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Research Article

Drug-Related Problems and Clinical Pharmacist Interventions in Intensive Care Unit Patients: A Cross-Sectional Study

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ABSTRACT

Background: Drug-related problems (DRPs) are highly prevalent among critically ill patients in intensive care units (ICUs) and may negatively influence clinical outcomes. Pharmacist-led interventions play a pivotal role in detecting and resolving DRPs; however, their implementation and acceptance vary across healthcare systems.
Methods: This cross-sectional, descriptive-analytical study was conducted in the ICUs of Al-Zahra Hospital, Isfahan, Iran, during the second half of 2024. Adult patients admitted for more than 24 hours were evaluated for DRPs using Cipolle's classification system. Data were obtained from medical charts, direct observation, and patient assessments. The severity of DRPs was graded using the NCC-MERP index, and pharmacist interventions as well as their acceptance by physicians were documented.
Results: A total of 100 patients were enrolled (60% male; mean age, 55.1 ± 18.1 years). A total of 324 DRPs were identified from 1,682 reviewed medication orders (mean of 3.24 DRPs per patient, with a median of 16.8 medication items received per patient). The most frequent categories were dosage too low (n = 68), ineffective drug therapy (n = 64), unnecessary drug therapy (n = 39), and dosage too high (n = 45). The most frequently implicated drugs were pantoprazole, acetaminophen (Apotel), vitamins and supplements, and broad-spectrum antibiotics including meropenem, vancomycin, and ceftazidime. Although 83% of drug-related problems (DRPs) caused no immediate harm, 18% led to actual patient harm. Clinical pharmacists offered several recommendations; however, only 18% of these were accepted by physicians.
Conclusion: Drug-related problems are very common among ICU patients, with dosing errors and unnecessary treatments being the most frequent types. The involvement of clinical pharmacists is essential for early detection and prevention, but the low rate of acceptance of their recommendations highlights the need for stronger interdisciplinary collaboration. Evidence from both international studies and Iranian research points to similar challenges, supporting the integration of clinical pharmacists into ICU teams as a key strategy to improve patient safety and treatment outcomes.

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Introduction

Patients who are critically ill and admitted to intensive care units (ICUs) face a high risk of experiencing both adverse drug events and drug-related problems (DRPs). These issues can become life-threatening when combined with organ dysfunction and the use of multiple medications [1]. DRPs are generally described as events or conditions tied to drug therapy that may negatively affect treatment outcomes. A large proportion of DRPs are both predictable and avoidable, and their occurrence can be lowered through rational prescribing practices and timely clinical actions [2].

Broadly speaking, DRPs fall into two main categories [3]: intrinsic (related to pharmacology or biology) and extrinsic (linked to human factors or errors). Intrinsic problems emerge from pharmacokinetic or pharmacodynamic interactions within a patient's biological system and frequently overlap with adverse drug reactions. Extrinsic problems, in contrast, result from inappropriate prescribing, dispensing, or administration by healthcare providers, as well as from patient non-adherence. Among the various classification systems proposed over time, the framework developed by Cipolle and colleagues [4] remains one of the most commonly used. This system divides DRPs into seven types: unnecessary drug therapy, the need for additional therapy, ineffective drug therapy, dosage too low, dosage too high, adverse drug reactions, and non-adherence. Such a structured approach offers a practical and thorough way to assess pharmacotherapy in critically ill individuals.

Incorporating clinical pharmacists into ICU teams is a promising method for preventing DRPs and improving the safety and efficacy of drug therapy [5]. By detecting and addressing DRPs, clinical pharmacists can help lower the frequency of adverse drug events. Prior research has shown that pharmacist involvement in intensive care settings is linked to shorter ICU stays and reduced mortality rates, with additional evidence pointing to possible cost savings for healthcare systems [6].

ICU patients are especially vulnerable to drug-related complications due to the presence of multiple coexisting illnesses, organ dysfunction (particularly kidney impairment), and complex medication regimens. In this population, ongoing monitoring of kidney function and daily dose adjustments are critically important, especially given the widespread use of antibiotics and other drugs [7].

In conclusion, DRPs are common and carry major clinical significance in ICUs, with substantial implications for patient safety and healthcare costs. A systematic approach to identifying, preventing, and managing DRPs—particularly through the active involvement of clinical pharmacists—has the potential to improve patient outcomes, shorten ICU stays, and lower healthcare expenses.

Although several international studies have reported the prevalence and types of DRPs in ICU patients, there is limited evidence from Iran, particularly in large tertiary centers. Given differences in prescribing culture, physician–pharmacist collaboration, and healthcare infrastructure, local data are essential to inform targeted interventions.

