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Original Article

The efficacy of empirical antibiotic treatment and resistance on mortality in an internal medicine intensive care unit

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ABSTRACT

Objectives: This study aimed to determine the efficacy and resistance of empirical antibiotics (EA) in patients admitted to the Internal Medicine Intensive Care Unit (ICU) due to community-acquired infections according to the infectious agents in the follow-up of patients and to determine its relationship on mortality.

Patients and methods: A total of 162 patients (78 males, 84 females; mean age 74.7±13.5 years; range 22 to 98 years) with community-acquired infections, followed in Medeniyet University, Göztepe Training and Research Hospital Internal Medicine Intensive Care Unit between March 2015 and March 2017, were included in this study. The patients' age, sex, comorbidities, diagnoses, EA, culture antibiogram, and mortality outcomes were all recorded retrospectively.

Results: The most common (50%) comorbidity was hypertension. The common diagnosis on admission was pneumonia (46.2%). *Acinetobacter Baumannii* was the most isolated bacterium. The most frequently used group of EA was carbapenems (46.9%). Culture antibiogram results showed resistance to the EA in 42.6% of the patients. Empirical antibiotics were replaced with other antibiotics in 46.9% of the patients. When compared to the susceptible group, mortality was higher in the resistant group to the EA.

Conclusion: In this study; antibiotic resistance was found to affect mortality in patients admitted to the Internal Medicine ICU for community-acquired infections.

Keywords: Antibiotic resistance, infection, intensive care, mortality.

Infections can be acquired in the community or the hospital by intensive care patients. Pneumonia and bacteremia, both community- and hospital-acquired infections, are the most common infections among intensive care patients.[1] Hospital-acquired infections do not have an incubation period during hospitalization and begin at least 48-72 h after being in hospitalization. Incidence of these infections in inpatients and intensive care unit (ICU) patients are 5-10% and 20-25% respectively.[2,3] Urinary tract infections (UTIs), ventilator-related pneumonia, bacteremia, and surgical region infections, as well as catheter infections, are the most common nosocomial infections in ICUs.[4,5] Due to their age and associatedcomorbidities, invasive life support units and interventional procedures, frequent and prolonged use of broad-spectrum antibiotics, and length of hospital stay inpatients in intensive care units are at a higher risk for hospital-acquired infections. Increased use of antibiotics also poses an issue of bacterial resistance and in turn, these

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resistant nosocomial pathogens are a major problem to hospital-acquired infections.[6,7]

Antibiotic resistance is a serious public health problem that affects people all around the world. Increased morbidity and mortality are induced by the need to adjust empiric therapy due to resistance, inadequate treatment, and prolonged hospitalization.[8]

In the study, we aimed to increase the awareness of Internal Medicine ICU flora and to promote rational use of antibiotics in our hospital by recording patients' age, accompanying comorbidity, causes of hospitalization and invasive mechanical ventilation (MV) applications, antibiotics used in empiric therapy, culture-isolated factors, antibiotic resistance data of these factors and the mortality of patients hospitalized in ICU because of community-acquired infectious diseases.

