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Comparison of the Effectiveness of Piperacillin-Tazobactam and Carbapenems in Nosocomial Infections with Extended-Spectrum Beta-lactamase-Producing *Escherichia coli* and *Klebsiella pneumoniae*

Genişlemiş Spektrumlu Beta-laktamaz Üreten *Escherichia coli* ve *Klebsiella pneumoniae* ile Gelişen Nozokomiyal Enfeksiyonlarda Piperasilin-Tazobaktam ve Karbapenemlerin Etkinliğinin Karşılaştırılması

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Abstract

Introduction: Infections with extended-spectrum beta-lactamase (ESBL)-producing strains are seen at increasing rates, resulting in increased morbidity, mortality, length of hospitalization, and cost. Effective and safe treatment of these infections is important. The aim of this study was to compare the effectiveness of piperacillin-tazobactam (PTZ) and carbapenems in nosocomial infections with ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* in hospitalized patients.

Materials and Methods: This study was performed retrospectively on patients who were infected with ESBL-producing *E. coli* and *K. pneumoniae* while hospitalized in Ankara Atatürk Tranining and Research Hospital between 2014 and 2017. Both PTZ- and carbapenem-susceptible isolates were included in the study. Patients with signs of infection who were older than 18 years, hospitalized for at least 48 hours, and received PTZ or carbapenem therapy were included in the study. Patients who received PTZ and carbapenem antibiotics consecutively in same infectious episode, received another antibiotic active against ESBL-producing microorganisms, received the selected antibiotic for less than 48 hours, or had polymicrobial infection were excluded from the study. Demographic characteristics, comorbid diseases, antibiotics used and their dose/duration, mechanical ventilation, presence of central catheter, clinical and microbiological responses to treatment, and end-of-treatment and 30-day mortality were recorded and compared.

Results: Of the total 113 patients, 60 (53.1%) were male and the mean age was 66.14±18.2 years. Of the patients, 73.5% had *E. coli* and 26.5% had *K. pneumoniae*. Seventy patients (61.9%) received carbapenem and 43 patients (38.1%) received PTZ treatment. Microbiological eradication rate was 71.7% (43/60) in patients with control cultures. Clinical response was observed in 72.6% of the cases. The overall mortality rate was 31.0% (n=35). There were no significant differences between the groups in clinical and microbiological response (p=0.055; p=0.303) or end-of-treatment and 30-day mortality (p=0.180, p=0.288). Age and bacteremia was found to be independent risk factors for mortality (p=0.006 for both).

Conclusion: PTZ is an important alternative for infections caused by ESBL-producing microorganisms. In recent years, the need for rational antibiotic use has increased and carbapenem-sparing treatments have became more important. Piperacillin-tazobactam is one of the best alternatives and has comparable effectiveness in infections caused by ESBL-producing *E. coli* and *Klebsiella* spp.

Keywords: Extended-spectrum beta-lactamase, carbapenems, piperacillin-tazobactam, *Escherichia coli, Klebsiella pneumoniae*

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Öz

Giriş: Genişlemiş spektrumlu beta-laktamaz (GSBL) üreten suşlarla gelişen enfeksiyonlar artan oranlarla görülmekte, morbidite ve mortalitede, hastanede yatış süresinde ve maliyette artış ile sonuçlanmaktadır. Gelişen enfeksiyonların etkin ve güvenli tedavisi önemlidir. Bu çalışmada, yatan hastalarda GSBL üreten *E. coli* ve *K. pneumoniae* ile gelişen nozokomiyal enfeksiyonlarda piperasilin-tazobaktam (PTZ) ve karbapenemlerin etkinliğinin karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Bu çalışmada Ankara Atatürk Eğitim ve Araştırma Hastanesi'nde 2014-2017 yılları arasında yatan, GSBL üreten *E. coli* ve *K. pneumoniae* ile enfekte hastaların sonuçları retrospektif olarak değerlendirildi. Çalışmaya hem PTZ hem karbapenemlere duyarlı olan üremeler dahil edildi. Enfeksiyon bulguları bulunan, 18 yaşından büyük, en az 48 saattir hastanede yatan, PTZ veya karbapenem tedavisi başlanan hastalar çalışmaya dahil edilirken aynı epizodda PTZ ve karbapenem grubu antibiyotikleri ardışık olarak alan, GSBL üreten mikroorganizmalara etkin başka bir antibiyotik kullanan, seçilen antibiyotiği 48 saatten az süre alan hastalar ve polimikrobiyal enfeksiyonu bulunan hastalar çalışma dışı bırakıldı. Hastaların demografik özellikleri, komorbid hastalıkları, aldığı antibiyotikler, doz ve süreleri, mekanik ventilasyon ve santral kateter varlığı, tedaviye klinik ve mikrobiyolojik yanıtları, tedavi sonu ve 30. gün mortalite verileri kaydedilerek karşılaştırmalı değerlendirildi.

