Original Article

# Impact of an Antimicrobial Stewardship Program on the Frequency of Drug-resistant Bacteria in an Intensive Care Unit

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## Abstract

**Background:** One of the major health problems in the intensive care unit (ICU) is the nosocomial infection caused by multidrug-resistant (MDR) pathogens. The antimicrobial stewardship program (ASP) is a solution to prevent antibiotic resistance. This study aimed to determine the impact of an antimicrobial stewardship program on the frequency of drug-resistant bacteria in an ICU.

**Materials and Methods:** This quasi-experimental study was conducted between 2019 and 2021 in Labbafinejad Hospital, Tehran, Iran. This study consisted of two time periods: 1) one year with no restriction of antibiotic prescription (before ASP), and 2) one year with restriction of antibiotic prescription based on the stewardship program (after ASP). We obtained demographic and clinical characteristics of patients from their medical records. Standard disk diffusion and broth microdilution were used to determine the antibiotic susceptibility of bacterial pathogens isolated from the patients.

**Results:** A total of 300 ICU-admitted patients were included in the study (150 for each period). We found out that the total length of hospitalization, length of hospitalization in ICU, and treatment duration were lower after ASP (P=0.022, P=0.383, and P<0.001, respectively). Also, the frequency of antibiotic resistance, including MDR and Vancomycin-Resistant Enterococci (VRE) strains, decreased significantly after performing ASP (P=0.013). However, in terms of mortality, there was no significant difference between the two periods (P=0.236).

**Conclusion:** The results of our study highlight the implementation of the antibiotic Stewardship program and the rational use of antibiotics in the ICU setting to inhibit the spread of antibiotic-resistant bacteria.

**Keywords:** Antimicrobial stewardship, Drug resistance, Intensive care unit, Nosocomial infections

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## Introduction

Antibiotic resistance is a serious threat to human health around the world[1]. Incorrect and excessive antibiotic consumption has led to the spread of antibiotic resistance. As a result, today, as in the era before the discovery of penicillin, some bacterial diseases have become incurable[2]. Also, Incorrect antibiotic consumption increases morbidity, mortality, and patient care costs[3].

Multidrug resistance among nosocomial infections is increasing, limiting treatment options[4]. Unscheduled treatment and long-term administration of antibiotics are two principal factors increasing antibiotic resistance[5]. Nosocomial infection with multidrug-resistant (MDR) causes various medical, social, and

economic problems in all countries. For instance, it has led to the spread of infectious diseases in the community, long-term hospitalization, increased treatment costs, and mortality[6,7].

Increasing resistant species and decreasing the effectiveness of antibiotics have also imposed huge costs on the healthcare systems, necessitating new and more effective policies to monitor antibiotic prescription[8]. Experts have considered following instructions in recent years, which improved the situation by appropriate antibiotic administration[9]. Although antibiotics are necessary to treat most bacterial infections, previous studies have shown that 30-60 percent of prescriptions are improper[10]. One of the most important issues to prevent drug resistance is a restriction of antibiotic administration. The antimicrobial stewardship program (ASP) is a solution to prevent the development of antibiotic resistance[11,12]. Implementation of ASP can effectively reduce microbial resistance and medical costs[13]. The main methods of ASP are as follows: providing instruction for proper antibiotic prescription, physician training, restriction of antibiotic prescription without approval by an infectious disease specialist, reviewing doctors' prescriptions, and providing feedback to them. The above methods can be used separately or simultaneously with others[14-16]. Thus, the present study aimed to determine the impact of an antimicrobial stewardship program on the frequency of drug-resistant bacteria in the intensive care unit (ICU) setting.

## Methods

**Study design and setting:** This quasi-experimental study was conducted between June 2019 and June 2021 in Labbafinejad Hospital, Tehran, Iran. This study consisted of two time periods: 1) one-year period with no restriction of antibiotic prescription (before ASP), and then 2) one-year period with restriction of antibiotic prescription based on the stewardship program (after ASP).

**Intervention:** In the present study, the intervention included teaching how to prescribe antibiotics to a specialist, using a spectrum chart of antibiotic effect, and controlling the administration of broad-spectrum antibiotics.

