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Drug Utilization Evaluation of Antibiotics in Intensive Care Units of a Referral Teaching Hospital

Rasool Soltani[1,2*], Atousa Hakamifard[3], Sarah Mousavi[1], Zohreh Amani[4]

[1]Department of Clinical Pharmacy and Pharmacy Practice, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran.
[2]Infectious Diseases and Tropical Medicine Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
[3]Department of Infectious Diseases, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
[4]Students Research Center, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran.

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ABSTRACT

Background: Drug Utilization Evaluation (DUE) studies are designed to assess drug usage appropriateness. This study aimed to evaluate the drug utilization of antibiotics in the intensive care units (ICUs) of a referral teaching hospital.

Methods: Patients hospitalized in ICU who received antibiotics were enrolled in this cross-sectional study. Patients' medical charts were reviewed and data including indication of antibiotics, dosing, dose adjustment, and culture sensitivity test were recorded in a predesigned data collection form. Related guidelines and references were used for judgement about the correctness of these parameters.

Results: Among 182 evaluated antibiotic prescriptions, 75.8% of the cases were prescribed empirically that for 31.88% of them microbial culture and sensitivity test were requested. Indication was appropriate in 51.6%. Fifteen patients needed antibiotic dose adjustment that was performed just for 4 patients. Doses of antibiotics were correct in 58.5% of cases. Meropenem (15.9%), Metronidazole (15.9%), and vancomycin (11.5%) were the most frequently prescribed antibiotics.

Conclusion: Use of antibiotics in ICUs of our hospital is associated with high rate of errors especially in the aspects of medical indication and dosage.

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Introduction

Drug utilization evaluation was defined by WHO in 1977 as "the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences" (1). It is an important tool to study the clinical use of drugs in populations and its impact on health-care system (2).

Early and appropriate treatment of patients in intensive care unit (ICU) is critical when managing infections, which could help to reduce mortality rates in patients with severe sepsis or septic shock (3). However, inappropriate use of antibiotics leads to detrimental effects including emergence of antibiotic resistance affecting treatment outcome (4). Nowadays, rapid development of antibiotic resistance is a serious public health problem worldwide (5). On the other hand, the rates of nosocomial infections range from 5% to 30% among ICU patients (6). The total antibiotic consumption is approximately ten times greater in ICU than in other hospital wards. Typically, 60 to 70 percent of hospitalized patients in the ICU receive antibiotics at any time interval which can increase the duration of hospitalization and mortality and can lead to antimicrobial

**Corresponding Author:* Dr Rasool Soltani
Address: Department of Clinical Pharmacy and Pharmacy Practice, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran.
Tel:+983137927067, Fax:+983136680011.
Email: soltani@pharm.mui.ac.ir

resistance (3). The emergence of resistant organisms is of grave concern, as they are associated with a three-fold higher rate of mortality, doubling in length of stay and significant increase in hospital costs (7). Antibiotic usage resistance rates vary from one country to another. It is observed that countries with the highest per capita antibiotic consumption have the highest resistance rates (8). Iran is one of the countries with high antibiotic consumption. According to a study by Hashemi et al. from 600 outpatient antibiotic prescriptions in Iran, the antibiotic prescribing was inappropriate in 42.7% of the cases (9).

As improper usage and dosage of antibiotics can lead to antimicrobial resistance, DUE as a tool to detect the antibiotics utilization flaws can lead to optimization of the antibiotic administration and reduction of resistance rate. The object of this study was to evaluate the appropriateness of antibiotic use in relation to diagnosis and bacteriological findings in the ICUs of an 850-bed referral and tertiary care hospital in center of Iran.

Methods

The study was a cross-sectional prospective DUE study, carried out from October 2017 to April 2018 on patients admitted to 3 (general, central, and surgical) ICUs at Alzahra hospital, a general multispecialty, referral, tertiary healthcare setting affiliated to Isfahan University of Medical Sciences, Isfahan, Iran.