PATIENTS AND METHODS

The study included 162 patients (78 males, 84 females; mean age 74.7±13.5 years; range 22 to 98 years) who were hospitalized to Medeniyet University Göztepe Training and Research Hospital Internal Medicine ICU between April 2015 and April 2017. Inclusion criteria were as follows: patients admitted to ICU with a diagnosis of any bacterial infection and performance of the admission from the emergency department to ICU. Exclusion criteria were as follows: patients with a history of hospitalization, patients transferred from other clinics, patients with a recent history of antibiotic use, and patients in nursing homes. A written informed consent was obtained from each patient. The necessary study permit was granted by the Medeniyet University Göztepe Training and Research Hospital Ethics Committee (decision dated 23.05.2017 and numbered 2017/0188). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Indications for admission to the ICU, age and sex information, associated comorbidities, and demographics were obtained from patient records and epicrisis. Data were collected on whether patients undergoing invasive or non-invasive MV during their intensive care hospitalization, antibiotics used for empiric therapy, and blood, urine, sputum, wound, and stool cultures, all of which are routinely conducted during the initial hospitalization of patients. The results of cultures and antibiograms performed during the hospitalization of patients and collected from their records and hospital data system. The number of cultures indicating growth or colonization, as well as whether the growth was significant, were all determined daily by the epicrisis of clinicians responsible for patient follow-up. In addition, the infectious diseases specialist's entries into the system were scrutinized. Antibiogram test (resistance or sensitivity) results were determined by a fully automated system. Antibiotic susceptibility of patients was evaluated empirically based on each patient's antibiogram results. The study also included mortality data of patients hospitalized for infectious diseases. Our ICU's community-acquired infectious pathogens have been identified, as well as the antibiotics to which they are sensitive.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA) and necessary corrections and error checks were made. Descriptive data were expressed in mean ± standard deviation. The Chi-square test was used to evaluate categorical variables. Continuous variables were analyzed using the Student t-test for independent samples. The Analysis of Variance (ANOVA) was used in the case of homogenous variance and normality of distributions in the analyses in which three groups were compared, and the Tukey's test was used for post-hoc comparisons. Pearson and Spearman correlation tests were used for correlation evaluations. A p value of <0.05 was considered statistically significant.

RESULTS

Hypertension and ischemic heart disease were found to be the most frequent comorbidities in both genders (Table 1). 77.1% of the patients were over the age of 70. At least one comorbidity was found in 95% of the patients.

Pneumonia (46.2%), sepsis (29%), UTI (21%) and, soft tissue infections (1.2%) were the most common reasons for ICU admission (Figure 1).

53.1% of the patients received invasive MV procedures, and it was found that 42% of these

Table 1. Demographic and clinical characteristics of the patients

	Male		Female	
	n	%	n	%
Hypertension	39	24	42	26
Ischemic heart disease	37	22	30	18
Diabetes mellitus	22	13	40	24
Malignancy	19	11	21	12
Congestive heart failure	20	12	15	9
Chronic obstructive pulmonary disease	19	11	10	6
Chronic renal failure	14	8	15	9
Previous cerebrovascular event	15	9	13	8
Dementia	16	10	11	6
Chronic liver disease	4	2	1	0.6

patients did not require MV. 4.9% of the patients received a non-invasive MV procedure.

In the ICU, carbapenems were the most commonly used antibiotics for empiric treatment (46.9%). Meropenem was the most used antibiotic in the carbapenem class (44.4%). Antibiotics in combination with beta-lactamase inhibitors (27.7%) (most commonly piperacillin/tazobactam) were the second most commonly used antibiotics (Table 2).

According to patient culture results, Gram-negative (GN) bacteria accounted for 83.6% of the reproducing factors, 10.7% for Gram-positive (GP) bacteria, and 5.6% for fungi. *Acinetobacter baumannii (A. baumannii)* which is a GN coccobacillus, was found to be the most common reproducing factor. Apart from the hospitalization diagnosis, Acinetobacter baumannii was found to proliferate in 35.1 % of patients. Other reproducing factors were observed as *Escherichia coli (E. coli)* 24%, Klebsiella pneumoniae *(K. pneumoniae)* 18.5%, Pseudomonas aeruginosa 9.8%, *Streptococcus pneumoniae (S. pneumoniae)* 6.1% in order of frequency.

A. baumannii was found to be the most common cause in routinely taken deep tracheal aspiration cultures from ICU patients, with a rate of 19.7%, E. coli being the most common cause in urine cultures with a reproductive rate of 15.4%, and *A. baumannii* being the most common cause in blood cultures with 11.1% (Table 3).