This study therefore aimed to quantify DRPs, evaluate their severity, and assess the acceptance of pharmacist recommendations in a major Iranian ICU.

Methods

This cross-sectional, descriptive-analytical study was conducted in the intensive care units (ICUs) of Al-Zahra Hospital, affiliated with Isfahan University of Medical Sciences, during the second half of 2024. The hospital comprises three ICUs, each with 23 beds. All consecutive patients admitted for more than 24 hours were screened for eligibility. A simple random sampling technique was then applied to select cases from this group, aiming to ensure that the sample was representative. Data collection was performed by a trained pharmacy student and independently validated by two ICU clinical pharmacists to minimize observer bias. The level of inter-rater agreement regarding DRP classification was above 90%.

The sample size was determined pragmatically, resulting in the inclusion of all qualifying ICU patients who were admitted during the study period (n = 100). This approach mirrors that of similar observational studies in the field and was viewed as sufficient to offer preliminary data on both the frequency and characteristics of DRPs among critically ill patients.

Data collection

Data were collected within 48 hours of ICU admission using a structured form designed to capture demographic information, medical history, presenting complaints, comorbidities, family history, laboratory parameters, and detailed medication records. Information was obtained from patient medical files, direct observation, and clinical visits. Clinical decision support tools such as UpToDate®, Medscape®, and Lexicomp® were used to verify drug indications, dosing, renal/hepatic adjustments, contraindications, and potential drug interactions.

Identification and classification of DRPs

Drug-related problems were identified and categorized using the classification proposed by Cipolle et al. [4], which includes seven main groups: unnecessary drug therapy, need for additional drug therapy, ineffective drug, dosage too low, dosage too high, adverse drug reaction, and non-adherence.

When a suspected DRP was identified, further details were recorded, and the case was discussed with the attending physician and nurse to confirm and classify the problem. In cases where DRPs were reported by healthcare staff (physicians, residents, interns, or nurses), a preliminary assessment was conducted by the pharmacy student, followed by validation with the clinical pharmacy specialist.

Clinical and outcome measures

Outcomes of DRP-related interventions, including physician acceptance and resolution of problems, were documented.

Severity assessment

The severity of DRPs was determined by adapting the NCC-MERP (National Coordinating Council for Medication Error Reporting and Prevention) index [8], categorizing outcomes as DRPs with no harm, potential harm, actual harm, or death. Severity assessments were independently conducted by two ICU clinical pharmacists.

Statistical analysis

Data were analyzed using SPSS for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were reported as frequencies and percentages for categorical variables and as medians for continuous variables.

Correlations between continuous variables were evaluated using Spearman's correlation test. To determine the impact of various patient-related characteristics on the presence of DRPs, binary logistic regression was applied. In logistic regression models, patient-related variables, including age, sex, comorbidities, length of stay, mechanical ventilation, and Glasgow Coma Scale at admission, were entered as predictors of DRP occurrence. A p-value < 0.05 was considered statistically significant.

Results

A total of 100 patients were enrolled, comprising 60% males and 40% females, with a mean age of 55.1 ± 18.1 years. The most common reasons for medical ICU admission were multiple trauma and intracerebral hemorrhage (12% each), followed by subdural hematoma (9%). The mean length of ICU stay was 30.5 ± 21 days, and 36 patients died during hospitalization. Hypertension (38%) and diabetes mellitus (26%) were the most prevalent comorbidities.

A total of 324 DRPs were identified from 1,682 reviewed medication orders (mean of 3.24 DRPs per patient, with a median of 16.8 medication items received per patient). According to Cipolle's classification, the most frequent categories were dosage too low (n = 68), ineffective drug therapy (n = 64), unnecessary drug therapy (n = 39), dosage too high (n = 45), and need for additional therapy (n = 37). Adverse drug reactions (n = 40) were also observed (Table 1,2). No cases of non-adherence were detected, which is expected in the ICU setting where medications are administered under direct nurse supervision. Severity analysis showed that 83% of DRPs were associated with no harm, 15% with potential harm, and 18% with actual harm (categories not mutually exclusive).

Table 1- Characteristics of medical intensive care unit patients.