Adult patients (>18 years-old) who were hospitalized in ICU and received at least one antibiotic (parenteral/oral/inhalational/topical) during the study period were enrolled in this study. The data were extracted from hospital computerized information system and patients' medical charts.

Patients were randomly selected from those who met the inclusion criteria using the last two digits of the medical record code and the random number table. Patients' data including demographic characteristics and initial diagnosis (the indication for antibiotic administration) as well as drug's indicator consisting of previous and present treatment regimen, indication, dosing, and dose adjustment in renal/hepatic impairment and laboratory data including microbiological culture and serum creatinine (for calculation of creatinine clearance using Cockroft-Gault formula) were recorded in a predesigned data collection form. Data gathering was done by a general pharmacist under the supervision of a senior clinical pharmacy attending.

The appropriateness of antibiotic usage (indication and dosing) was assessed according to the culture results and based on the indications mentioned in the related guidelines (10, 11) and references (12-15). Also, the expert opinion including the judgments of an infectious diseases specialist, an infectious diseases clinical pharmacist, and an intensive care clinical pharmacist was considered.

The primary outcomes were the most frequently prescribed antibiotics as well as the rate of correctness of their indication and dosages based on the indication and renal/hepatic function. The secondary outcome was the rate of basis for antibiotic prescriptions (empirical vs. culture-based) and culture request for empirical prescriptions.

Descriptive analyses of data were performed using SPSS software (version, 23). For each variable, the frequency distribution and the corresponding percentages were determined.

Results

During the study period, 72 patients and 182 cases of antibiotic prescriptions were evaluated. Mean ± SD age of patients was 55.29 ± 18.55 years. Forty-two patients (58.3%) were male.

As shown in Table 1, the most common prescription indication of antibiotics was pre-operative prophylaxis (22.2%). Ventilator-associated pneumonia (VAP) with 6.9% and hospital-acquired pneumonia (HAP) with 5.6% were the following indications. Ten patients (13.9%) had no clear medical diagnosis.

Table 1. Frequency of medical indications for antibiotic prescriptions.

Diagnosis	Number of patients	Percentage
Preoperative prophylaxis	16	22.2
Ventilator-associated pneumonia (VAP)	5	6.9
Hospital-acquired pneumonia (HAP)	4	5.6
Community-acquired pneumonia (CAP)	3	4.2
Fever	3	4.2
Meningitis	3	4.2
Peritonitis	3	4.2
Empyema	3	4.2
Intra-abdominal infection	3	4.2
Postoperative prophylaxis	3	4.2
Urinary tract infection	2	2.8
Cholecystitis	2	2.8
Cellulitis	1	1.4
Osteomyelitis	1	1.4
Pneumonia + Urinary tract infection	1	1.4
Colostomy site infection	1	1.4
Bedsore (pressure ulcer)	1	1.4
Aspiration pneumonia	1	1.4
Sepsis	1	1.4
Gastrectomy site infection	1	1.4
Urosepsis	1	1.4
Pneumonia + pseudomembranous colitis	1	1.4
Wound infection prophylaxis	1	1.4
Toxic epidermal necrolysis	1	1.4
None (no diagnosis)	10	13.9
Total	**72**	**100**

Forty-six patients (63.9%) received 2 antibiotics simultaneously, while 16 patients (22.2%) received 3 antibiotics and 8 patients (11.1%) received 4 antibiotics. Five concurrent antibiotics were used for only 2 patients (2.8%).

Table 2 shows the most common administered antibiotics. Meropenem and metronidazole, each prescribed for 29 patients (15.9%), were on the top of the list followed by vancomycin (11.5%) and ceftizoxime (8.8%).

Of 182 prescriptions, 138 cases (75.8%) had been administered empirically and based on clinical data, while in 44 cases (24.2%), the antibiotics were prescribed based on the culture results and antibiogram tests. Of the 138 empirically administered antibiotics, there was a culture application and report for only 44 cases (31.88%).

Table 2. Frequencies of prescribed antibiotics in patients.