According to the results of cultures and antibiograms, empiric therapy was effective

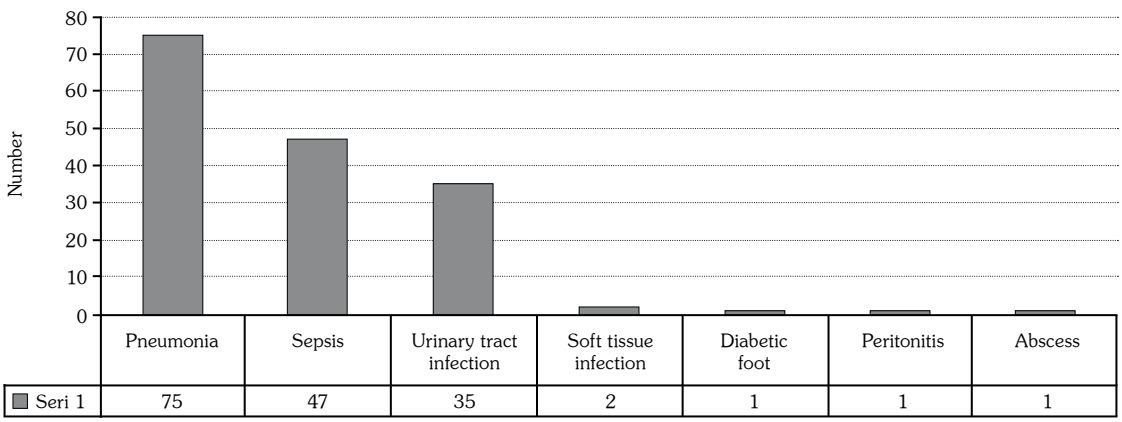


Figure 1. Hospitalization diagnoses of patients.

Table 2. Antibiotics used in empirical treatment

	Antibiotic used	
	n	%
Carbapenems	76	46.9
Meropenem	72	44.4
Imipenem	2	1.2
Ertapenem	2	1.2
Beta-Lactamase Inhibitors/ penicillin-cephalosporin combination	45	27.7
Piperacillin/tazobactam	34	20.9
Ampicillin/sulbactam	10	12.9
Oxazolidinones	32	19.1
Linezolid	32	19.7
Macrolides	30	18.5
Clarithromycin	30	18.5
Cephalosporins	27	16.6
Ceftriaxone	13	8.0
Ceftazidime	12	7.4
Cefepime	1	0.6
Glycopeptides	15	9.2
Vancomycin	11	9.7
Teicoplanin	4	2.4
Fluoroquinolones	12	7.4
Moxifloxacin	8	4.9
Levofloxacin	2	1.2
Ciprofloxacin	2	1.2
Lipopeptides	8	4.9
Daptomycin	8	4.9
Polymyxins	5	3.0
Colistin	5	3.0
Sulfonamide derivatives	5	3.0
Timetoprim/sufometaxazole	5	3.0
Lincosamides	2	1.2
Clindamycin	2	1.2
Aminoglycosides	1	0.6
Amikacin	1	0.6
Fluoroquinolones	12	7.4
Moxifloxacin	8	4.9

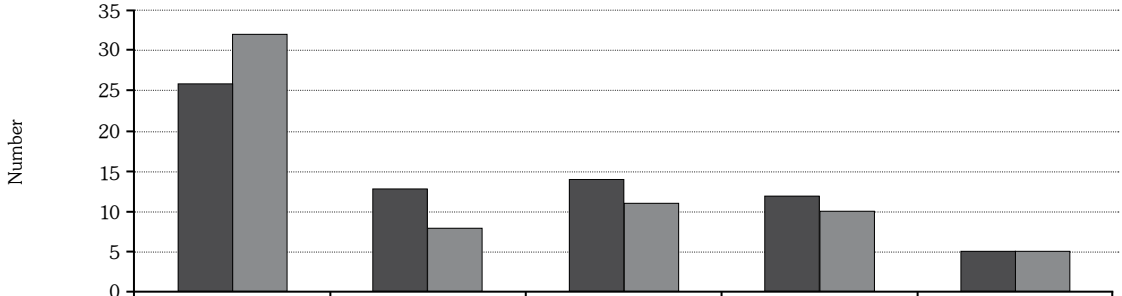
against the reproducing factor in 32.7% of patients, whereas the reproducing factor was resistant to empiric therapy in 42.6%. Empirically initiated antibiotic medication was replaced in 46.9% of patients, while the initial therapy was continued in 53.1%.In the ICU, patients with any infectious disease had a 55.6% mortality rate. 44.4% of ICU patients were transferred to other clinics after treatment.

