Usage of antibiotics in the Intensive Care Unit at Hue University of Medicine and Pharmacy Hospital

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Abstract

Background: In Vietnam, a number of recent epidemiological studies demonstrated that the prevalence of antibiotic-resistant bacteria has been rapidly increasing, especially in intensive care units (ICUs). The implementation of comprehensive and long-term measures through antibiotic stewardship programs (AMS) is necessary. **Objectives:** For patients in the ICU of Hue University of Medicine and Pharmacy Hospital: (1) To survey of usage of antibiotics, and (2) to find out patient-related factors for antibiotic use. **Materials and methods:** A cross-sectional study was carried out on 102 medical records of patients who were treated in the ICU from 01/2019 to 10/2020, at Hue University of Medicine and Pharmacy Hospital. **Results:** The average age of patients was quite high at 70.71±19.70 years. Initial antibiotic with monotherapy accounted for 41.2%, mainly was ceftriaxone (28 prescribed), combined two antibiotics accounted for 49.0%, the most popular was the combination of third generation cephalosprins with fluoroquinolones. Most of participants prescribed a total of two or three types of antibiotics in their medical records (accounted for 68.6%). Patient-related factors associated with antibiotics usage included: antibiogram results (OR=4.7, p=0.039), sepsis diagnosis (OR=12.0, p=0.04), and initial therapeutic change (OR=14.5, p=0.002). **Conclusion:** The majority of initial antibiotic therapies are monotherapy and a combination of two antibiotics in accordance with the recommendation. The number of used antibiotics were associated with the sepsis diagnosis, antibiogram results, and changing antibiotic therapy.

Keywords: *The intensive care unit (ICU), antibiotics, antibiotic-resistant.*

1. INTRODUCTION

Antibiotic resistance has become a global concern. The main problems of antibiotic resistance include improper prescription, inappropriate antibiotic combinations, unnecessary use of antibiotics, long-term treatment with broad-spectrum antibiotics [1], [2]. The inappropriate and ineffective use of antibiotics could lead to therapy failure, increase morbidity and mortality rates and healthcare costs [2].

In Vietnam, a number of epidemiological studies demonstrated that the prevalence of antibiotic-resistant bacteria has been rapidly increasing in intensive care units (ICU) [3]. The rate of antibiotic resistance to ciprofloxacin and ceftazidime was recorded up to 65%, while cefotaxime, ceftriaxone, cefoperazone were resistant to 80% [4]. In critically ill patients, antibiotic therapy should be initiated immediately before having a result of antibiotic susceptibility testing. Antibiotics choosing often based on clinical symptoms and laboratory findings. The prescribers need to be adherent to the treatment guidelines and also follow a standard process of prescribing [5], [6]. The analysis resulted from some studies showed the factors that can influence the antibiotic prescribing decision include the clinical situation, advanced care plans, utilization of diagnostic resources, the influence of others and the environment [7]. Khilnani's study has also shown the relationship between antibiotic therapy to the outcome, cost and duration of treatment [8].

Antibiotic stewardship is the most important way to optimize the use of antibiotics to prevent the development of resistance and improve patient outcomes. The implementation of comprehensive and long-term measures through antibiotic stewardship programs (AMS) is necessary and recommended by IDSA/SHEA and the Ministry of Health [9], [10], [11]. In order to understand the prevalence of antibiotic use in the ICU, the prevalence of drug-resistant, and the rational use of antibiotic therapy as well as patient-related factors for antibiotic usage. We conducted the research on ***"Usage of antibiotics in the intensive care unit at Hue University of Medicine and Pharmacy Hospital"*** with the following objectives:

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1. To survey the usage of antibiotics in the ICU of Hue University of Medicine and Pharmacy Hospital.

2. To find out patient-related factors for antibiotic use in the ICU of Hue University of Medicine and Pharmacy Hospital.

2. METHODS

2.1. Participants:

Medical records of inpatients treated in the ICU of Hue University of Medicine and Pharmacy Hospital.

Inclusion criteria: (a) Patients ≥ 18 years who were admitted to the ICU of Hue University of Medicine and Pharmacy Hospital and with more than 48 hours of length of stay were included, (b) Patients who were given at least one oral or intravenous antibiotic in the course of treatment.