Antibiotic	Frequency	Percentage
Meropenem	29	15.9
Metronidazole	29	15.9
Vancomycin	21	11.5
Ceftizoxime	16	8.8
Levofloxacin	13	7.1
Ceftazidime	9	4.9
Fluconazole	8	4.4
Cefazolin	8	4.4
Linezolid	8	4.4
Clindamycin	7	3.8
Ciprofloxacin	6	3.3
Piperacillin/Tazobactam	5	2.7
Colistin	4	2.2
Gentamicin	4	2.2
Tobramycin (inhalational)	3	1.6
Erythromycin	2	1.1
Co-trimoxazole	2	1.1
Cephalexin	1	0.5
Imipenem	1	0.5
Ampicillin/Sulbactam	1	0.5
Teicoplanin	1	0.5
Nystatin (Topical)	1	0.5
Caspofungin	1	0.5
Amphotericin B	1	0.5
Amikacin	1	0.5
Total	**182**	**100**

Our results showed that 94 cases of prescriptions (51.6%) had appropriate indications and 88 cases (48.4%) had inappropriate indications. Furthermore, in 25 patients (34.7%), all of the used antibiotics had appropriate indications, while in 18 patients (25%), none of the antibiotics had a correct indication. In 29 patients (40.3%) some of the utilized antibiotics had appropriate indications.

Of 94 cases of appropriately prescribed antibiotics, 55 prescriptions (58.5%) were used in a correct dosage based on the indication and liver/kidney function and 39 cases (41.5%) had an incorrect dosage. Fifteen out of 94 cases (15.95%) required dosage adjustment due to renal impairment, of which only 4 cases (26.6%) had dosage adjustment. None of the cases needed dosage adjustment for hepatic dysfunction.

In Table 3, information for each antibiotic is presented separately.

Table 3. Frequency of prescriptions, medical indications, and correct dosage and dosage adjustment for each evaluated antibiotic

Antibiotic	Number of prescriptions	Medical indications (n)	Correct indication n (%)		Correct dosage n (%)		Required renal dose adjustment n (%)		Correct adjusted dose	
			Yes	No	Yes	No	Yes	No	Yes	No
Meropenem	29	VAP (4), HAP (4), CAP (3), Fever (2), Meningitis (2), Cholecystitis (1), UTI (1), Empyema (1), Pneumonia + UTI (1), Intra-abdominal infection (1), TEN (1), Bedsore (1), Aspiration pneumonia (1), Sepsis (1), Urosepsis (1), Pneumonia + Pseudomembranous colitis (1), No diagnosis (3)	15 (51.7)	14 (48.3)	9 (60)	6 (40)	2 13.3	13 86.7	-	2 (100)
Metronidazole	29	Prophylaxis (10), Peritonitis (3), Empyema (1), CAP (1), Cholecystitis (1), Colostomy infection (1), Intra-abdominal infection (1), HAP (1), Gastrectomy site infection (1), Pseudomembranous colitis (1), Post-operation Prophylaxis (2), No diagnosis (6)	17 (58.6)	12 (41.4)	7 (41.2)	10 (58.8)	-	17 (100)	-	-
Vancomycin	21	CAP (2), HAP (2), Prophylaxis (2), Fever (2), Meningitis (2), Cholecystitis (1), Empyema (1), Pneumonia + UTI (1), Intra-abdominal infection (1), TEN (1), Bedsore (1), Urosepsis (1), No diagnosis (4)	11 (52.4)	10 (47.6)	9 (81.8)	2 (18.2)	1 9.1	10 90.9	-	-
Ceftizoxime	16	Prophylaxis (4), Peritonitis (2), Cholecystitis (1), Colostomy infection (1), Intra-abdominal infection (1), Post-operative prophylaxis (2), No diagnosis (5)	10 (62.5)	6 (37.5)	6 (60)	4 (40)	3 (30)	7 (70)	-	3 (100)
Levofloxacin	13	CAP (3), UTI (2), VAP (1), Fever (2), Empyema (2), Bedsore (1), Aspiration pneumonia (1), HAP (1), Sepsis (1), Urosepsis (1)	8 (61.5)	5 (38.5)	7 (87.5)	1 (12.5)	1 (12.5)	7 (87.5)	1 (100)	-
Ceftazidime	9	Prophylaxis (6), Empyema (2), Meningitis (1)	5 (55.6)	4 (44.4)	2 (40)	3 (60)	-	5 (100)	-	-
Fluconazole	8	VAP (3), Peritonitis (1), Intra-abdominal infection (1), HAP (2), Pneumonia (1)	2 (25)	6 (75)	1 (50)	1 (50)	-	2 (100)	-	-
Cefazolin	8	Prophylaxis (5), Osteomyelitis (1), Post-operative prophylaxis (1), Wound infection prophylaxis (1)	5 (62.5)	3 (37.5)	-	5 (100)	2 (40)	3 (60)	1 (50)	1 (50)
Linezolid	8	VAP (2), HAP (2), CAP (1), Intra-abdominal infection (1), Sepsis (1), Gastrectomy site infection (1)	5 (62.5)	3 (37.5)	5 (100)	-	-	5 (100)	-	-