The antimicrobial activities of antibiotics commonly used in empiric therapy at the ICU were examined When resistance rates were analyzed, it was found that the antibiotic with the highest activity rate was linezolide (43.7%), and the antibiotic with the highest resistance rate was meropenem (44.4%). In 40.1% of cultures (blood or trachea aspirate) of patients hospitalized with pneumonia, no factors were isolated. Acinetobacter baumannii was determined to be the most commonly isolated bacteria (28%). In 37.3% of patients, the agent could not be produced in tracheal aspirate cultures. E. coli was the most common proliferating bacteria in patients with sepsis and UTI, accounting for 30.6% and 28.5%, respectively.

Antibiotic resistance rates of *A. baumannii*, were examined. Acinetobacter baumannii was found to be completely resistant to the antibiotics ampicillin-sulbactam, ceftazidime, cefriaxone, vancomycin, daptomycin. Patients who were administrated meropenem, linezolide, and piperacillin-tazobactam had resistance rates of

Table 3. Distribution of growing agents by culture

	Tracheal aspiration culture	Blood culture	Urine culture	Wound culture	Stool culture
	n	n	n	n	n
Acinetobacter baumannii	32	18	1	6	0
Escherichia coli	2	9	25	3	0
Klebsiella pneumoniae	9	10	9	2	0
Pseudomonas aeruginosa	10	3	2	1	0
Streptococcus pneumoniae	10	0	0	0	0
Candida albicans	0	2	8	0	0
Enterococcus faecium	0	0	4	0	0
Stenotrophomonas maltophilia	2	0	1	0	0
Proteus mirabilis	0	0	3	0	0
Staphylococcus epidermis	0	3	0	0	0
Staphylococcus hominis	0	1	0	0	0
Staphylococcus aureus	0	1	0	0	0



	Meropenem	Piperacillin	Linezolid	Clarithromycin	Ceftriaxone
Sensitive	26	13	14	12	5
Resistant	32	8	11	10	5

Figure 2. Sensitivity and resistance numbers of frequently used antibiotics.

93.8%, 85.7%, and 83.3%, respectively (Figure 3). The resistance rate of E. coli, the second most commonly reproducing bacteria, to ceftriaxone and meropenem was found to be 25% and 14.3%, respectively. Sensitivity to meropenem, ampicillin-sulbactam, and piperacillin-tazobactam -the most frequently used antibiotics in the empiric therapy of patients with *S. pneumonia*- was found to be 100%.

The reproductive rates of *A. baumannii* differed among patients who had undergone invasive MV, patients who had undergone non-invasive MV, and patients who had not undergone MV; the reproductive rate of *A. baumannii* in the group who had undergone invasive MV was 35.6%, while the reproductive rate of *A. baumannii* in the other groups was 18.7%. The difference between the groups was statistically significant (p=0.016).

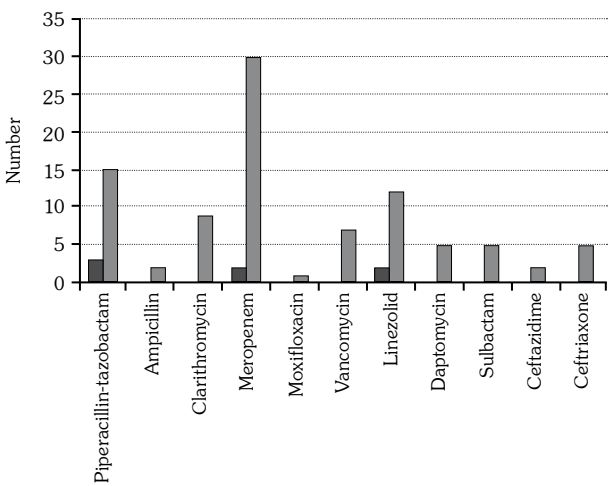


Figure 3. *Acinetobacter baumannii* resistance rates.

