houve uma demanda importante pela atuação farmacêutica no manejo de fluidos. Os achados indicam a potencialidade na atuação do farmacêutico intensivista como protagonista no manejo da fluidoterapia de pacientes críticos.

**Palavras-chave:** fluidoterapia; cuidado crítico; farmácia clínica.

## Introduction

The intravenous use of fluids is one of the most common therapies in intensive care, with the primary indications being the management of hypovolemia, sepsis, correction of fluid loss, hemodynamic alterations, and oliguria[1]. However, like all medications, fluids are not exempt from adverse effects, and their improper use can cause harm, especially those associated with fluid overload and its consequent accumulation[2-4].

The accumulation of fluids due to improper management impacts organ systems, being associated with the following events: (i) acute kidney injury (AKI), (ii) increased need for invasive procedures, (iii) worsening of the clinical condition, (iv) longer postoperative recovery time, (v) extended stay in intensive care units (ICUs) and hospitals, (vi) higher mortality rates, as well as (vii) electrolyte imbalances and (viii) dysglycemia[2-10]. These negative outcomes demonstrate the need for attention from the healthcare team.

To ensure appropriate fluid therapy, it is also useful to differentiate between discretionary fluids (those specifically prescribed for volume resuscitation and maintenance) and hidden fluids (which are part of the dilution of intermittent medications, blood components, and enteral nutrition and are not necessarily prescribed). The latter can often be overlooked as contributors to the administered[11-13] volume. Collectively, hidden fluids can account for up to 80% of the volume administered in the first three days of ICU and, when considering intravenous medications, this percentage can reach 30% in the same period and 40% in seven days[11-13].

In this context, it is the responsibility of the intensivist pharmacist to evaluate, within their care system, the different types of fluids administered to the patient and propose their management[12-15]. Pharmaceutical contributions suggested or already established include the indication of fluid responsiveness techniques, management of discretionary fluids, adjustments in the dilution of medications to the smallest possible volumes, modification of the characteristics of diluents, modification of the administration route, with an emphasis on switching from intravenous to enteral route[12,13,16].

As a strategy to address and reduce adverse events, Hawkins et al. established the "four rights of fluid therapy," which consider the review of pharmacotherapy and incorporate practical actions by the intensivist pharmacist in evaluating the right patient, right drug, right route, and right dose[14].

In Brazil, studies evaluating fluid stewardship by clinical intensivist pharmacists are scarce. Thus, the present study aimed to describe and analyze the pharmaceutical interventions (PIs) that impacted fluid therapy management in a teaching hospital, using the adapted concept of the "four rights of fluid therapy."

## Methods

### Study Type and Location

An observational, descriptive, and retrospective study was conducted in the clinical ICU of a tertiary teaching hospital in the state of Ceará, with 197 beds, from January 2018 to December 2022. The ICU had eight beds and was composed of a multidisciplinary team, including clinical pharmacists: two resident pharmacists supervised by an assistant intensivist pharmacist.

### Sample and Instruments

Convenience sampling was used, wherein all secondary data related to pharmaceutical interventions (PIs) for patients meeting the inclusion criteria were selected. These interventions, described and analyzed in the study, resulted from the daily routine of pharmaceutical therapy review that involved fluid management.

The interventions pertained to patients evaluated by clinical pharmacists from Monday to Friday regarding the necessity, effectiveness, safety, convenience, and process of pharmacotherapy use; these interventions were conducted alongside the multidisciplinary team during clinical visits or case discussions directly with the prescriber. On Saturdays and Sundays, the institution's pharmacy service was dedicated to the technical evaluation of prescriptions, without the involvement of the clinical pharmacy team in the ICU, and thus, possible PIs during this period were not considered for the study.

These PIs were recorded on a pharmacotherapy review form developed by the institution's intensive care pharmacy team, structured to collect clinical, laboratory, and imaging data for ICU patients, respecting the cranial-caudal order. Subsequently, the data were entered into Microsoft Office Excel® spreadsheets for processing and analysis.

Inclusion criteria encompassed patients aged 18 years or older, admitted to the Clinical ICU of the teaching hospital from January 2018 to December 2022, who received some type of pharmaceutical intervention related to fluid therapy. Exclusion criteria included cases that involved (i) blood component management, as this action was not part of the pharmaceutical review system in the ICU where the study was conducted, or (ii) interventions with incomplete records in the institutional database.

