

Antimicrobial stewardship practices in the intensive care unit: a pre-post interventional study

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ABSTRACT

Objective: This study aims to assess the frequency of drug-related problems (DRPs) related to antimicrobial drugs in the ICU and to examine changes in the use of antibiotics in the 'Reserve' group of the World Health Organization (WHO) AWaRe classification during the antimicrobial stewardship (AMS) team intervention, including the clinical pharmacist.

Methods: In this single-center intervention study, the pre-intervention period between November 2021 and August 2022 and the post-intervention period between November 2022 and August 2023 were evaluated. In the post-intervention period, a clinical pharmacist was also included in the AMS team. Post-intervention medication-related problems (DRPs) were categorized using only the "problem" and "cause" domains of the Pharmaceutical Care Network Europe (PCNE) V9.1 classification system. Additionally, recommendations and their acceptance rates were recorded. The antibiotic use density of the 'Reserve' group, defined in the WHO AWaRe classification, was evaluated in terms of days of therapy (DOT) per 1000 patient-days.

Results: After the intervention, 175 DRPs were detected in 67.1% of 173 patients; 70% were related to antimicrobial drugs. The 90.1% of the interventions suggested by the clinical pharmacist were evaluated and accepted by infectious diseases and intensive care specialists. The total use of "Reserve" group antibiotics decreased, but not significantly; significant decreases were observed for some agents such as linezolid and daptomycin.

Conclusion: Multidisciplinary antimicrobial stewardship practices involving the clinical pharmacist can contribute to the prevention of antimicrobial resistance development by facilitating the detection and solution of DRPs, especially by reducing the use of 'Reserve' group antimicrobials.

Keywords: antimicrobial resistance, antimicrobial stewardship, intensive care unit

Introduction

Antimicrobial resistance (AMR) poses a substantial threat to global public health and progress. In 2019, bacterial antimicrobial resistance (AMR) directly caused 1.27 million deaths and indirectly caused 4.95 million deaths over the world (1). The 2015 OECD data

indicates that Turkey has the highest resistance rate among OECD countries at 38.8%, despite a 15-year antibiotic limitation program in hospitals (2).

Intensive care units (ICUs) use a high number of broad-spectrum antibiotics, emphasizing the need for conservation efforts (3). Using antibiotics

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inappropriately in ICUs can result in drug-resistant organisms emerging, posing a serious threat to patient health (4). In addition, subtherapeutic drug concentrations may promote the growth of resistant microorganisms in critically ill patients (5).

Antimicrobial stewardship (AMS) has become an important strategy to tackle antimicrobial resistance. In 2017, the WHO classified antibiotics into three categories: Access, Watch, and Reserve (WHO's AWaRe classification) (6). In the Reserve group, antibiotics should be regarded as a "last resort," available for prescription solely to very specific patients and circumstances where all other options have proven ineffective or inappropriate. The WHO Model List of Essential Medicines includes seven antibiotics from the Reserve group (7). In hospitals, these are commonly used, and so have been targeted for AMS interventions (6,8,9). Integrating clinical pharmacy services, including AMS practices, in intensive care settings is crucial to optimizing antimicrobial use, improving patient outcomes, and combating antimicrobial resistance. In ICUs, it is vital that clinical pharmacists, infectious disease physicians, and intensivists to drive successful AMS initiatives (10-15).

Although various national strategy documents (2,16) have been published in Turkey to combat antimicrobial resistance, the implementation of the AMS program is still not mandatory at the national level. Therefore, AMS implementations largely depend on the individual initiative and institutional motivation of healthcare institutions. The lack of a standard legislative infrastructure indicates a significant policy gap in terms of the sustainability and widespread impact of these programs. An effective AMS approach requires not only technical implementations but also strong health policy support (17). In this context, making AMS programs, which are carried out by multidisciplinary teams including clinical pharmacists, mandatory at the institutional level by supporting them with legal regulations will contribute to Turkey creating a stronger and more sustainable roadmap in the fight against antimicrobial resistance.

The objective of this study is to assess the effects of AMS team interventions, including those by clinical pharmacist, on the subsequent outcomes: (i) the prevalence of antimicrobial drug-related problems (DRPs) by using the Pharmaceutical Care Network Europe (PCNE) V9.1 classification. (ii) the change in the frequency of antibiotic usage via the "Reserve" group of the WHO's AWaRe classification.

Materials and methods

Study design and patients

This single-center intervention study was carried out in two phases: the pre-intervention phase from November 2021 to August 2022, and the post-intervention phase from November 2022 to August 2023, at the adult medical and surgical ICU of Baskent University Ankara Hospital, a tertiary academic institution with a capacity of 500 beds. The ICU is a closed unit with 18 beds and is a mixed unit that accepts critically ill patients from internal medicine and surgical branches. This is the only ICU in the hospital and all adult patients requiring intensive care (including internal medicine, surgical, neurological and oncological patients) are admitted to this unit. The unit has the infrastructure to provide advanced life support such as mechanical ventilation, renal replacement therapy and continuous hemodynamic monitoring.