Characteristics (total n = 100)	Value
Male, n	60
Female, n	40
Age, years (mean ± SD), range	55.1±18.1, 15-93
Causes of medical intensive care unit admission, n	12
Multiple trauma	12
Intracerebral hemorrhage	9
Subdural hematoma	7
Cancer	6
Loss of conscious	3
Stroke	3
Guillan barre syndrome	3
Pneumonia	
Past medical history, n	38
Hypertension	26
Diabetes	12
Cancer	11
Hyperlipidemia	9
Cerebrovascular accident	8
Hypothyroidism	6
Ischemic heart disease	3
Brain tumor	3

Hydrocephalus	3
Atrial fibrillation	2
Seizure	10
Others	
Length of medical intensive care unit stay, days (mean ± SD), range	30.5±21 (3-94)
Mortality, n	
Death	36
Alive	64

The most commonly implicated drugs included pantoprazole (n = 39), acetaminophen/Apotel (n = 31), vitamins and supplements (n = 32), meropenem (n = 15), labetalol (n = 14), fentanyl (n = 10), linezolid (n = 9), methadone (n = 8), and ceftazidime (n = 8) (Table 3). Clinical pharmacists' interventions primarily involved dose adjustments based on renal function or body weight, discontinuation of duplicate or unnecessary therapies, initiation of preventive or therapeutic agents (e.g., anticoagulants, antidiabetic drugs), and recommendations for safer alternatives. Despite the range of proposed interventions, only 18% of pharmacist recommendations were accepted and implemented by the medical team.

Patient-related factors such as age, sex, length of hospitalization, Glasgow Coma Scale (GCS), and mechanical ventilation at admission were not statistically significant predictors of DRP occurrence.

Table 2- Classification of DRPs according to drug-related problems defined by Cipolle et al.

Drug-related problem category	Common causes of drug-related problems	n
1.Unnecessary drug therapy	There is no valid medical indication requiring drug therapy (no medical indication).	39
	Multiple drug products are used for a condition that requires single drug therapy (duplicate therapy).	29
	Drug therapy is taken to treat and avoid adverse reaction associated with another medication.	1
2. Need additional drug therapy	Preventive drug therapy is required to reduce the risk of developing a new condition (preventive therapy).	19
	A medical condition requires the initiation of drug therapy (untreated condition).	18
3. Ineffective drug	The drug is not the most effective for the medical condition and a different drug is needed (more effective drug available).	8
	The dosage form of the drug product is inappropriate.	32
	The drug product is contraindicated in the patient.	5
	The drug product is not an effective product for the indication being treated.	19
4. Dosage too low	The dose is too low to produce the desired response.	17
	The dosage interval is too infrequent to produce the desired response.	48
	A drug interaction reduces the amount of active drug available.	3
5. Adverse drug reaction	The drug product causes an undesirable reaction that is not dose-related.	4
	A safer drug product is required due to risk factor.	3
	A drug interaction causes an undesirable reaction that is not dose-related.	28
	The drug product is contraindicated due to risk factors.	5
6. Dosage too high	The dosage is too high, resulting in toxicity.	14
	The dosage interval is too short.	31
7. Non-adherence		0

Table 3- Description of common problem-related drugs frequently detected in medical intensive care unit and pharmacists' interventions.

Problem-related drugs	Description of drug-related problems	Pharmacist's interventions
1. Unnecessary drug therapy Vitamin D3	The routine uses of vitamin D3 (cholecalciferol) as a preventative or therapeutic intervention for vitamin D deficiency in critically ill patients is controversial. However, patients 25(OH)D is within the normal range	Discontinuing Vitamin D3 when no indication.
Fentanyl	Administering two opioids with overlapping receptor targets or similar pharmacologic effects concurrently or	discontinue duplicative agents.