### Analysis

The study considered the outcome of the pharmaceutical therapy review service, an assignment of the clinical pharmacist, which involved a detailed analysis of the medications in use, including the route, dose, posology, drug interaction, timing, and therapeutic indication. After analysis, a PI could be made related to the necessity, effectiveness, safety, convenience, among other aspects of the patients' therapy[17] .

The necessity evaluation included verifying the indispensable or non-indispensable use of the prescribed or non-prescribed medications (that the patient needs to use) or medications that were potentially misselected. Safety analysis involved examining the profile of adverse drug events related to the dose or not. Effectiveness analysis was related to the efficacy of the medication's effect on the critically ill patient, which could also be dose-related or not. Finally, convenience referred to the best way to administer a medication, considering its safety and effectiveness for the patient[18].

The analyzed variables included demographic data (gender and age); number of fluid therapy interventions per patient; acceptability of interventions; adapted classification of the "four rights"; type of fluid described in the "four rights" classification; hidden fluids group and the medications associated with this category.

Regarding the classification of the "four rights of fluid therapy" by Hawkins et al.[14], the "right patient" concerns the clinical indication of the fluid to be administered and included interventions related to the initiation or discontinuation of resuscitation fluid,

maintenance fluid, or enteral water. Resuscitation fluid was considered to be administered intermittently or continuously to correct relative or absolute hypovolemia, while maintenance fluid was prescribed to meet daily basal water, glucose, or electrolyte needs when the patient could not do so enterally.

The "right drug" correlates the fluid characteristics and the patient's condition in selecting the most appropriate fluid and included PIs modifying the type of administered fluid for both continuous and intermittent fluids represented by: saline 0.9%, saline 0.45%, saline 3%, lactated Ringer's, and glucose 5%.

For the "right route," focusing on transitioning from intravenous to enteral, subcutaneous, intramuscular, or sublingual routes, all target medications for such transitions were included in this classification. The "right dose," which considers the adjustment in the dose or quantity of administered fluid, included PIs resulting from adjustments that led to reduced administered volume, regardless of the fluid type involved.

Regarding the classification of hidden fluids, included PIs were described as "right route" and "right dose," with the involved medications categorized into antimicrobials, electrolytes and vitamins, gastric antiulcer agents, sedatives and analgesics, vasoactive drugs, and others, according to an adaptation of the classification by Gamble et al.[12], which considers the specificity of hidden fluids in the ICU.

Acceptability was assessed during the period in which PIs were made by each clinical pharmacist responsible for the intervention, checking whether the physician had modified the patient's prescription as suggested. After verifying acceptability, the professional formally recorded the information in the institutional database used in this study.

### Ethical Aspects

The study was approved by the ethics committee of Hospital Universitário Walter Cantídio, affiliated with the Federal University of Ceará, under opinion number 5.409.579.

## Results

During the study period, 760 patients in the ICU under study received some type of pharmaceutical intervention. Of these, 415 met the inclusion criteria, with 213 (51%) being male. The mean age was 57.4 ± 17.2 years, with 229 (55.2%) aged 60 years or older.

The 415 patients included in the study received 993 fluid therapy interventions out of the 8165 performed during the study period, corresponding to 12.2% of the total interventions. The average number of fluid therapy PIs per patient was 2.4, with 894 (90%) being accepted.

Regarding the relationship of PIs with the "four rights," 72 (7.2%) were related to the "right patient," with a predominance of interventions in maintenance fluids, followed by the initiation or discontinuation of enteral water, without any records related to resuscitation fluid management.

Interventions on the "right route" accounted for 163 (16.4%), strictly related to intermittent medications and mainly involving the modification of the administration route from intravenous to enteral for gastric antiulcer agents, corticosteroids, antimicrobials, and analgesics.

The "right drug" totaled 167 interventions (16.9%) and included modifications in the composition of both maintenance fluids and intermittent medications, with antimicrobials being the main representatives. These PIs were represented in all medications established in the methodology: saline 0.9%, saline 0.45%, saline 3%, lactated Ringer's, and glucose 5%.

For the "right dose," there was a predominance of intermittent medications with 591 (59.5%) PIs: reductions in dilution volumes of solutions containing antimicrobials, electrolytes, sedatives, and vasoactive drugs were the most involved.

Considering hidden fluids, these collectively comprised 722 (72.7%) interventions, divided between the "right route" (22.6%) and the "right dose" (77.4%) **(Table 1)**.