**Patients:** The study population included infections caused by drug-resistant bacteria admitted to the ICU. Using the formula mentioned below, considering α=5% and a 7% reduction in resistance (27% before and 20% after intervention) in a previous study[17], the sample size was calculated at 150 for each period.

$$n_D = \left[ \frac{(z_{1-\alpha/2}\sqrt{p_1(1-p_1)} + z_{1-\beta}\sqrt{p_0(1-p_0)}}{p_1 - p_0} \right]^2$$

**Data collection:** In the beginning, written informed consent was obtained from the patients. The patient's baseline characteristics, including age, gender, length of treatment, length of hospitalization, length of hospitalization in ICU, frequency and type of nosocomial infections during hospitalization, patient outcomes, and the result of cultures, were recorded by reviewing the patient's medical record.

**Evaluation of Antibiotic Susceptibility:** The present study used standard disc diffusion and broth microdilution to determine the antibiotic susceptibility of bacterial pathogens isolated from the patients. Müller-Hinton agar culture medium and bacterial suspension were prepared for the disk diffusion method. Then, all bacterial isolates were cultured for 18-24 hours using the agar disk diffusion method according to Clinical & Laboratory Standards Institute (CLSI) standards. Also, to determine the minimum inhibitory concentration (MIC) by broth microdilution method, antibiotic dilutions were prepared according to CLSI standards.

According to CLSI standards, *double* antibiotic dilution was prepared in Müller-Hinton Broth (100µl) and placed in 96-well plates. Then, 100µl of bacterial suspension was injected into the wells with a final dilution of $5\times10^5$ CFU / ml. Müller-Hinton Broth and bacterial suspension alone were used as a negative and positive control, respectively. The plates were incubated for 18 hours (24 hours for Vancomycin) at 37 ° C. The last antibiotic dilution in which no growth was observed was considered MIC.

**Statistical analysis:** Data were analyzed using SPSS version 18. Descriptive data were reported as frequency (%) or mean±SD. Also, Pearson's Chi-Square or Fisher's exact and independent-samples t-test were used to compare groups. The P-value less than 0.05 was considered a significant level.

**Ethical considerations:** This study was approved by the Ethics Committee of School of Medicine of Shahid

Beheshti University of Medical Sciences (ID: IR.SBMU.MSP.REC.1398.201). The study was conducted following the Declaration of Helsinki (2000).

## Results

**Baseline characteristics:** A total of 300 ICU-admitted patients were included in the study (150 for each period). Baseline characteristics of the patients are shown in Table 1. The mean length of hospitalization and treatment before ASP was significantly higher than after ASP (P=0.022 and P<0.001 receptively).

**Frequency of nosocomial infections:** Based on our results, the frequency of nosocomial infections was not significantly different compared to before and after ASP (P=0.580) (Table 2). Also, the most common pathogens in both periods were gram-negative bacteria such as *E. coli*. (Before ASP: 44 and after ASP: 40).

**Evaluation of antibiotic administration and antibiotic sensitivity:** Generally, the administration of antibiotics, as well as the administration of specific antibiotics including meropenem/imipenem (112 vs. 105), vancomycin (52 vs. 43), linezolid (1 vs. 0), and ceftazidime (8 vs 4), decreased after performing ASP. Additionally, the frequency of antibiotic resistance, including MDR and VER strains, significantly reduced after performing ASP (P=0.013) (Table 3).

**Patient outcomes:** As shown in Figure 1, the mortality rate was higher after performing ASP; however, it was not significantly different (P=0.236).

**Table 1:** Baseline characteristics of the patients (before and after intervention).

| Variables | Before ASP | After ASP | P-value |
|---|---|---|---|
| Age | 56.2 ± 15.7 | 62.9 ± 15.1 | < 0.001 |
| Male | 61 (40.7) | 68 (45.3) | 0.414 |
| Female | 89 (59.3) | 82 (54.7) | |
| Length of | | | |
| Treatment | 11.2 ± 5.2 | 11.0 ± 3.4 | < 0.001 |
| Hospitalization | 8.9 ± 7.6 | 6.1 ± 3.7 | 0.022 |
| Hospitalization in ICU | 8.4 ± 6.6 | 3.7 ± 2.0 | 0.383 |

Values are expressed as No. (%) or mean ± SD.