Exclusion criteria: (c) Patients who are pregnant and breastfeeding women, (d) Medical records are not fully accessible.

2.2. Study design and sample size:

A descriptive cross-sectional study was conducted in the ICU of Hue University of Medicine and Pharmacy Hospital from January 1st 2019 to October 1st 2020.

We collected 102 medical records of inpatients who were treated in the ICU of Hue University of Medicine and Pharmacy Hospital, which met the inclusion and exclusion criteria

2.3. Data collection

Data were collected by using a data collection form which was built based on the structure of the complete medical record

- General characteristics of patients: age, sex, renal function, the number of comorbidities, length of hospital stay, previous antibiotics history, interventions, signs of infection, microbiological testing, etc.

Note: We assessed the latest signs of infection before using antibiotics or changing therapy.

- Regarding the assessment of renal function is to get an estimated glomerular filtration rate (eGFR). Using the 4-variable Modification of Diet in Renal Disease Study (MDRD) equation to evaluate as follows [12], [13] :

$eGFR\ (ml/min/1.73m^2) = 186 \times SCr^{-1.154} \times (age\ in\ years)^{-0.203} \times 0.742\ (if\ female) \times 1.21\ (if\ black)$

Note: SCr (Serum creatinine) is reported as milligrams of creatinine to a deciliter of blood (mg/dL)

Table 1. Assessments of signs of infection and renal function

SIGNS OF INFECTION	
Index	**Abnormal reviews**
Fever	Temperature > 38 °C
WBC (White Blood Cell)	Out of range 4-10 G/L
NEU% (Neutrophil)	Out of range 37-72%
LYM% (Lympho)	Out of range 20-50%
CRP (C-Reactive Protein)	Increase > 20 mg/l
Procalcitonin	Increase > 0.5 ng/ml
RENAL FUNCTION	
eGRF(ml/min/1.73m²) range	**Description**
≥ 90	Normal or high
60-89	Mildly decreased
45-59	Mildly to moderately decreased
30-44	Moderately and severely decreased
15-29	Severely decreased
<15	Kidney failure

- General characteristics of antibiotic use, initial antibiotic therapy
- Finding out patient-related factors for the number of prescribed antibiotics.

+ Dependent variables: the number of antibiotics

+ Independent variables: demographic characteristics (age, sex,…), renal function, the number of co-

morbidities, length of hospital stay, previous antibiotic history, interventions, initial antibiotic therapy.

2.4. Statistical Analysis

Data were stored and processed by using Microsoft Excel 2016 and IBM SPSS statistics 20.0.

Qualitative variables were displayed as frequencies and percentages. If having a normal distribution, continuous quantitative variables were presented as mean and standard deviation (Mean ± SD). If having non-normal distribution, it was presented as the median and interquartile range (interquartile range: 25^{th} to 75^{th} percentile), Chi-squared test for two proportions, multivariate logistic regression analysis for determining related factors.

A p-value less than 0.05 (typically ≤ 0.05) is statistically significant.

3. RESULTS

3.1. General characteristics of patients

The average age was 70.7±19.7, the elderly accounted for a high percentage (68.6%). The high proportion of respiratory disease (58.8%) and sepsis/septic shock (22.5%). The majority of patients (87.3%) have comorbidities, mainly with 1-2 comorbidities. Over 90% of patients had interventions (procedures) including ventilator (77.5%) is the most common.

There were 81 patients with adequate data to evaluate renal function, including (47%) patients with eGFR < 60 ml/min/1.73m^2. *[table 2]*

Table 2. General characteristics of patients in the ICU (N=102 medical records)

Characteristics		Number	Percentage
Age[a]	18 - <65	32	31.4
	≥ 65	70	68.6
	Mean ± SD	70.7 ± 19.7	
	Max	96	
	Min	19	
Sex	Male	47	46.1
	Female	55	53.9
Primary disease	Respiratory disease (COPD, pneumonia, respiratory failure)	60	58.8
	Sepsis/septic shock	23	22.5
	Gastrointestinal tract	2	2.0
	Soft tissue infection	1	1.0
	Cardiovascular	1	1.0
	Other conditions	15	14.7
SOFA score	Yes	34	33.3
	No	68	66.7
	Mean ±SD	6.6 ± 3.4	
Previous antibiotic history	Yes	33	32.4
	No	61	59.8
	No available	8	7.8
Interventions (procedures) on patients*	Intravenous catheters	55	53.9
	Sputum suctioning	51	50.0
	Ventilator	79	77.5
	Gastrostomy tube/Urinary catheter	70	68.6
	Intubation	47	46.1
	Other procedures	42	41.2
	No interventions	6	5.9

