Research Article

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# Evaluation of the Appropriateness of Antimicrobial Drug Dosages in Intensive Care Unit Patients

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**ABSTRACT**

The purpose of this study was to investigate the factors that required dose adjustments of antimicrobial drugs in intensive care unit (ICU) patients and to identify the drugs that required the most dose adjustments. The current prospective study was conducted in the reanimation ICU with 26-bed capacity of a university-affiliated hospital from September to December 2022. Two clinical pharmacists on duty examined patients' antimicrobial drug dosages daily. The acceptance status of the recommendations and the patients' demographic information were recorded. The study involved 133 ICU patients, and antimicrobial drug recommendations were made for 48 patients, 31 (64.6%) of whom were male. The median (IQR) age of the 48 patients was 67 (54–77). The count of recommendations was 94, and the acceptance rate was 100%. The recommendation rates were as follows: 71.3% for renal function, 11.7% for presence of continuous renal replacement therapy, 10.6% for indication, 4.3% for body weight, and 2.1% for loading dose. The top 3 drugs for which recommendations were made the most were colistin (21.3%), meropenem (18.1%), and piperacillin-tazobactam (12.8%). The most troublesome drug was colistin, which is frequently used to treat Acinetobacter pneumonia. Clinical pharmacist and physician collaboration may help rationalize ICU antimicrobial drug use.

**Keywords:** Antimicrobial drugs, Clinical pharmacist, Colistin, Intensive care unit, Meropenem

## 1. Introduction

Antimicrobial drugs are utilized extensively in intensive care settings (ICUs) [1]. Antimicrobial pharmacokinetics (PK) – pharmacodynamics (PD) may be affected by patient and microorganism-related factors, as well as drug-related factors [2]. In order to acquire a better knowledge of the effect that antibiotic exposure has on the killing of bacteria, various antimicrobial drugs have been allocated to some PK-PD indices [3]. Examples of PK-PD indices include the area under the curve (AUC) of the unbound drug divided by the minimum inhibitory concentration (MIC) of the target microorganism for the specific antimicrobial ($fAUC_{0-24}$/MIC), the maximal unbound drug concentration ($C_{max}$) divided by the MIC of the target microorganism ($fC_{max}$/MIC), and the cumulative percentage of a dosing interval in which the antimicrobial concentration exceeds the MIC of the target microorganism (%$f$T>MIC) [4]. Beta-lactam antibiotics, aminoglycosides, and glycopeptides can be given as examples for the PD indices %$f$T>MIC, $fC_{max}$/MIC, $fAUC_{0-24}$/MIC, respectively [5]. After the appropriate antimicrobial agent has been selected, it is important to make sure the dose of the agent is correct to maximize the effect of the antimicrobial therapy [6]. In previously conducted studies, it has been demonstrated that clinical outcomes have improved with the optimization of antimicrobial exposure [7, 8]. Furthermore, the incorrect use of antimicrobials has been linked to the occurrence of bacterial resistance [9].

In ICU patients, the antimicrobial drug dosages may need to be adjusted in the setting of extracorporeal circuits (e.g. renal replacement therapy, extracorporeal membrane oxygenation, sustained low-efficiency dialysis) because of organ dysfunction [10]. Moreover, patients with severe sepsis or septic shock commonly suffer from acute kidney injury [11]. So, the dosages of the antimicrobials often require adjustment. Clinical pharmacists may help rationalize the usage of antimicrobial drugs in ICUs.

The purpose of this study was to investigate the factors that required dose adjustments of antimicrobial drugs in ICU patients and to identify the antimicrobials that required dose adjustments the most.

## 2. Material and Methods

In the scope of the current study, it was evaluated that the suggestions made by two clinical pharmacy residency students during their intensive care training between September 2022 and December 2022. Ethics approval was granted by the Ethics Committee of Selcuk University (April 11, 2023; 2023/194). The study was performed in the reanimation ICU with a total capacity of 26 beds at a university-affiliated tertiary care hospital in Malatya, Türkiye. All patients who stayed in the unit for at least 24 hours were included. The appropriateness of antimicrobial drug dosages was evaluated by the two clinical pharmacy residents. UpToDate®, Micromedex®, and Sanford Antimicrobial Therapy Guide® were utilized in the evaluation of the antimicrobial drug dosages. The recommendations were conferred with the infectious disease specialist in charge and recorded along with their acceptance status. The hospital's electronic database was used to gather information about the patients' demographics, Glasgow Coma Scale (GCS) score at admission, Acute Physiology and Chronic Health Evaluation II (APACHE II) score at admission, and laboratory results. Daily medication charts were accessed from patient files. Descriptive statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) v27.0. Continuous and categorical data were demonstrated as median [25th percentile–75th percentile] and number (percentage), respectively.