Bulgular: Toplam 113 hastanın 60'ı (%53,1) erkek, yaş ortalaması 66,14±18,2 yıl idi. Hastaların %73,5'inde etken *E. coli*, %26,5'inde *K. pneumoniae* idi. Hastaların 70'i (%61,9) karbapenem, 43'ü (%38,1) PTZ tedavisi almıştı. Kontrol kültür alınan hastaların %71,7'sinde (43/60) mikrobiyolojik eradikasyon mevcuttu. Olguların %72,6'sında klinik yanıt izlendi. Kaba mortalite hızı %31,0 (35) idi. Klinik ve mikrobiyolojik yanıt (p=0,055; p=0,303), tedavi sonu ve 30 günlük mortalite açısından (p=0,180, p=0,288) gruplar arasında anlamlı fark saptanmadı. Yaş ve bakteriyemi varlığı mortalite için bağımsız risk faktörü olarak saptandı (her ikisi için p=0,006).

Sonuç: Sonuçta, PTZ, GSBL üreten mikroorganizmalar ile gelişen enfeksiyonların tedavisinde önemli tedavi seçeneklerindendir. Antimikrobiyal ajanların uygun kullanımına duyulan ihtiyacın arttığı, karbapenem koruyucu tedavilerin ön plana çıktığı günümüzde, PTZ en iyi alternatiflerden biridir ve GSBL üreten *E. coli* ve *Klebsiella* spp. enfeksiyonlarında kıyaslanabilir etkinliğe sahiptir.

Anahtar Kelimeler: Genişlemiş spektrumlu beta-laktamaz, karbapenem, piperasilin tazobaktam, *Escherichia coli, Klebsiella pneumoniae*

Introduction

Infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* strains have become an increasingly important public health problem in recent years[1]. Higher morbidity and mortality result in prolonged hospitalization and increased cost[2]. It is critical to balance the effective and reliable treatment of infections caused by these agents with the principles of rational antibiotic use[3].

Escherichia coli and *Klebsiella pneumoniae* are the two most common ESBL-producing species, and are frequently seen in common infections such as urinary tract infections, pneumonia, and bacteremia[2,4,5]. Delays in appropriate antimicrobial treatment due to multidrug resistance in ESBL-producing microorganisms result in clinical failure and increased mortality[6,7]. Extended-spectrum beta-lactamase - type enzymes are in group A according to the Ambler classification and are inhibited by beta-lactamase inhibitors such as clavulanic acid[8]. This property is frequently exploited in phenotypic testing to detect ESBL-producing strains[9]. Extended-spectrum beta-lactamase enzymes can degrade penicillin, oxyimino-cephalosporins, and monobactams. In addition, ESBL-producing *Enterobacteriaceae* can often be resistant to other classes of antibiotics such as fluoroquinolones, aminoglycosides, trimetoprim-sulfamethoxazole, and tetracyclines[1,10]. Therefore, reliable antibiotic options are limited[11,12]. Beta-lactam/beta-lactamase inhibitor combinations have been used in the treatment of infections caused by ESBL-producing strains and their treatment efficacy has been tested. Clinical failures have been reported, and they were attributed to the inoculum effect. However, the inoculum effect may be overcome in regions such as the urinary and biliary tracts, where piperacillin-tazobactam (PTZ) can reach high concentrations and be an effective treatment[13]. Carbapenems are not hydrolyzed by ESBL enzymes. Due to their safety profile and high efficacy, they are used as first-line agents in invasive infections caused by ESBL-producing strains, especially bloodstream infections[9].