Glomerular filtration rate (eGFR)	≥ 60 ml/min/1.73m^2	33	32.4
	30-59 ml/min/1.73m^2	34	33.3
	< 30 ml/min/1.73m^2	14	13.7
	No assessment	21	20.6
Number of comorbidities	0	13	12.7
	1	31	30.4
	2	29	28.4
	3	14	13.7
	> 3	15	15.8
Duration of antibiotic therapy	< 5 days	42	41.2
	5-14 days	35	34.3
	> 14 days	25	24.5
	Median of duration[b]	6.0 (3.0-14.5)	
Types of antibiotics used	1	17	16.7
	2	41	40.2
	3	29	28.4
	4	10	9.8
	5	3	2.9
	6	2	2.0
Route of antibiotic administration*	Oral/gastrostomy tube administration	3	1.0
	Intravenous/infusion therapy	287	99.0
Number of signs of infection	0	11	10.8
	1	18	17.6
	≥ 2	73	71.6

a: Mean ± standard devitation, b: Median (interquartile range: 25%, 75%).

The most common of cultured specimens were sputum (66 times) with the highest positive rate (18/66). The majority of isolated bacterial pathogens were *Acinetobacter baumannii, Pseudomonas aeruginosa*, *Klebsiella pneumonia* và *Escherichia Coli*. *[table 3]*

Table 3. Result of microbiological testing

	Resistance percentage / Total antibiogram			
Antibiotics tested	***A. baumanii***	***P. aeruginosa***	***K. pneumoniae***	***E. Coli***
Amikacin	2/3	0/5	1/6	0/4
Cefoxitin	N/A	N/A	4/4	1/3
Ceftriaxone	2/3	N/A	5/6	3/4
Ciprofloxacin	3/4	2/4	4/6	1/2
Meropenem	3/3	2/6	3/6	0/4

N/A: No Available

3.2. Treatment regimens

Of the 290 antibiotic prescriptions, the majority of substances were cephalosporin and Fluoroquinolone (with 100 and 73 prescriptions, respectively). The classification of antibiotics in this study was the most active against gram-negative bacteria, including beta-lactams, fluoroquinolones, aminoglycoside and the antibiotic against anaerobic organisms was nitroimidazole. *[Figure 1]*

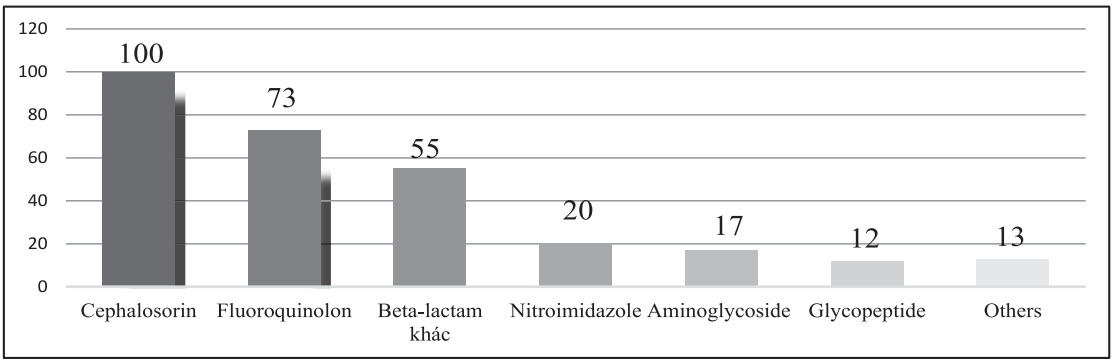

Figure 1. Distribution of antibiotic consumption (N=290 prescriptions)

The mean duration of antibiotic therapy was 6.0 (3.0-14.5) days, 75.5% of patients who have a duration of therapy < 14 days. Initial antibiotic with monotherapy accounted for 41.2%, mainly was ceftriaxone (28 prescribed), combined two antibiotics accounted for 49.0%, the most popular was the combination of CG3 with fluoroquinolones to expand the spectrum, increase bactericidal action and combined three antibiotics only accounted for 8.8%. *[table 4]*