In this study, all patients admitted to the ICU and receiving antimicrobial drugs were included. The Declaration of Helsinki was followed during the conduct of this study.

Description of AMS team

The AMS team, which consisted of infectious disease physicians, intensivists, and a clinical pharmacist, followed patients in the 18-bed ICU. In November 2022, a clinical pharmacist joined the AMS team of intensivists and infectious disease physicians. The November-August 2021 data and the November-August 2022 data, which included a multidisciplinary team, were evaluated.

In the pre-AMS period, antimicrobial treatment processes were carried out only by infectious diseases and intensive care specialists. During this period, there was no clinical pharmacist, and DRPs were not systematically evaluated. Treatment decisions were generally made individually based on clinical observation, culture results, and physician experience. During the AMS period, with the clinical pharmacist on the team, each patient's antimicrobial medication was checked on a regular basis, DRPs were found using the PCNE V9.1 classification, and ideas for solutions were offered. During this period, AMS practices acquired a multidisciplinary structure and antimicrobial use processes became more structured.

Inclusion criteria

Adult patients hospitalized in the intensive care unit for ≥ 7 days and treated with antimicrobial therapy were included in this study. In clinical practice, all intensive care patients are evaluated by the AMS team; however, in this study, only patients who stayed in the ICU for ≥ 7 days were included in the analysis in order to systematically observe DRPs and to make meaningful comparisons between the two periods.

Drug-related problems and PCNE

Drug-related problems (DRPs) are occurrences or circumstances that hinder the achievement of intended therapeutic outcomes, as defined by Pharmaceutical Care Network Europe (PCNE). The PCNE is a mechanism employed to categorise Drug-Related Problems (DRP). The report comprises five primary sections: issues, causes, proposed interventions, acceptance of interventions, and DRP status (16). In the post-intervention period, DRPs were classified using only the "problem" and "cause" domains of the PCNE V9.1 classification system. The recommendations made for these problems and the acceptance rates of the recommendations were also recorded and analyzed.

Clinical pharmacist intervention

During the study period, a clinical pharmacist participated in rounds with physicians. Pharmacist conducted the primary review, screened cases for appropriateness, determined DRPs, and recommended therapy. The clinical pharmacist's purpose was to assist physicians in identifying, preventing, or resolving issues linked to medications, including side effects, misuse, needless usage, interactions, missing or overdosed medications, and adverse events. The clinical pharmacist made therapeutic recommendations regarding antimicrobial and non-antimicrobial drug treatments; these recommendations were discussed with the infectious diseases specialist and the intensive care specialist, the final decision was made and implemented.

Data collection and measurement of antimicrobial use

The collected data encompassed clinical and demographic information, in addition to antibiotic usage, quantified in days of therapy (DOT). To determine the amount of "Reserve" group antibiotic (7) used, days of therapy were calculated per 1000 patient days (PDs).

Statistical analysis

The study's statistical analysis showed quantitative data using mean, standard deviation, median, maximum and lowest values, and percentages. Qualitative data were shown as counts and percentages. The Shapiro-Wilk test was employed to evaluate the normality of the data. The Chi-square test with Fisher's exact correction was used to look at differences between groups for categorical data, and the t-test was used for continuous variables. A P-value of less than 0.05 was used to show that the results were statistically significant. The analysis was done with IBM SPSS version 25.0 software.

Results

The pre-IP included 168 patients, while the post-IP included 173 patients. The quantity of female patients increased in the post-IP period (47.0% vs 58.1%, $p=0.040$). In both periods, most patients had 3-5 comorbidities (55.9% vs 50.8%, $p=0.557$). Apache II score was higher post-IP (17.3 ± 6.2 vs 19.2 ± 7.7 , $p=0.015$) (Table 1).

A total of 175 DRPs were identified in 116 patients, constituting 67.1%, by clinical pharmacy (CP) in the post-intervention period (post-IP). The predominant class of medication in DRPs was antibacterial agents, accounting for 70.0%. The predominant antimicrobial-associated drug-related problems were dose-related (53.1%) (Table 2). Ninety percent of the measures proposed by the clinical pharmacist were assessed and approved by specialists in infectious illnesses and intensive care.

The total number of "Reserve" group antibiotic DOTs per 1000 PDs decreased from 43.7 in the pre-IP to 28.5 in the post-IP, but not significantly ($p > 0.340$). When the pre-interventional and interventional periods were compared, the DOTs of polymyxin B, linezolid, daptomycin, and tigecycline were 0.0 vs 5.9 ($p=0.048$), 14.4 vs 4.6 ($p=0.012$), 3.8 vs 0.0 ($p=0.042$), 0.0 vs 5.9 ($p=0.003$) days, respectively (Table 3).