Various studies have shown that PTZ and carbapenems can have comparable efficacy in the treatment of ESBL infections. However, the applicability of these data is limited due to numerous factors, such as varying foci of infections caused by ESBL-producing microorganisms, differences in treatment dosage and duration, treatment with other antibiotics that are effective against ESBL-producing microorganisms, and differences in study endpoints[14]. Sharing real-world data on the effectiveness of treatments used for ESBL-producing *Enterobacteriaceae* strains will contribute to our knowledge with regards to an optimum therapeutic approach.

The aim of this study was to compare the clinical and microbiological effects of PTZ and carbapenem antibiotics in ESBL-producing *E. coli* and *K. pneumoniae* infections developed by inpatients in our hospital.

Materials and Methods

Study Design

In this study, we retrospectively compared the effectiveness of PTZ and carbapenem group antibiotics used as monotherapy

in nosocomial infections caused by ESBL-producing *E. coli* and *Klebsiella* spp. among inpatients being treated in our hospital. Approval for the study was obtained from Ankara Yıldırım Beyazıt University Clinical Research Ethics Committee (approval date: 24.10.2018, no: 214). Due to the retrospective study design, informed consent form was not sought.

Patient Selection

Patients infected with ESBL-producing, PTZ- and carbapenem-sensitive *E. coli* and *K. pneumoniae* strains in Ankara Yıldırım Beyazıt University Hospital between 2014 and 2017 were evaluated according to the inclusion criteria. Strains that were sensitive to both PTZ and carbapenems were included in the study. Patients with clinical signs of infection who were older than 18 years of age, hospitalized for at least 48 hours, and treated with PTZ or carbapenem (ertapenem, meropenem, imipenem) were included in the study. A single episode of infection was included in the analysis for each patient. Patients who used PTZ and carbapenem group antibiotics consecutively during the same episode of infection, used another antibiotic effective against ESBL-producing microorganisms (e.g., quinolones, aminoglycosides, cotrimoxazole, phosphomycin), used the selected antibiotic for less than 48 hours, or had polymicrobial infection were excluded from the study (Figure 1). If patients exhibited signs and symptoms of systemic infection together with signs specific to a focus of infection, treatment was initiated empirically and later adjusted according to agent and susceptibility when culture results became available. Microbiological identification was performed using conventional methods. Antibiotic susceptibility testing was performed using Vitek-2 (bioMerieux, France) and ESBL production in all *E. coli* and *K. pneumoniae* strains was confirmed using disc diffusion and evaluated according to Clinical and Laboratory Standards Institute standards[15]. Because strain-specific minimal inhibitory concentration (MIC) values were not in the patients' records, these could not be evaluated. Demographic and clinical data such as age and sex, history of surgery and comorbidities, antibiotics used, their dosage and duration, mechanical ventilation, central catheterization, and treatment response were recorded in patient information forms. Carbapenem and PTZ were compared in terms of clinical response, microbiological response, and end-of-treatment and 30-day mortality. In patients who did not need dose adjustment for any reason, treatment regimens were as follows: PTZ 4.5 g by 1-hr infusion every 6 hours; meropenem 1 g by 3-hr infusion every 8 hours; imipenem 500 mg by 30-min infusion every 6 hours; ertapenem 1 g by 1-hr infusion every 24 hours.

Infection Definitions

Primary bacteremia: Positive blood cultures that were laboratory-confirmed and not secondary to infection in another part of the body[16].

Pneumonia: Fever and other signs of systemic infection accompanied by presence of rales on physical examination, recent change in sputum volume or character, findings of progressive infiltration and consolidation on radiographic examination, and pathogen growth in cultures of significant sputum sample and deep tracheal aspirate.