Patients in the ICU with factors reproducing in the culture that were sensitive to empiric antibiotic therapy had a 45.3% mortality rate, while patients in the ICU with factors reproducing in the culture that was resistant to empiric antibiotic therapy had a 66.7% mortality rate. A significant difference was found between the two groups (p=0.018).

DISCUSSION

Because of bacterial resistance, nearly half of the patients in this trial had their empiric antibiotic medication changed, and the death rate in the resistant group was greater than in the sensitive group.

When we look at the ICU inpatient profile, we notice factors like age, comorbidity, overuse of invasive MV treatment and other interventional procedures, and misuse of broad-spectrum antibiotics. Because of bacterial resistance, nearly half of the patients in this study had their empiric antibiotic therapy adjusted, and the mortality rate in the resistant group was higher than in the sensitive group. Because *A. baumannii* is the most commonly reproducing bacterium and is more than 90% resistant even to carbapenems, one of the broadest-spectrum antibiotics, this reveals that nosocomial infection factors are a major concern in our ICU, despite the fact that the patients enrolled in this study were initially hospitalized due to community-based infections. The frequent occurrence of reproducing factors in follow-up suggests that antibiotic use, caution

during invasive procedures, disinfection methods in intensive care, duration of hospitalization, and regular medical staff training should all be revised. Invasive MV patients have a higher prevalence of Acinetobacter baumannii than non-invasive MV. Adult ICUs have higher rates of mortality and morbidity, as well as higher treatment costs for resistant microorganisms than other hospital units. Optimization of antibiotic strategies and rational use of antibiotics reduces mortality, morbidity, duration of stay in intensive care and treatment costs.[9,10]

In developed countries, life expectancy and population growth are gradually increasing. In Turkey, 7.7 % of the population is over the age of 65.[11] The fact that a patient is over the age of 70 is a risk factor for infections in an ICU.[12] The mean age of patients in this study was 74.7 years. In our study, 77.1% of the patients were over the age of 70. A study conducted by the Turkish Ministry of Health in 2015 involving 5,784 patients found that 41.5% of patients over the age of 65 were admitted to an ICU.[13] In the same study, the mortality rate of ICU patients was 18.5% and 55.6% in this study. In the Turkish Ministry of Health study, all patients were enrolled regardless of their diagnosis, however, in this study, only patients hospitalized due to infectious diseases were enrolled. It is remarkable that the Internal Medicine ICU of our hospital has a higher mean patient age and mortality rate.

Comorbidities and age are important risk factors for both community-based infections and the development and prognosis of nosocomial infections. According to studies, hypertension is the most common comorbidity in intensive care patients.[14,15] Hypertension was also the most common comorbidity (50%) in patients admitted to the Internal Medicine ICU in our study. 95% of patients had at least one accompanying comorbidity, which was compatible with literature that notes comorbidities as one of the important factors that could affect hospitalization in the ICU.

Infections have an important place among the reasons for hospitalization of patients in an ICU. According to literature data, infectious diseases are the cause of hospitalization at rates between 22-35% in ICU hospitalization. Community-acquired pneumonias are also the most common infectious diseases.[16,17] Community-acquired pneumonia (46.2%) was also the most common cause of hospitalization in our study, supporting the literature data.

In an ICU, age, immunosuppression, shock or coma, length of stay, invasive MV application and duration, and other invasive procedures are all shown to be risk factors for infection.[18] In our study, 53.09% of the patients had undergone invasive MV procedures for at least 48 h. 41.9% of the patients had not undergone MV procedure, and 4.9% of the patients had undergone a non-invasive MV procedure. In our study, we found a statistically significant difference in the reproduction rates of *A. baumannii*, one of the most common causes of nosocomial infections, among patients who had undergone invasive MV versus patients who had not. This result is consistent with data from the literature.