The mean duration of hospital stay was 12.4 ± 5.0 days prior to the intervention and 12.9 ± 3.9 days following the intervention ($p = 0.988$). The thirty-day

all-cause mortality rates were determined to be 28.0% during the pre-intervention period and 27.7% in the post-intervention period ($p = 0.962$).

Discussion

This study shows that the integration of clinical pharmacists into the AMS program in the intensive care unit enables more effective identification of DRPs related to antimicrobial drugs. The vast majority of these interventions are accepted by the AMS team and incorporated into the treatment processes. The high rate of DRPs in the post-intervention period, 31.4%, reveals how common these problems can be in clinical practice and supports the necessity of an active pharmaceutical perspective in AMS practices.

In particular, the fact that 70% of the detected DRPs are related to antimicrobial drugs shows that this drug group has both a high frequency of use and a delicate balance between incorrect/correct use in intensive care. Although the majority of DRPs were for antimicrobial drugs, the AMS team also identified and intervened in problems with non-antimicrobial drugs. Approximately 30% of DRPs were for other drug groups and included problems such as dosage errors, drug interactions, and repeat treatments. This also demonstrates the contribution of the clinical pharmacist to the overall optimization of pharmacotherapy in the ICU. This makes it even more important for the clinical pharmacist to recognize problems such as dosing errors in antibiotic use,

Table 1. Patient characteristics.

Parameters	Pre-IP (n= 168)	Post-IP (n= 173)	p-value
Age, mean $\pm$ sd	75.3 $\pm$ 14.8	74.6 $\pm$ 13.1	0.162
Female sex, n (%)	79 (47.0)	100 (58.1)	0.040*
Number of comorbidities, n (%)			
0	4 (2.4)	4 (2.3)	0.557
1-2	51 (30.3)	61 (35.3)	
3-5	94 (55.9)	88 (50.8)	
>5	19 (11.4)	20 (11.6)	
Apache II score, mean $\pm$ sd	17.3 $\pm$ 6.2	19.2 $\pm$ 7.7	0.015*

* p value < 0.05.

inappropriate antibiotic selection, or unnecessary combination therapies. Similarly, it has been reported in the literature that DRP rates in intensive care patients can be reduced with clinical pharmacist interventions

and that the clinical outcomes of the patients are also improved (11,13). Studies conducted by clinical pharmacists in the intensive care unit in Türkiye and aimed at identifying drug-related problems also

Table 2. Aetiologies of DRPs according per PCNE.

Cause of the problem	PCNE Code	Number and Frequency (%)
Drug selection Inappropriate drug according to guidelines/formulary No indication for drug Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements Inappropriate duplication of therapeutic group or active ingredient No or incomplete drug treatment in spite of existing indication Too many different drugs/active ingredients prescribed for indication	C1	48 (37.5)
Dose selection Drug dose too low Drug dose of a single active ingredient too high Dosage regimen not frequent enough Dosage regimen too frequent Dose timing instructions wrong, unclear or missing	C3	68 (53.1)
Drug use process Inappropriate timing of administration or dosing intervals by a health professional Drug under-administered by a health professional Drug over-administered by a health professional Drug not administered at all by a health professional Wrong drug administered by a health professional Drug administered via wrong route by a health professional	C6	5 (3.9)
Other No or inappropriate outcome monitoring (incl. TDM) Other cause; specify No obvious cause	C9	7 (5.5)

Table 3. Compared to the use of DOT of "reserve" group antimicrobials.

Antimicrobial drugs	Pre-IP (n= 168)	Post-IP (n= 173)	p-value
Ceftazidime avibactam	5.8	2.9	0.445
Colistin	14.4	7.5	0.225
Polymyxin B	0.0	5.9	0.048*
Fosfomycin	5.3	1.7	0.215
Linezolid	14.4	4.6	0.012*
Daptomycin	3.8	0.0	0.042*
Tigecycline	0.0	5.9	0.003*
Total	43.7	28.5	0.340

* p value < 0.05.

show consistent results. For example, Albayrak et al. reported that DRP was detected in 71.5% of intensive care patients and that most of these problems were due to dosing and drug selection errors; it was shown that these problems were resolved by 90.8% after clinical pharmacist interventions (18). Similarly, in the study by Ayhan et al., a decrease in drug costs and an increase in patient safety were achieved with the reduction of DRPs (19).