Table 4. General characteristics of antibiotic therapy (N=102 medical records)

Characteristics		Number	Percentage
Duration of antibiotic therapy	< 5 days	42	41.2
	5-14 days	35	34.3
	>14 days	25	24.5
	Median of duration[b]	6.0 (3.0 - 14.5)	
Types of antibiotics used	1	17	16.7
	2	41	40.2
	3	29	28.4
	4	10	9.8
	5	3	2.9
	6	2	2.0
Route of antibiotic administration*	Oral/gastrostomy tube administration	3	1.0
	Intravenous/infusion therapy	287	99.0
Number of signs of infection	0	11	10.8
	1	18	17.6
	≥ 2	73	71.6
Initial therapy			
Monotherapy (n=42)	Ceftriaxone	28	41.2
	Cefoxitin	3	
	Cefotiam	2	
	Ciprofloxacin	2	
	Piperaclin_tazobactam	2	
	Other antibiotics	5	

Combination of two antibiotics (n=50)	CG3 + Flouroquinolon	21	49.0
	Carbapenem + Flouroquinolon	10	
	Carbapenem + Nitroimidazole	4	
	CG3 + Aminoglycoside	4	
	CG3 + Nitroimidazole	2	
	Others	9	
Combination of three antibiotics (n=9)	Ciprofloxacin + Cephalosporin + metronidazol	2	8.8
	Cephalosporin + Amikacin + metronidazol	1	
	Ciprofloxacin + meropenem + metronidazole	1	
	Ciprofloxacin + Cephalosporin + meropenem	1	
	Ciprofloxacin + fosfomycin + vancomycin	1	
	Others	3	
Combination of four antibiotics (n=1)	Cephalosporin + ciprofloxacin + metronidazole + tinidazole	1	1.0%

Cephalosporin: ceftriaxone, cefotaxim, cefoxitin

There were 66.7% of medical records that have the initial therapeutic change in the duration of antibiotic therapy. The majority of types of therapy changes were generic name change (33.8%) and additional medications (50.0%). *[table 5]*

Table 5. Characteristics of initial therapeutic change (N=102 medical records)

Assessment	Number	Percentage (%)
Do the initial therapy change		
No change	34	33.3
1 time	37	36.3
2 times	11	10.8
3 times	10	9.8
> 3 times	10	9.8
Reasons for initial therapeutic change		
The disease does not improve	22	32.4
New symptoms appear	15	22.1
Severe prognostic disease	6	8.8
Antibiotic susceptibility testing results	4	5.9
Improving diseases	2	2.9
Others	19	27.9
Types of therapy change		
Additional medications	34	50.0
Dosage regimen change	23	33.8
Generic name change	19	27.9
Less fewer medications	8	11.8
Brand name change	4	5.9

3.3. Patient-related factors for antibiotic usage

Chi-squared tests indicated statistical significance associations between types of used antibiotics and duration of antibiotic therapy (p=0.001), antibiogram (p=0.001), signs of infection (p=0.001), interventions/ procedures (p=0.035), number of comorbidities (p=0.011), site of infection (p=0.006), and initial therapeutic change (p=0.001). *[table 6]*

Table 6. Correlation between the number of antibiotics and categorical variables (N=290)