A study conducted by Kiremitçi et al.[19] found that more than half of the factors isolated in the ICU were GN bacteria and a third were GP bacteria. The frequency of reproductive rates in cultures also corresponds to the literature data in our study, but, remarkably, the reproductive rates of GN bacteria were even higher. It was observed that 83.6% of the factors that reproduce in our hospital's Internal Medicine ICU were GN bacteria, 10.7% were GP bacteria, and 5.6% were fungi. The infectious agents in the ICU were as follows in order of frequency among GN bacteria:[20] *A. baumannii*, *P. aeruginosa, K. pneumoniae*, and *E. coli. Staphylococcus aureus (S. aureus)* was the most commonly isolated bacteria among the GP bacteria. Again, in a study conducted by Büyüktuna et al.,[21] *P. aeruginosa* ranked first in GN, followed by *A. baumannii* and *K. pneumoniae*. Staphylococcus aureus was the most commonly isolated bacteria among the GP bacteria. Reproducing agents in our study were determined as follows in order of frequency: *A. baumannii*, *E. coli, K. pneumoniae, P. aeruginosa, S. pneumoniae*. The most commonly reproducing GP bacterium in our study was *S. pneumoniae*. It is believed that *E. coli, K. pneumoniae, P. aeruginosa, S. pneumoniae* may have been reproduced more frequently in contrast to the literature as only community-acquired infectious diseases were included in our study.

The etiologic agent was isolated in culture in 22-35.8% of community-acquired pneumonia studies conducted in our country. When these agents were examined, it was found that *S. pneumoniae*, Haemophilus influenza, and Moraxella catarrhalis constitute 85% of etiologic agents.[22] In our study, reproduction was achieved in cultures in 59.9% of cases clinically diagnosed with pneumonia. The fact that cultures are routinely examined in ICU and carried out at frequent intervals increases the likelihood that the factor will be isolated. However, in our study, unlike literature, *A. baumannii* was the most common pneumonia factor (28%). It was observed as *S. pneumoniae, K. pneumoniae, P. aeruginosa* when examined in order of frequency. Although the frequent occurrence of *A. baumannii* in our study indicates the development of nosocomial pneumonia or ventilation-related pneumonia, incidence studies of nosocomial pneumonia and ventilation-related pneumonia can be conducted using data such as the duration of patients' stay in the ICU and the frequency of invasive attempts. Higher reproductive rates of *A. baumannii* in patients who had undergone invasive MV than in patients who had not supported our interpretation. *E. coli* is the most common cause of community-acquired UTI, accounting for 80-85% of infections, followed by *Staphylococcus saprophyticus* (15%). The most common factor in hospital-acquired UTI is E. coli with a rate of 50%. Other important factors of hospital-acquired infections are GN bacilli, *Enterococcus faecalis*, and other enterococci.[23,24] *E. coli* was the most prevalent factor among the patients in our study, and, it was also the most common factor in the literature (28.5%). When we looked at other isolated factors in order of frequency, we found *K. pneumoniae* (20%), Candida (11.4%), and Proteus (5.7%), respectively. *E. coli*, which is the most common factor of community-acquired and nosocomial UTI, was isolated to a lesser extent in our study compared to the literature. *K. pneumoniae* and Proteus, which are complicated UTI and nosocomial UTI factors, have been observed more frequently than in the literature.