**Table 1.** Distribution of Medication Categories in Pharmaceutical Interventions hidden fluids (Fortaleza, 2023).

| Hidden fluids | N (%) | Classe de medicamento (%) |
|---|---|---|
| "Right route" | 163 (22,6%) | UCL (17,2%), OUT (3,5%), ATB (1%), SDA (0,6%) e EEV (0,4%) |
| "Right dose" | 599 (77,4%) | ATB (34,5%), EEV (31,3%), OUT (6,8%), SDA (3%), DVA (1,8%) |
| Total | 722 (100%) | - |

Source: Prepared by the authors. ATB: antimicrobials; DVA: vasoactive drugs; EEV: electrolytes and vitamins; OUT: others; SDA: sedatives and analgesics; ULC: antiulcer agents.

Regarding the contribution of medication categories to the four criteria, antimicrobials were the most significant, totaling 256 (35.4%) PIs, with the most involved medications being Polymyxin B (11.5%), Vancomycin (6.2%), Meropenem (3.7%), and Teicoplanin (3.7%).

Electrolytes and vitamins, with 229 (31.7%) PIs, comprised the second most relevant group, with the following medications predominating: 1. Concentrated potassium chloride (10.2%); 2. Concentrated magnesium sulfate (7.6%); and 3. Thiamine (4.4%).

Gastric antiulcer agents were also a significant source of interventions in the hidden fluids group with 124 PIs (17.2%), mainly consisting of Omeprazole (16.3%), which was the single most contributing medication in the study, and Ranitidine (0.8%). Sedoanalgesia, vasoactive drugs, and other medications had lower expression with 26 (3.6%), 13 (1.8%), and 74 (10.2%), respectively.

## Discussion

The findings pointed to a demand for pharmaceutical actions and interventions in patient fluid therapy, given that the observed rate of PIs in fluid therapy per patient was higher than described in the study by Hawkins et al.[16] (1.52) and approximated recent studies on general PIs conducted in ICUs, reaching 1.6 and 5.45 per patient [19,20].

It is noteworthy, however, that the percentage of PIs related to the use of fluids in relation to the total PIs during the study period was lower than the percentage described in the work of Hawkins et al.[16] (19%). It is important to highlight that these authors evaluated pharmaceutical interventions in the context of implementing a fluid stewardship service, meaning the pharmacists involved were trained to carry out such activity.

With high acceptability, it is evident that prescribers tend to consider PIs related to fluid therapy, reflecting the recognition of the clinical pharmacist as a relevant agent for fluid management and patient care. A similar percentage was observed in studies that evaluated clinical pharmacist interventions in ICUs, which ranged between 85% to 99.3% [19-22].

Regarding the "four rights," the fact that PIs related to the "right patient" were less frequent may be linked to the discretionary characteristic dependent on the opportune moment for intervention, such as the moment of suspending enteral nutrition, detecting hypovolemia, and bedside clinical evaluation of the patient's volemic state, which was not a reality during the studied period. It is noted that, due to having a specialized service, Hawkins et al.[16] reported 39% of PIs in this same item.

The lack of interventions in resuscitation fluids, besides requiring a strategic moment and bedside clinical evaluation, may demand techniques or procedures in their decision-making, more restricted to medical practice, such as passive leg raising, pulse pressure variation, inferior vena cava collapsibility index, and stroke volume variation.

Reaching quantitatively the third position (16.4%), the "right route" holds the importance of contributing to reducing fluid overload and its harmful consequences, as well as stimulating the gastrointestinal tract physiologically, simplifying therapy, and reducing costs. In their study, Hawkins et al.[16] obtained 33% of the PIs.

A common practice in pharmaceutical care also gained prominence in sequential oral therapy in antimicrobial management programs, with the pharmacist playing a predominant role in its consolidation and potentially serving as a basis for application in fluid[23,24] management.

The "right drug" was the second in volume of PIs, quantitatively equivalent to Hawkins et al.[16] (17%), highlighting the correlation of knowledge embedded in the daily clinical pharmacy practice, the most appropriate diluent for each drug, and the adaptation of dilutions, with the evaluation of the need for the most appropriate fluid for certain clinical characteristics of the patient.

Knowledge about the minimum dilutions of drugs to be practiced safely, as well as dose adjustment and evaluation of the need for a particular drug, is intrinsic to the systematic care of the intensive care pharmacist and resulted in the "right dose" being the main type of intervention performed, as expertise applied to fluid[21,25,26] management.