**Table 2:** Frequency of nosocomial infections (before and after intervention). **P-value=0.580**.

| Variables | Before ASP | After ASP |
|---|---|---|
| Urinary tract infection | 97 | 67 |
| Pneumonia | 31 | 52 |
| Soft tissue infection | 35 | 18 |
| Bloodstream infection | 1 | 0 |
| Fistula infection | 0 | 0 |
| Others | 14 | 2 |
| **Total** | **148** | **139** |

## Discussion

Nosocomial infection with multidrug resistance (MDR)

**Table 3:** Results of cultures isolated from the patients (before and after intervention).

| Results of cultures | Before ASP | After ASP | P-value |
|---|---|---|---|
| ESBL | 22 (14.7) | 35 (23.3) | |
| MDR | 50 (33.3) | 35 (23.3) | |
| VRE | 12 (8.0) | 7 (4.7) | 0.013 |
| Sensitive | 21 (14.0) | 11 (7.3) | |
| Negative | 45 (30.0) | 62 (41.3) | |

Values expressed as No. (%). ESBL: Expended-spectrum beta-lactamase, MDR: Multidrug resistant, VRE: Vancomycin-resistant Enterococci.

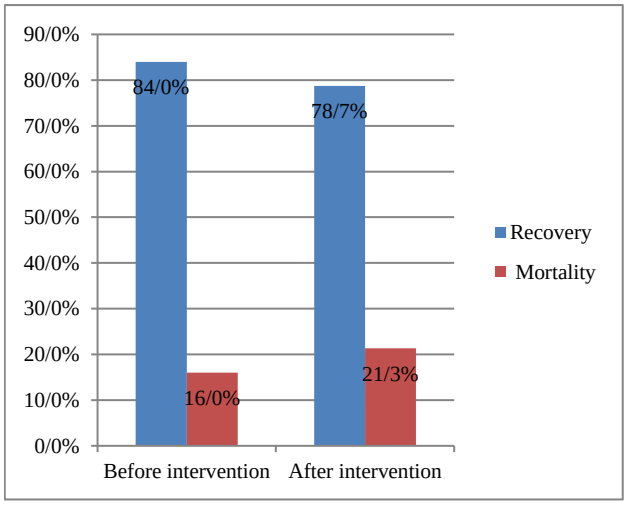


**Figure 1.** Patient outcomes in terms of time periods.

caused various medical, social, and economic problems in all countries. For instance, it has led to the spread of infectious diseases in the community, long-term hospitalization, increased treatment costs, and mortality[18]. World Health Organization (WHO) has made many recommendations to prevent and control antibiotic resistance, including assessing antibiotic resistance, using antibiotics accurately, prohibiting selling antibiotics as over the counter, and controlling infections[19,20]. An antibiotic management system program (stewardship) can prevent the development of antibiotic resistance by restricting antibiotic administration[12].

Our results showed that the length of hospitalization and treatment significantly was reduced after performing stewardship programs, which aligns with the previous studies. In this regard, Hussain *et al.* showed that hospitalization in the ICU, readmission, and length of treatment decreased after ASP[21]. In addition, a reduction in ICU hospitalization after ASP has been shown in other studies[17,22-24]. These results indicate the importance of proper antibiotic administration and antibiotic stewardship in reducing the length of treatment and ICU hospitalization.

Moreover, our results showed that the frequency of nosocomial infections decreased significantly after ASP. In contrast, Ruiz *et al.* reported that nosocomial infections did not change among 100 patients 25 after one year of ASP implementation. This discrepancy may be due to the low hygiene practices in hospitals after the implementation of ASP in the above study. Additionally, antibiotic administration decreased after the implementation of ASP, consistent with studies from China, Spain, and Brazil[25-27].

In our study, *E. coli* was the most common cause of bacterial infection in ICU patients. Also, the frequency of bacterial infections and antibiotic resistance, including MDR and Vancomycin-Resistant Enterococci (VER) strains, were significantly reduced after the implementation of ASP, consistent with several previous studies[25,26,28-31].

## Conclusion

In conclusion, proper antibiotic administration through the implementation of an antimicrobial stewardship program can reduce the frequency of MDR strains among bacterial pathogens causing nosocomial infections. Thus, implementing antimicrobial stewardship programs should be considered in all hospitals.

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## Conflict of interest

The authors further declare that they have no conflict of interest.

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