Factors		Total types of antibiotics in medical records		Total	p-value
		1-2	≥ 3		
Sex	Female	29 (52.7)	26(47.3)	55	p = 0.362
	Male	29 (61.7)	18 (33.3)	47	
Age	18- <65	18 (56.2)	14 (43.8)	32	p = 0.933
	≥ 65	40 (57.1)	30 (42.9)	70	
Duration of antibiotic therapy	< 5 days	32 (76.2)	10 (23.8)	42	**p = 0.001**
	5-14 days	22 (62.9)	13(37.1)	34	
	> 14 days	4 (16.0)	21 (84.0)	28	
Previous antibiotics used	No	41 (59.4)	28 (40.6)	69	p = 0.451
	Yes	17 (51.5)	16 (48.5)	33	
Antibiogram	Yes	6 (25.0)	18 (75.0)	78	**p = 0.001**
	No	52 (66.7)	26 (33.3)	24	
SOFA score	Yes	15 (44.1)	19 (55.9)	34	p = 0.066
	No	43 (63.2)	25 (36.8)	68	
Signs of infection	0	10 (90.9)	1 (9.1)	11	**p = 0.001**
	1	15 (83.3)	3 (16.7)	18	
	≥ 2	33 (45.2)	40 (54.8)	73	
Interventions/Procedures	No	6 (100)	0 (0.0)	6	**p = 0.035**
	Yes	52 (54.2)	44 (45.8)	96	
Number of comorbidities	0	10 (76.9)	3 (23.1)	13	**p = 0.011**
	1-2	38 (63.3)	22 (35.7)	60	
	≥ 3	10 (34.5)	19 (65.5)	29	
Glomerular filtration rate	No assessment	16 (76.2)	5 (23.8)	21	p = 0.084
	< 60 ml/min/1.73m^2	27 (56.2)	21 (43.8)	48	
	≥ 60 ml/min/1.73m^2	15 (45.5)	18 (54.5)	33	
Site of infection	Respiratory tract	29 (48.3)	31 (51.7)	60	**p = 0.006**
	Sepsis	12 (52.2)	11 (47.8)	23	
	Other	17 (89.5)	2 (10.5)	19	
Initial therapy	Monotherapy	28 (66.7)	14 (33.3)	42	p = 0.094
	Combination therapy	30 (50.0)	30 (50.0)	50	
Initial therapeutic change	No	32 (94.1)	2 (5.9)	34	**p = 0.001**
	Yes	26 (38.2)	42 (61.8)	68	

The output of the multivariable logistic regression analysis found that a significant association was obtained between patient-related factors and antibiotic usage, including: having antibiogram (OR=4.7, p=0.039), sepsis diagnosis (OR=12.0, p=0.04), and initial therapeutic change (OR=14.5, p=0.002).

Table 7. Patient-related factors for antibiotic usage (N=290)

Factors	1-2 types of antibiotics	≥ 3 types of antibiotics	OR (95%CI)	p- value
Duration of antibiotic therapy				
< 5 days	32	10	1	-
5-14 days	22	13	0.9 (0.2-3.7)	p = 0.922
> 14 days	4	21	5.1 (0.9-32.7)	p = 0.073
Antibiogram				
No	6	26	1	-
Yes	52	18	4.7 (1.0-21.0)	p = 0.039
Signs of infection				
No	10	1	1	-
1	15	3	0.4 (0.02-9.3)	p = 0.562
≥ 2	33	40	0.8 (0.04-16.0)	p = 0.899
Interventions/Procedures				
No	6	0	1	-
Yes	52	44	2.8×10^{7}	p = 0.999
Number of comorbidities				
0	10	3	1	-
1-2	38	22	0.8 (1.0-5.5)	p = 0.841
≥ 3	10	19	2.6 (0.3-20.1)	p = 0.390
Site of infection				
Respiratory tract	29	31	3.4 (0.4-30.6)	p = 0.278
Sepsis	12	11	12.0 (1.1-128.6)	p = 0.040
Other	17	2	1	-
Initial therapeutic change				
No	32	2	1	-
Yes	26	42	14.5 (2.6-80.9)	p= 0.002

4. DISCUSSIONS

4.1. General characteristics of patients

There were 102 medical records in the study, the average age was 70.71±19.70 years old. Patients in the ICU are mainly elderly with many differences in the pharmacokinetics of medicines, using antibiotics should follow the prescribing principles [2], [6]. Only 33.3% of the medical records had SOFA scores with a fairly high mean score was 6.6±3.4. Similar to the study in the US was 7 (2-4) points [14]. The SOFA score is one of the common scales to assess the severity of the patient and is one of the guiding factors for antibiotic prescribing in the ICU [6]. However, the proportion of medical records that had this scale in the study is still limited.

The main disease in the ICU was lower respiratory tract infections (included pneumonia, COPD, respiratory failure) accounted for 58.8%. Sepsis and septic shock (22.5%) are also serious diseases requiring antibiotic treatment. Similar to the study of Choudhuri A.H (2017) at the Indian ICU, the incidence of pneumonia was highest (33%) [15]. The majority of patients (87.3%) have comorbidities, including circulatory system diseases (39.7%),

endocrine and metabolic diseases (15.7%). These were all complex diseases and affected the response to treatment in patients. Most of the antibiotic treatment duration was under 14 days suitable to the Guidelines for antibiotic use and depends on the infection status [2].