## 3. Results and Discussion

A hundred and thirty-three patients were included in the study. In total, 94 antimicrobial drug recommendations were made for 48 patients. The characteristics of the 48 patients are given in Table 1.

The acceptance rate of the recommendations was 100%. The distribution rates of the 94 recommendations according to the causes are given in Table 2.

In some recommendations, the dose and/or the dose frequency of the subject antimicrobial were changed. Figures 1 and 2 depict the relevant results.

The antimicrobials were categorized according to the various factors that caused inappropriate dosages, and the corresponding results are given in Table 3.

The pharmacist recommendations' samples are given in Table 4.

In the literature, the effect of pharmacist collaboration in antimicrobial therapy management was investigated. In an observational study conducted


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**Table 1.** The characteristics of the patients

| | |
|---|---|
| **Sex, n (%)** | |
| **Male** | **31, (64.6)** |
| **Female** | **17, (35.4)** |
| Age, years, median (25th - 75th percentile) | 67 (54 - 77) |
| GCS score at admission, median (25th - 75th percentile) | 3 (3 - 10) |
| APACHE II score at admission, median (25th - 75th percentile) | 24 (15 - 27) |
| Mechanical ventilation rate at admission, n (%) | 30 (62.5) |
| Length of stay in the unit, days, median (25th - 75th percentile) | 15 (6.25 - 41.25) |
| Presence of surgery, n (%) | 23 (47.9) |
| Admitted from, n (%) | |
| Emergency | 13 (27.1) |
| Another ward | 14 (29.2) |
| Another hospital | 21 (43.7) |
| Discharged to, n (%) | |
| Another ward | 15 (31.3) |
| Home | 4 (8.3) |
| Mortality rate, n (%) | 29 (60.4) |

GCS: Glasgow Coma Scale
APACHE II: Acute Physiology and Chronic Health Evaluation II

**Table 2.** The distributions of the recommendations based on causes

| **Inappropriate Dosages Caused by;** | **Number of Recommendations (%)** |
|---|---|
| Renal functions | 67 (71.3) |
| Continuous renal replacement therapy | 11 (11.7) |
| Indication | 10 (10.6) |
| Body weight | 4 (4.3) |
| Loading dose | 2 (2.1) |