Urinary tract infection: Fever and other signs of systemic infection accompanied by dysuria, urinary urgency, suprapubic tenderness, flank pain, and growth of $\geq 10^5$ CFU/ml in clean-catch urine culture.

Intraabdominal abscess: Fever and other signs of systemic infection accompanied by presence of intraabdominal abscess and positive culture of abscess drainage fluid[17-19].

Deep tissue infection: Positive tissue culture with signs of systemic infection was considered deep tissue infection[20], while pathogenic growth in culture of purulent synovial fluid (white blood cell count of 50,000-150,000/mm^3) with signs of systemic infection was considered septic arthritis[21]. Foci of infection were evaluated based on order of frequency. Foci other than primary bacteremia, pneumonia, and urinary tract infection were evaluated together in the "other" category due to small patient numbers in each group.

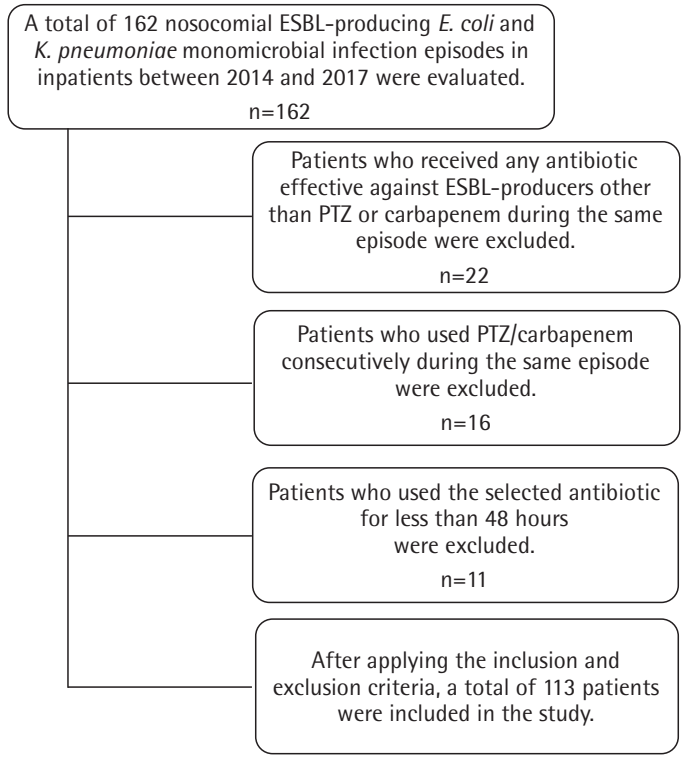

Figure 1. Flow chart of inclusion and exclusion of patients with extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* infections

Treatment Response

Clinical response was defined as resolution of systemic symptoms (e.g., fever and hypotension) and site-specific symptoms within 48-72 hours after initiation of appropriate treatment. Microbiological response was defined as the absence of growth in control cultures obtained no earlier than 48-72 hours after the initiation of appropriate treatment. End-of-treatment mortality and 30-day mortality were recorded and compared between the groups.

Statistical Analysis

SPSS 18.0 software was used for the statistical analysis of the data. As descriptive statistics, number and percentage were calculated for categorical variables and mean, standard deviation, median, and minimum-maximum values were used for numerical variables. Chi-square test was used for comparison of categorical variables between two groups and Fisher's exact test was used when the assumptions for chi-square test were not met. Continuous variables were compared using Student's t-test, and Mann-Whitney U test was used when parametric test conditions were unmet. Backward logistic regression analysis was used for multivariate analysis. A p value <0.05 was considered statistically significant.