The main pathogens were gram-negative bacteria (*Acinetobacter baumanii, Pseudomonas aeruginosa, Klebsiella pneumonia* and *Escherichia Coli*) that cause common diseases such as pneumonia, sepsis. This result is similar to the study of Choudhuri A. H. (2017) at the Indian ICU [15] and P.H. Tran's research (2018) at the ICU of Tien Giang's Center hospital [16]. However, due to the small number of antibiotic susceptibility testing, it is not possible to exact conclusions about antibiotic resistance at the Unit.

4.2. Treatment regimens

There were a lot of antibiotic classifications were prescribed out of 290 prescriptions. In which, the majority of cephalosporins (34.4%), fluoroquinolone (25.3%), and beta-lactam (19.0%) with common ingredients were 3rd generation cephalosporin (ceftriaxone, ciprofloxacin, meropenem). This result was equivalent to P.H. Tran's study with the most frequently prescribed were cephalosporins (ceftriaxone, ceftazidime and cefotaxime) accounted for 48.14% [16], the most common antibiotic in Williams's study was also the 3rd generation cephalosporin group [17]. Other antibiotics such as vancomycin, fosfomycin, or amikacin were also used in the ICU at a low rate. These antibiotics cause a high potential for nephrotoxicity if used inappropriately, so caution should be exercised in intensive patients.

The initial therapy with monotherapy accounted for 41.2%, mainly was ceftriaxone (28 prescribed), combined two antibiotics accounted for 49.0%, the most popular was the combination of CG3 with fluoroquinolones to expand the spectrum, increase bactericidal action and combined three antibiotics only accounted for 8.8%. The combination therapies were considered appropriate in the treatment of pneumonia and bacteremia according to the antibiotic use guidelines [2]. A large proportion of participants (68.6%) prescribed a total of 2 or 3 types of antibiotics in their medical records. Whereas, William's study described that 70.0% of patients using two or fewer antibiotics [17], a study in a German surgical ICU reported cases were treated with only one or two antibiotics accounted for 36.7% and 14.1%, respectively [18]. The growth of resistant antibiotics recently is also causing the more prioritized antibiotic combinations in treatment. Empiric therapy or treatment of severe disease often recommends antibiotic combinations to increase bactericidal capability [2].

There were (66.7%) medical records changed treatment regimen from 1 to 3 times. The main regimen changes were additional medications (50.0%) and changing the dosage regimen (33.8%). Infection that did not improve (32.4%) was the most common reason for doctors to change antibiotic regimens. Change regimen after having antibiotic susceptibility testing results is clear evidence for reasonable antibiotic change, although accounted for only 5.9% in the study. Because of the long waiting time, it is important to change the regimen based on the course of the disease.

4.3. Patient-related factors for antibiotic usage

On multivariate analysis of the factors contributing to an increased antibiotic prescribed at the ICU, it was found that patients who with antibiogram results had 4.7 times more likely to be prescribed over 3 antibiotics than those without antibiogram results (95% CI: 1.0-21.0; p= 0.039). In the comorbidities group, the number of antibiotics prescribed correlated significantly with sepsis. Patients with sepsis diagnosis were 10.7 times more likely to use 3 antibiotics than other infections (95% CI: 1.1-126.8; p=0.040). The group that changed the antibiotic regimen had a 14.5 times higher risk of using over 3 antibiotics than the group that did not change the initial regimen (95% CI: 2.6-80.9; p=0.002). The number of prescribed antibiotics was an important indicator of prescription quality. It is recommended that this figure should be kept as low as possible to minimize the risk of resistance, treatment costs and fail treatment outcomes [17], [19]. The results of the analysis showed that choosing the right empiric initial antibiotic regimens had an important role in decreasing the number of prescribed antibiotics, which benefits patients and reduces cost. Therefore, updating antibiotic resistance status and treatment guidelines at the institution should be regularly promoted.

5. CONCLUSION

The majority of initial antibiotic therapies are monotherapy and a combination of two antibiotics in accordance with the recommendations. The number of used antibiotics were statistically significant associated with the sepsis diagnosis, antibiogram results, and changing antibiotic therapy.

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