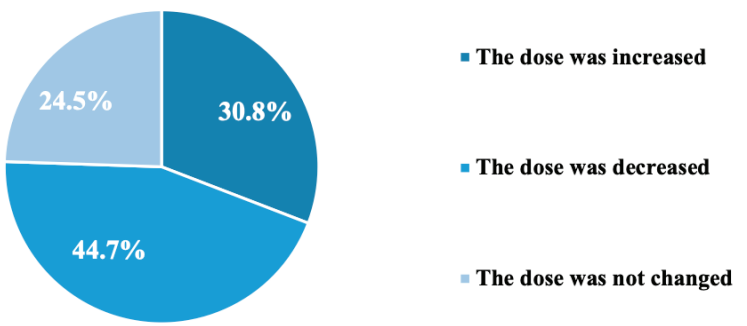


**Figure 1.** Distribution of recommendations for dose modification

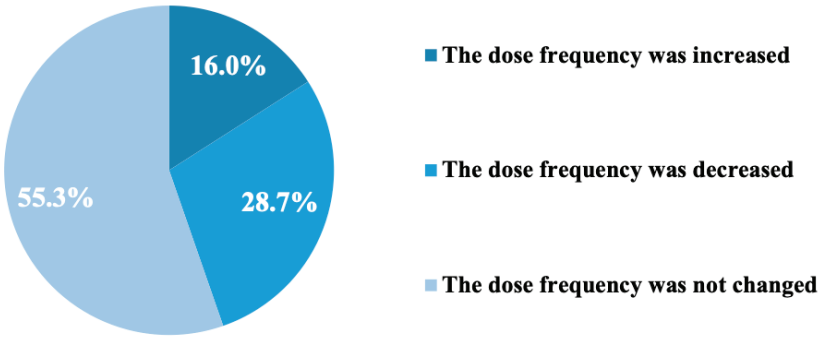


**Figure 2.** Distribution of recommendations for dose frequency modification

**Table 3.** The distribution of the antimicrobials according to the various factors that led to inappropriate dosages

| Inappropriate dosages based on | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Renal function** | | **Presence of continuous renal replacement therapy** | | **Indication** | | **Body weight** | | **Loading dose** | | **Total** | |
| Drug | n (%) | Drug | n (%) | Drug | n (%) | Drug | n (%) | Drug | n (%) | Drug | n (%) |
| Colistin | 17 (25.4) | Colistin | 3 (27.3) | Vancomycin | 2 (20.0) | Amikacin | 2 (50.0) | Teicoplanin | 2 (100) | Colistin | 20 (21.3) |
| Meropenem | 13 (19.4) | Meropenem | 2 (18.2) | Ampicillin-sulbactam | 2 (20.0) | Vancomycin | 1 (25.0) | | | Meropenem | 17 (18.1) |
| Piperacillin-tazobactam | 11 (16.4) | Fluconazole | 2 (18.2) | Meropenem | 1 (10.0) | Meropenem | 1 (25.0) | | | Piperacillin-tazobactam | 12 (12.8) |
| Fluconazole | 7 (10.4) | Piperacillin-tazobactam | 1 (9.1) | Clarithromycin | 1 (10.0) | | | | | Fluconazole | 9 (9.6) |
| Teicoplanin | 6 (9.0) | Teicoplanin | 1 (9.1) | Acyclovir | 1 (10.0) | | | | | Teicoplanin | 9 (9.6) |
| Levofloxacin | 3 (4.5) | Cefepime | 1 (9.1) | Azithromycin | 1 (10.0) | | | | | Vancomycin | 5 (5.3) |
| Vancomycin | 2 (3.0) | Ciprofloxacin | 1 (9.1) | Linezolid | 1 (10.0) | | | | | Ampicillin-sulbactam | 4 (4.3) |
| Ampicillin-sulbactam | 2 (3.0) | | | Ceftriaxone | 1 (10.0) | | | | | Levofloxacin | 3 (3.2) |
| Ceftazidime-avibactam | 2 (3.0) | | | | | | | | | Cefepime | 3 (3.2) |
| Cefepime | 2 (3.0) | | | | | | | | | Amikacin | 2 (2.1) |
| Clarithromycin | 1 (1.5) | | | | | | | | | Clarithromycin | 2 (2.1) |
| Trimethoprim-sulfamethoxazole | 1 (1.5) | | | | | | | | | Ceftazidime-avibactam | 2 (2.1) |
| | | | | | | | | | | Acyclovir | 1 (1.1) |
| | | | | | | | | | | Azithromycin | 1 (1.1) |
| | | | | | | | | | | Linezolid | 1 (1.1) |
| | | | | | | | | | | Ceftriaxone | 1 (1.1) |
| | | | | | | | | | | Ciprofloxacin | 1 (1.1) |
| | | | | | | | | | | Trimethoprim-sulfamethoxazole | 1 (1.1) |


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**Table 4.** The pharmacist recommendations for modifying the dose or dose frequency of the antimicrobials

| Factor | Drug | Recommendation |
|---|---|---|
| Renal function | Colistin | The patient was being administered colistin 150 mg q12h despite the fact that the estimated glomerular filtration rate of the patient was 30 mL/min/1.73m$^2$. The dosage of the drug was decreased to 100 mg q12h. |
| Presence of continuous renal replacement therapy | Fluconazole | The patient was being administered continuous veno-venous hemodiafiltration. It was recommended to give fluconazole as an 800 mg loading dose and thereafter 400 mg q12h. |
| Indication | Ceftriaxone | The patient in whom bacterial meningitis was suspected was receiving ceftriaxone 1 g q12h. It was recommended to increase the dose to 2 g q12h. |
| Body weight | Amikacin | The patient was being administered amikacin 1 g q24h. The patient's adjusted body weight was 81 kg, so 1.5 g q24h was recommended. |
| Loading dose | Teicoplanin | The patient was being administered teicoplanin 400 mg q24h without loading dose. It was recommended that the first three doses of the drug be given at 12-hour intervals and thereafter q24h. |

in an ICU, a clinical pharmacist detected 212 drug-related problems in 114 patients [12]. The clinical pharmacist made one intervention for each of the drug-related problems (DRPs) detected. Physicians accepted 97.6% of the interventions. In our study, all of the interventions made by the clinical pharmacists were accepted by the infectious diseases physicians.