The clinical pharmacist's proposed therapies were accepted at a rate of 90.1%. This rate can be considered as a successful example of multidisciplinary teamwork. In the ICU, rapid and effective decisions regarding treatment are required, especially due to time pressure and complex patient profiles. The participation of the clinical pharmacist in patient visits allows them to contribute to the treatment process directly; this both increases the applicability of the recommendations and provides support to the physician. These findings are parallel to the study conducted by Hashimoto et al. (10) it was reported that more than 80% of the recommendations of clinical pharmacists in the intensive care unit were accepted and guided the treatment.

An important indicator of antibiotic use monitored in the study was the change in the use of the "Reserve" group antibiotics in the WHO AWaRe classification. Although the total use rate decreased after the intervention (from 43.7 to 28.5 DOT/1000 patient-days), this difference was not found to be statistically significant. However, significant decreases were detected for some agents (e.g. linezolid, daptomycin). This suggests that the AMS team focused on using high-risk and broad-spectrum agents more selectively, considering not only the total antibiotic use but also the rationality of antimicrobial therapy. Similarly, in the study conducted by Özger et al., it was stated that gram-positive spectrum antibiotics such as linezolid and daptomycin were frequently used empirically, and 83% inappropriate prescribing was detected (20). This situation emphasizes the necessity of using reserved group antibiotics carefully and in accordance with the

guidelines. WHO recommends that these drugs be used only in serious, resistant infections and when alternatives have failed (7). In this context, it can be said that the AMS team brought their treatment choices closer to these principles.

In contrast, a significant increase in the use of polymyxin B was observed in the post-intervention period. This increase may be related to the lower nephrotoxicity of polymyxin B compared to colistin, which is frequently used in the treatment of multidrug-resistant gram-negative infections. In clinical practice, polymyxin B has been preferred over colistin because it offers a safer profile (21,22) despite having similar antimicrobial activity in patients with renal dysfunction. Therefore, it can be said that the increase in the use of polymyxin B reflects the rational agent choices made by the AMS team based on patient characteristics and drug safety profiles.

The study found no significant difference in mortality rates (28% vs. 27.7%) and length of hospital stay. However, since the aim of the study was to improve antimicrobial treatment processes rather than directly change these parameters, no significant difference in short-term clinical outcomes is expected. Long-term effects of AMS implementations—such as changes in resistance rates, prevention of adverse events, and reduction of healthcare system costs—usually require longer follow-up periods (6,9). A similar result was also observed in a study focusing on colistin use by Albayrak et al.; while the appropriate use rate increased thanks to clinical pharmacist interventions, the nephrotoxicity rate decreased significantly, but no significant difference was found in mortality rates (23). A majority of the interventions evaluated in the study were optimizing interventions, such as dose adjustments or de-escalation, which have a positive effect on the quality of care without directly impacting mortality.

An important aspect of this study is that it is one of the few studies conducted in a university hospital in Turkey that evaluates the integration of clinical pharmacists

into the AMS team. However, some limitations should be taken into account. The study is single-center and the sample size is limited; therefore, its generalizability is limited. In addition, secondary outcomes such as cost-effectiveness of the interventions, changes in resistance profiles, and prevention of adverse drug reactions were not evaluated. Also, the inclusion of only patients with ≥ 7 days in the ICU may be an important limitation, considering that patients with shorter hospitalizations may also develop DRP. However, this criterion was determined for systematic analysis purposes, as shorter hospitalizations do not provide sufficient observation time for the development of DRP and follow-up of interventions. Another limitation is detailed clinical data such as comorbidities, reasons for hospitalization, infection indications and renal function of the patients included in the study were not recorded systematically due to limitations in the retrospective data collection process. Therefore, they could not be included in the analysis. This was considered an important limitation of the study and detailed clinical characteristics are planned to be included in future studies. In the study, only the intensity of use of the “Reserve” group antibiotics was evaluated, and comparative data for all antibiotic classes were not collected. In addition, since the dosage and application errors were not recorded in detail, detailed analysis of these DRP types could not be presented. These situations are among the important limitations of the study. These areas provide important ground for future studies.

In conclusion, the participation of clinical pharmacists in the AMS team contributed to more effective identification of drug-related problems in the intensive care unit and optimisation of treatment processes. A trend towards a decrease in the use of “reserve” group antibiotics and total DOT values was observed, but these changes were not statistically significant. Since there is no data on the development of antimicrobial resistance in this study, no conclusions can be drawn on this issue. Future studies should evaluate patient-centred outcomes and their impact on resistance development.

Ethical approval

This study has been approved by the Baskent University Institutional Review Board (approval date: January 2, 2025, number: KA24/458). Written informed consent was obtained from the participants.

Author contribution

Study conception and design: AP, BB; data collection: AP, TYY, FİY, HŞ, NS; analysis and interpretation of results: AP, TYY, FİY, HŞ, NS, ÖKA, PZ, BB; draft manuscript preparation: AP. The author(s) reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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