	sequentially without clear justification. (e.g. fentanyl and methadone)	
Nephrovit	NephroVit" (a hypothetical or brand-specific nephroprotective/CKD-targeted multivitamin) is being used concurrently with other standard vitamins (e.g., Vitamin B1 (thiamine), Vitamin C (ascorbic acid)) and possibly other micronutrient supplements.	Keep nephrovit and discontinue other vitamins
2. Need additional drug therapy Pantoprazole	Patients who had high risk of gastrointestinal bleeding during critically ill period should be prescribed acid suppression prophylaxis.	PPIs prophylaxis was always advised to be prescribed in mechanically ventilated patients.
Anticoagulants	Reducing venous thromboembolism (VTE) risk in critically ill patients, who are often immobile, have endothelial injury, and hypercoagulable states.	emphasize pharmacologic VTE prophylaxis for all eligible patients unless contraindicated.
Antidiabetic agent	Not receiving anti-diabetes medications despite a history of diabetes	Suggestion to initiate appropriate drug regimen for diabetes
3. Ineffective drug Extended-release delivering medications	Crushing medications for a nasogastric tube administration was a general practice. However, crushing method of extended-release dosage form was not appropriate due to a potential risk of toxic peak and insufficient drug concentration.	The alternative dosage form or alternative drugs which were suitable for a nasogastric tube administration were suggested.
Furosemide	Diuretic for non-edematous, unstable patient. E.g in septic shock	Furosemide was suggested to be discontinued
4. Dosage too low Apotel	Apotel was prescribed as prn without proper interval	Suggest to correct the dose and interval
1. Ceftazidim 2.levofloxacin 3. meropenem 4. colistin	The top five problem-related antimicrobial agents were detected for dosage too low in critically ill patients when renal function improved but proper dosage adjustment was not prescribed.	Increasing drug dosage based on calculated creatinine clearance was advised.
5. vancomycin		Suggest to increase dose based on weight
Enoxaparin	Weight based dose adjustment needs in obese patients for VTE prophylaxis	The alternative anticonvulsants were considered.
Valproic acid	Combining of valproate acid with carbapenem antibiotics was associated with a potential drug interaction that decreased serum concentration of valproaic acid and might expose the patient to uncontrolled seizure risk from subtherapeutic valproic acid concentrations.	
5. Adverse drug reaction Linezolide	Linezolid is a monoamine oxidase inhibitor (MAOI)-like antibiotic with the potential to cause serotonin syndrome when combined with serotonergic agents.	suggestmonitoring for signs of serotonin syndrome or use alternative agents
Diclofenac suppository	NSAIDs in the ICU carry amplified risk for AKI, GI bleeding, fluid overload, and interactions; use only when benefits outweigh risks and typically for short durations.	suggest to discontinue and use alternative analgesics
Dosage too high 1. Ceftazidim 2.levofloxacin 3. meropenem 4. colistin 5. Vancomycin	antimicrobial agents were detected for dosage too high in critically ill patients when renal function declined but no proper dosage adjustment.	Decreasing drug dosage based on calculated creatinine clearance was advised.
Pantoprazole	Pantoprazole 40 mg IV once daily is a common prophylactic regimen. Which most of our patients receive twice daily	Recommend to reduce dose to once daily

Discussion

This study revealed a high prevalence of drug-related problems (DRPs) among critically ill patients admitted to the medical ICU, underscoring the complexity of pharmacotherapy in this vulnerable population.

The most frequent categories—unnecessary drug therapy, inappropriate dosing, and need for additional therapy—are consistent with findings from previous ICU studies. Findings from Blix et al. [9] and Gallagher et al. [10] similarly reported that dosing errors and polypharmacy ranked as leading factors behind DRPs in ICU patients. Likewise, Alazzam and coworkers (2016) [11] emphasized the excessive prescribing of gastrointestinal prophylaxis and supplements lacking clear medical justification—a pattern that echoes our own results showing pantoprazole and vitamins as frequent contributors.

Our findings are also consistent with international reports concerning antimicrobial-related DRPs, especially those involving drugs like meropenem, vancomycin, and ceftazidime. Research conducted across Europe and Asia consistently indicates that incorrect antibiotic dosing in patients with fluctuating kidney function represents a significant source of patient harm. For example, Leape and colleagues [12] as well as LeBlanc et al. [13] showed that renal impairment and failure to adjust doses in a timely manner considerably raise the risk of DRPs.

Within the Iranian healthcare context, our results correspond with those of studies by Farsad et al. [14] and Mahini et al. [15], which also reported high rates of inappropriate antibiotic prescribing and inadequate monitoring of drug therapy in ICUs. Furthermore, research carried out in hospitals located in Tehran and Shiraz has revealed similar challenges concerning the overuse of proton pump inhibitors and the low rate of acceptance of pharmacist recommendations [16].

Interestingly, the acceptance rate we observed (18%) was lower than many international figures (which range from 60–80%), yet it was close to rates reported in several other Iranian studies. This finding points to possible cultural and systemic obstacles to physician–pharmacist collaboration within our specific setting. One notable observation is that, although 83% of DRPs resulted in no immediate harm, 18% did lead to actual patient harm—underscoring the clinical importance of timely detection and intervention.

Among the strengths of this study are the use of Cipolle's validated classification system, thorough documentation of DRPs, and severity assessment carried out by two clinical pharmacists. Despite being a single-center investigation, the findings are likely to be generalizable to similar Iranian ICUs, given the comparable patient characteristics and healthcare delivery systems across these units.

Nevertheless, multicenter studies featuring larger sample sizes are needed to confirm these results. We did not evaluate long-term outcomes such as ICU length of stay, mortality, or cost savings. Future research should incorporate these clinically meaningful measures to better quantify the impact of pharmacist interventions on patient care.

Conclusion

To summarize, drug-related problems are highly common among ICU patients, particularly in the forms of dosing errors and unnecessary drug therapies. Clinical pharmacists can serve a key role in identifying and preventing these issues. Our results highlight the potential advantages of integrating clinical pharmacists into ICU teams; however, larger multicenter studies are necessary before any broad policy recommendations can be considered.

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