In another observational study, the impact of pharmacist-driven antimicrobial stewardship on the prescription of antibiotics in an ICU was investigated [13]. The study showed that the optimal antibiotic selection rate had improved significantly after the five-year intervention by the clinical pharmacist. In addition, the study found a decrease of 11% in *Pseudomonas aeruginosa* resistant to meropenem and a reduction of 11% in extended-spectrum beta-lactamase in *Escherichia coli* rate. However, in our study, the resistance rate of bacterial isolates and the antimicrobial prescribing attitudes of the physicians have not been evaluated. Further studies are needed to elucidate the impact of clinical pharmacists on these issues.

In a multicenter study focusing on the risk factors of infection caused by *Acinetobacter baumannii*, it was demonstrated that mechanical ventilation was associated with multi-drug-resistant *A. baumannii* infections [14]. In our unit, patients were frequently mechanically ventilated. Although carbapenems, alone or combined with a second agent, are thought to be the best options to treat *A. baumannii* infections, resistant strains limit their use as monotherapy [15, 16]. In our unit, the resistant strains of *A. baumannii* were frequently encountered, so colistin and meropenem were often administered. Especially colistin required dose modification very often based on the estimated glomerular filtration rate. In ICUs, it was stated that acute kidney injury affects up to 50% of critically ill patients [17]. In addition to this, colistin itself is nephrotoxic [18]. So, in this study, it is not surprising that colistin was the drug that mostly required the dose adjustment.

Many dosing strategies have been defined for aminoglycosides in the literature [19]. According to the Hartford Nomogram, a once-daily dosing schedule, if the actual body weight (ABW) of the patient was at least 20% greater than the ideal body weight (IBW), the dose of the aminoglycoside should be calculated using adjusted body weight ($BW_{adj}$) which is calculated as follows [20]:

$$BW_{adj} = IBW + 0.4(ABW-IBW)$$

Besides, the aminoglycosides are well-known for nephrotoxicity and ototoxicity [21], so therapeutic drug monitoring of the aminoglycosides is necessary to prevent these adverse drug events. However, in our institute, the therapeutic drug monitoring of the aminoglycosides was not performed. In addition to that, the clinicians were keeping the doses of the aminoglycosides low unconsciously out of fear of these adverse drug events. So, the dose of amikacin was mostly adjusted according to body weight.

Teicoplanin, a glycopeptide antibiotic, has a long elimination half-life, so it requires an initial loading dose for rapid achievement of target plasma concentration [22-25]. According to the package insert of the teicoplanin, the first three doses should be given in 12-hour intervals and then q24h [26]. This may be

confusing sometimes for healthcare providers; thus, teicoplanin was the drug that mostly required dose adjustment for loading doses.

Intermittent hemodialysis, prolonged intermittent renal replacement therapy, and continuous renal replacement therapy are types of renal replacement therapies used in the setting of the intensive care unit, and systemic drug clearance is affected by these therapies [27]. Continuous renal replacement therapy prescriptions vary in modalities, hemofilters, and effluent flow rates, all of which can have a significant impact on antibiotic dose [28]. Pharmacists could help adjust the dose of the antimicrobial drugs in the case of renal replacement therapy [29-31].

In ICUs, clinical pharmacists can collaborate with healthcare professionals in: adjusting the dose of a drug, changing the route of administration of a drug, changing a drug, managing nutrition, administering a drug via enteral feeding tubes, detecting early potential drug-drug interactions, counseling on drug compatibility, preventing or managing adverse drug events, and helping clinical decision-making with literature appraisal.

## 4. Conclusions

In the current study, the most common problem with dose inappropriateness of antimicrobial drugs was a lack of dose adjustment according to renal functions. The most troublesome drug was colistin, which is frequently used to treat *Acinetobacter* pneumonia. The dosages of the antimicrobial drugs should be strictly monitored, especially in fragile patient populations like critically ill patients, to prevent treatment failure. Clinical pharmacists can effectively manage antimicrobial therapy. When the contributions of the clinical pharmacists, as discussed in the previous section, are considered, the integration of the clinical pharmacist into the ICU is paramount.

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The current study has been presented orally at the International Multidisciplinary Symposium on Drug Research & Development 2023.

## Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Statement of Contribution of Researchers

Concept – A.Ç., H.M.; Design – A.Ç., H.M., Z.Ü.G.; Supervision – Z.Ü.G.; Resources – A.Ç., H.M.; Materials – A.Ç., H.M.; Data Collection and/or Processing – A.Ç., H.M.; Analysis and/or Interpretation – A.Ç., H.M., Z.Ü.G.; Literature Search – A.Ç., H.M., Z.Ü.G.; Writing – A.Ç., H.M., Z.Ü.G.; Critical Reviews – A.Ç., H.M., N.Ö., Z.Ü.G.

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