The high prevalence of the "right dose" likely relates to the need for fluid de-escalation, i.e., reducing the amount or rate of administration, especially considering the unit where the study was conducted, predominantly admitting elderly patients, within a national context of high prevalence and increasing incidence of sepsis and the use of broad-spectrum antimicrobials, sometimes with nephrotoxic characteristics, leading to acute kidney injury and preventing the patient from physiologically eliminating excess fluids, reinforcing[27] this hypothesis.

The degree of discrepancy between this study and the model work conducted by Hawkins et al.[16], which obtained 11% of PIs related to the "right dose," may be related to the type of policy or protocol adopted for prescribing intermittent medications, especially concerning dilutions, and the level of specialization in fluid therapy of the clinical pharmacy service, which seems to tend to perform more PIs in the "right patient" aspect as it becomes more specialized.

Reducing the infused volume is desirable, especially when the patient cannot, at the appropriate time, eliminate the amount of fluid received, making the identification of the main sources of fluids essential.

Studies have shown that discretionary fluids lose quantitative relevance over the course of hospitalization, being prominent in the first 24 hours. After this period, they are supplanted by hidden fluids in their entirety (medications, diet, and blood components). Within the hidden fluids component, intravenous medications can account for about 30% of the infused volume in the first three days and 40% in the first seven days [11-13].

The categories "right route" and "right dose" fit into the classification of hidden fluid and, corresponding to 72.2% of the PIs, show a demand for fluid de-escalation in these patients and its relevance in proper fluid management, given the new findings related to the topic. Furthermore, due to these characteristics, intensive care pharmacists can be considered key agents in managing hidden fluids, either actively or by prescriber[13,14] request.

The findings related to hidden fluids were similar to those of Gamble et al.[12], also with a greater contribution from antimicrobials and electrolytes and vitamins. These authors evaluated and found that these categories of drugs have the highest fluid load in average volume in the first three days of ICU admission.

The results obtained in this study reinforce key actions that intensive care pharmacists can develop, considering (i) the ability to contribute to the evaluation of fluid indications; (ii) selecting the most appropriate fluid for the patient's clinical situation associated with the most suitable diluent for each drug; (iii) promoting the modification of administration routes to those alternatives to the intravenous route and safely reducing the volume of drug diluents. The role of this professional in implementing services, strategies, or fluid management programs was also discussed in other countries[12-14].

It is emphasized that the design of the clinical pharmacists' workflow during the studied period may have been a limitation or source of bias in developing interventions related to the "right patient," and the availability of more time integrated into the unit, along with training and creating strategies involving the pharmacist in the fluid therapy evaluation process, can enhance their influence in this clinical context.

Although the interventions analyzed in the study were implemented when accepted, with a direct impact on patient care, the extent of their impact and the assessment of adequacy were not evaluated, requiring further investigation. In the same sense, information is needed on the correlation between PIs and the clinical profile of patients who benefit from them. The possibility of biases arising from recording errors and underreporting of PIs is also emphasized.

Overall, this study found results similar to those published in the literature, noting that the studied clinical pharmacy service did not have a systematic evaluation in fluid management, indicating the potential of the pharmacist as a relevant agent in the proper management of fluid therapy, aiming, through this, for positive clinical outcomes and patient safety.

There are also elements that can support the role of the intensive care pharmacist in fluid management in critically ill patients in a context of relative national novelty, given the recent discussion about the consequences of inadequate fluid therapy, the deleterious effect of fluid overload in this group of patients, and the role of the pharmacist in this process. This topic calls for further discussions, studies, and collaboration among professionals involved in care, aiming to seek interdisciplinary and resolutive actions.

## Conclusion

The analyzed PIs obtained representativeness in the "four rights of fluid therapy," with the majority related to the "right dose." The interventions were considered highly acceptable. The rate of PIs in fluid therapy found indicated a significant demand for the clinical pharmacist in fluid management. The findings indicate the potential role of the intensive care pharmacist as a protagonist in managing fluid therapy for critically ill patients.

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### Contributors

CEJ participated in the project design, intellectual content review, and manuscript writing. LAM and NJA participated in the project design and intellectual content review. SRM and FLM contributed to data analysis and interpretation. SJA and FIP performed the critical review of the manuscript.

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### Conflict of Interest Statement

The authors declare no conflict of interest regarding this article.

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