The combination of sulbactam and ampicillin, a beta-lactamase inhibitor, is one of the antibiotics with bactericidal activity against *A. baumannii* isolates.[25,26] In our study, it was found that all *A. baumannii* strains that were reproduced using ampicillin-sulbactam were resistant, and no clinical response was achieved in patients. Carbapenems, one of the groups with the broadest spectrum among all antibiotics, are also an important option in the treatment of *A. baumannii*. However, due to the extensive use of these antimicrobials and hospital-related outbreaks, resistance rates have increased to 90% in recent years.[27] In our study, the rate of *A. baumannii* resistance was found to be 93.7% in accordance with the literature data in patients using meropenem. The rate of *A. baumannii* resistance was also found to be 83.3% in patients using piperacillin-tazobactam. It does not seem sufficient to reduce the *A. baumannii* treatment to only antibiotic therapy, where high resistance rates to antibiotherapies commonly used in empiric therapy are observed. It is thought that great care should be taken to minimize risk factors for *A. baumannii* infections such as central venous catheters, foley probes, invasive MV duration, frequent use of broad-spectrum antibiotics such as carbapenems, and use of hypnosedatives, all of which are preventable, and that the best disinfection methods should be used.

All antibiotics used in empiric therapy were found to be sensitive to reproducing pneumococci in our study, including ampicillin-sulbactam, piperacillin-tazobactam, and meropenem which are all empirically initiated. It shows that in community-acquired pneumonias admitted to the ICU, starting aminopenicillins instead of broad-spectrum antibiotics such as carbapenem or antipseudomonal penicillin will lead to less use of broad-spectrum antibiotics. Furthermore, it is shown that in pneumococcal pneumonia, all of the reproducing bacteria are sensitive to aminopenicillins. In these patients, it is believed that the use of broad-spectrum antibiotics, such as carbapenems or piperacillin-tazobactam, should be less used less often. Carbapenems, on the other hand, are one of the most broad-spectrum antibiotics, with extremely high sensitivity rates in the treatment of pathogens including *A. baumannii*, *K. pneumoniae*, and *P. aeruginosa*. Antibiotics' broad-spectrum action does not imply that they are also very potent.[28] As mentioned in the literature, if the causative

agent is unknown, antibiotic therapy with a broad spectrum of action should be initiated to cover microorganisms that may be potential causative agents, and methods of isolating the agent should be performed. After the factor is isolated, it is believed that it is required to switch to an antibiotic treatment that targets the factor. This reduces the rate at which resistance is developed, as well as reduces the cost of treatment.[29]

A study conducted by Kollef et al.[29] in an ICU found a significant association between inadequate treatment and mortality, both in community-acquired infections and in hospital-acquired infections. Inadequate antibiotic therapy is defined as the administration of antibiotics that are only slightly effective or ineffective against the infectious agent *in vitro*.[30] Furthermore, a single-center study also showed an association between inadequate treatment and mortality.[31] In our study, the mortality rates between the empiric therapy sensitive group and the empiric therapy-resistant group were compared; the mortality rate of the therapy-resistant group was statistically significantly higher, supporting the literature data.

The main limitation of this study is that it is retrospective. Examinations in this study are based on the notes and epicrisis kept by the infection's physician or subsequent physicians, and the patients only from the Internal Medicine ICU were included.

In conclusion, in the Internal Medicine ICU, the mortality of patients who were resistant to antibiotic therapy was higher than that of sensitive. Antibiotics were replaced in 46% of inpatients because of bacterial resistance. Antibiotics, especially aminopenicillins, were observed to be effective against pneumococci, a cause of community-acquired pneumonia. However, factors such as *A. baumannii* and *K. pneumoniae*, which reproduce the most frequently showed more than 90% resistance to even the broadest-spectrum antibiotics, such as carbapenems. Dual combinations (rifampicin-colistin, carbapenem-colistin, etc.) can be tried, but due to *A. baumannii*'s high resistance, we were unable to identify an antibiotic therapy that we could recommend for treatment. The shortest possible hospitalization period, the shortest intubation period, the application of catheters and other interventional procedures only in the presence of absolute indications, and the administration of broad-spectrum antibiotic therapies for the shortest time are some of the measures used to combat these infections. Further studies on this problem, in our opinion, would increase awareness of the struggle against infections.

Declaration of conflicting interests

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