Results

Of the total 113 patients included in the study, 60 (53.1%) were men and the mean age was 66.14±18.2 years. History of surgery within the last 3 months was present in 58.4% of the patients. The most common comorbidity was malignancy (24.8%). Of the patients with malignancy, none had hematological malignancy. The causative pathogen was *E. coli* in 73.5% of the patients and *K. pneumoniae* in 26.5%. The most common primary sites of infection were the urinary tract (37.2%), bloodstream (15.9%), and lung (15.9%). Bacteremia was detected in 29.2% of the patients. Seventy patients (61.9%) were treated with carbapenems, while 43 (38.1%) received PTZ. Of 60 patients (53.1%) who had control cultures, 43 (71.7%) showed microbiological eradication. Clinical response was observed in 72.6% of the patients. The crude mortality rate was 31% (35). The patients' demographic characteristics and treatment responses are summarized in Table 1.

Table 1. Demographic and treatment characteristics of the patients (n=113)

Age, mean±SD (min.-max.)		66.14±18.2 (18-99)
Sex, % (n)	Male	53.1% (60)
	Female	46.9% (53)
Comorbidities, % (n)	Surgical history	58.4% (66)
	Malignancy	24.8% (28)
	Diabetes mellitus	21.2% (24)
	Chronic obstructive pulmonary disease	8.8% (10)
	Immunosuppression	8.8% (10)
Invasive procedure, % (n)	Central venous catheter	53.1% (60)
	Mechanical ventilation	38.1% (43)
Isolated pathogen, % (n)	*E. coli*	73.5% (83)
	Klebsiella spp.	26.5% (30)
Primary infection site, % (n)	Bloodstream	15.9% (18)
	Urinary tract	37.2% (42)
	Lung	15.9% (18)
	Other	30.9% (35)
Bacteremia, % (n)	Present	29.2% (33)
Control culture, % (n)	Present	53.1% (60)
Microbiologic response (n=60), % (n)	Present	71.7% (43)
Clinical response, % (n)	Present	72.6% (82)
End-of-treatment mortality, % (n)	Deceased	31.0% (35)
	Surviving (discharged or transplant)	69.0% (78)
30-day mortality (n=91), % (n)		40.6% (37)

SD: Standard deviation, min.: Minimum, max.: Maximum

Other than median age and prevalence of central venous catheter, the groups were similar in terms of comorbidities, demographic characteristics, isolated pathogen, infection site, and prevalence of bacteremia. Univariate analysis revealed no significant differences in clinical and microbiological response, treatment duration, mortality, or 30-day mortality between the groups (Table 2). No difference was detected between the treatment groups in terms of mortality (Table 3).

Table 2. Comparison of demographic, clinical, and laboratory characteristics and treatment responses in the piperacillin–tazobactam and carbapenem groups

	PTZ (n=43)	Carbapenem (n=70)	p value
Age, years (median, min.–max.)	72 (32-91)	67 (18-99)	<0.05
Sex, male, % (n)	46.5% (20)	57.1% (40)	0.183
Surgical history, % (n)	58.1% (25)	58.6% (29)	0.559
COPD, % (n)	11.6% (5)	7.1% (5)	0.312
Malignancy,%(n)	27.9% (12)	22.9% (16)	0.350
Immunosuppression, % (n)	2.3% (1)	12.9% (9)	0.051
Diabetes mellitus, % (n)	20.9% (9)	21.4% (15)	0.573
Central catheter, % (n)	67.4% (29)	44.3% (31)	0.013
Mechanical ventilation, % (n)	41.9% (18)	35.7% (25)	0.324
Isolated pathogen, % (n)			0.315
E. coli	69.8% (30)	75.7% (53)	
Klebsiella spp.	30.2% (13)	24.3% (17)	
Infection site, % (n)			0.452
Primary bacteremia	13.9% (6)	17.1% (12)	
Pneumonia	18.6% (8)	14.3% (10)	
Urinary tract infection	44.2% (19)	32.9% (23)	
Other	23.2% (10)	35.7% (25)	
Bacteremia (primary and secondary), % (n)	32.6% (14)	27.1% (19)	0.342
Clinical response, % (n)	62.8% (27)	78.6% (55)	0.055
Control culture, % (n)	46.5% (20)	57.1% (40)	0.253
Microbiologic response, % (n)	65.0% (13)	75.0% (30)	0.303
Mortality, % (n)	37.2% (16)	27.1% (19)	0.180
30-day mortality (n=91), % (n)	43.2% (16) Piperacillin-tazobactam (n=37)	38.8% (21) Carbapenem (n=54)	0.288