Table 3. Continued.

Clindamycin	7	CAP (1), Prophylaxis (3), Cellulitis (1), Empyema (1), No diagnosis (1)	4 (57.1)	3 (42.9)	2 (50)	2 (50)	-	4 (100)	-	-
Ciprofloxacin	6	Prophylaxis (1), Fever (2), Cellulitis (1), Post-operative Prophylaxis (1), No diagnosis (2)	-	6 100	-	-	-	-	-	-
Tazocin	5	VAP (1), Fever (1), UTI (2), Intra-abdominal infection (1), Gastrectomy site infection (1)	3 (60)	2 (40)	2 (66.7)	1 (33.3)	-	3 100	-	-
Colistin	4	VAP (2), Meningitis (1), HAP (1)	3 (75)	1 (25)	1 (33.3)	2 (66.7)	1 (33.3)	2 (66.7)	-	1 (100)
Gentamycin	4	Prophylaxis (1), Osteomyelitis (1), Wound infection prophylaxis (1), No diagnosis (1)	-	4 (100)	-	-	-	-	-	-
Tobramycin (inhalational)	3	VAP (2), HAP (1)	3 (100)	-	2 (66.7)	1 (33.3)	-	3 (100)	-	-
Erythromycin	2	UTI (1), No diagnosis (1)	-	2 (100)	-	-	-	-	-	-
Co-trimoxazole	2	VAP (1), Empyema (1)	-	2 (100)	-	-	-	-	-	-
Cephalexin	1	No diagnosis (1)	-	1 (100)	-	-	-	-	-	-
Imipenem	1	Peritonitis (1)	-	1 (100)	-	-	-	-	-	-
Ampicillin/Sulbactam	1	HAP (1)	1 (100)	-	1 (100)	-	-	1 (100)	-	-
Teicoplanin	1	VAP (1)	1 (100)		1 (100)			1 (100)		
Nystatin	1	Oral candidiasis (1)	1 (100)	-	1 (100)	-	-	1 (100)	-	-

Table 3. Continued.

Caspofungin	1	Urosepsis (1)	-	1 (100)	-	-	-	-	-	-
Amphotericin B	1	Gastrectomy site infection (1)	-	1 (100)	-	-	-	-	-	-
Amikacin	1	Pneumonia + pseudomembranous colitis (1)	-	1 (100)	-	-	-	-	-	-

Discussion

Based on the results, we observed a high level of errors in antibiotic prescription in ICUs of a university related referral hospital.

There have been some similar studies in different cities in Iran. In a study performed in 2014 in surgical wards of a hospital in Yazd, 68.8% of prescribed antibiotics were administered based on the guidelines and instructions (16) but here in the present study, we indicated that the accuracy of antibiotics prescriptions was 51.6% in Alzahra hospital. Eighty-seven percent of antibiotics had been prescribed in accurate dosage in the study of Yazd, while in Alzahra hospital, this rate was 58.5% (16). In their study, the most common antibiotics were first-generation (cephalothin 72.1% and cefazolin 3.9%) and third-generation (ceftriaxone 24%) cephalosporins (16), but here we indicated that meropenem (15.9%), metronidazole (15.9%), and vancomycin (11.5%) were mostly prescribed agents in our hospital. These differences could be due to differences in evaluated wards, because generally, in surgical wards, antibiotics are administered for surgical site infections accompanied by less errors, while in ICUs, patients have more complicated infections (e.g., sepsis) necessitating use of more extended-spectrum antibiotics. In another study performed in three intensive care units of Dr. Shariati hospital in Tehran, the use of carbapenems (imipenem and meropenem) was evaluated in critically ill patients (17). They reported that 51% of carbapenem prescriptions were correct and the accuracy of administered dosage was 72% based on the medical indications (17). A significant note of this study was that 19% of patients required dosage adjustment, while none of them received the correct adjusted dose (17). Similarly, in our study, 51.7% of patients had received meropenem properly. However, in contrast, only 31% of our patients had received accurate meropenem dose. This shows high rate of this type of error in our hospital necessitating more attention of prescribing physicians to the recommended doses by the references.

In another study conducted in 2014 in Sari, 101 ICU patients who were receiving at least one antibiotic were evaluated (18). The most common admission cause was reported to be brain injuries (63.4%). The most frequently administered antibiotics were ceftriaxone (72.3%) and meropenem (10.9%) in the first levels, while in the second levels when antibiotics were changed or discontinued, meropenem was still the most common agent (18). As mentioned above, meropenem was also the most common prescribed antibiotic in our study (15.9%). This indicates an increasing trend in carbapenem usage in the hospitals of Iran resulting in the emergence of carbapenem resistance among microorganisms especially gram-negative pathogens (19-21). Therefore, the use of carbapenems should be restricted because they have the greatest value for empiric treatment of serious infections or those caused by multidrug-resistant pathogens (22, 23). Furthermore, in the above-mentioned study, there were no samples or cultures for 23.8% of cases (18). This was 68% (94/138) in our study showing higher rate of this error in our center. Therefore, the physicians should pay more attention to this stage of antibiotic therapy, since many empirical treatments of infections should be adjusted or de-escalated based on the sample culture results if necessary (24, 25).

Also a survey on antibiotic prescription patterns in other countries is available. In a DUE study in Pakistan, meropenem usage was evaluated in a university hospital in Karachi in 2013 (26). Accuracy of meropenem administration was reported to be 97.5% (26) which is a higher rate compared with our results of Alzahra hospital in Iran (51.7%). Furthermore, dosage accuracy of meropenem was reported 74.6% which was also higher than our results (31%). In 2018, a study was performed in Indonesia evaluating 60 septic patients admitted in ICU regarding antibiotics administration (27). It was reported that 33.3% of patients were prescribed inappropriate types of antibiotics and 51.7% were given an inappropriate dosage (27). Similar to our pattern, most treatments (93%) were empirical. The most common administered antibiotics were meropenem (41.1%), levofloxacin (20%), and amikacin (11.3%) (27). Higher rates of correct prescriptions could be due to the fact that the most common source of infection in patients was hospital-acquired pneumonia (61.7%), as meropenem, levofloxacin, and amikacin have indication in this type of infection.

In conclusion considering high rate of errors in the use of antibiotics in our hospital, especially in the aspects of indication, dosage, concomitant antibiotic, and application of culture and antibiogram results, measures for improvement of utilization pattern of these drugs is very important. In this regard, educational programs could play a pivotal role.

Use of antibiotics in ICUs of our hospital is associated with high rate of errors especially in the aspects of medical indication and dosage. Updated educational and correctional programs are necessary to reduce such errors.

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