COPD: Chronic obstructive pulmonary disease, PTZ: Piperacillin-tazobactam, min.: Minimum, max.: Maximum

Table 3. Mortality rates by infection site

	Piperacillin-tazobactam	Carbapenem	p value
Pneumonia (n=18)			
Deceased (n=9)	6/8 (75%)	3/10 (30%)	0.077
Survived (n=9)	2/8 (25%)	7/10 (70%)	
Urinary tract infection (n=42)			
Deceased (n=13)	6/19 (31.6%)	7/23 (30.4%)	0.599
Survived (n=29)	13/19 (68.4%)	16/23 (69.6%)	
Primary bacteremia (n=18)			
Deceased (n=10)	3/6 (50%)	7/12 (58.3%)	>0.05
Survived (n=8)	3/6 (50%)	5/12 (41.6%)	
Bacteremia (primary and secondary) (n=33)			
Deceased (n=17)	5/14 (35.7%)	12/19 (63.2%)	0.114
Survived (n=16)	9/14 (64.3%)	7/19 (36.8%)	

Discussion

ESBL-producing microorganisms are among the more difficult to treat pathogens due to the limited antibiotic options. The incidence of infection caused by ESBL-producing *E. coli* and *K. pneumoniae* strains has increased in recent years[22,23]. Carbapenems are frequently used in the treatment of infections caused by these microorganisms[24]. An increase in the frequency of carbapenem-resistant gram-negative bacteria has been observed over the last decade due to widespread carbapenem use[25]. Recent emphasis on the rational use of antimicrobial agents has necessitated the investigation of alternatives to carbapenems for the treatment of infections with ESBL-producing microorganisms[26]. Piperacillin-tazobactam, a broad-spectrum drug active against gram-negative bacilli, is one of the antimicrobial agents most commonly used as an alternative to carbapenem and is a beta-lactam/beta-lactamase inhibitor effective against most ESBL-producing strains[27]. Different studies investigating the efficacy of PTZ and carbapenem in the empirical treatment of ESBL-producing gram-negative bacteremia have yielded conflicting results[14].

In a study comparing empirical PTZ and carbapenem therapy in bacteremia caused by ESBL-producing *E. coli* and *K. pneumoniae* in a large series of 394 patients, no difference was observed between the two groups in terms of 30-day mortality or length of hospital stay, whereas the PTZ group showed much lower rates of multidrug-resistant microorganisms and fungal infections compared to the carbapenem group[6]. In another study performed in Turkey, no significant difference in 7-day and 30-day mortality rates was detected between the PTZ and carbapenem groups in a series 94 patients with ESBL-producing *E. coli* and *K. pneumoniae* bacteremia[28]. Unlike these studies, Tamma et al.[14] reported that carbapenems were more effective in the treatment of infections caused by ESBL-producing microorganisms. They retrospectively compared the effectiveness of empirical PTZ and carbapenem therapy in 331 cases of bacteremia caused by ESBL-producing microorganisms and found that the use of empirical PTZ increased the mortality rate by 1.92-fold. Therefore, they emphasized that carbapenem should be preferred in bacteremia caused by ESBL-producing pathogens in order to overcome the inoculum effect observed with gram-negative bacteria. Unlike these studies, we observed no significant difference between the PTZ and carbapenem groups in terms of mortality.

Most previous studies comparing these two groups of drugs involved bacteremic patients; those that include other infection sites are limited in number[3,9,29]. The present study included all infections caused by ESBL-producing microorganisms and evaluated the effectiveness of both groups of antibiotics in all nosocomial infections, including urinary tract infections, pneumonia, and bacteremia. Due to differences in the pharmacodynamic and pharmacokinetic characteristics of antibiotics, optimum antibiotic choices must be determined for the treatment of infections other than bacteremia. The review by Tamma and Rodriguez-Bano[4] analyzed studies evaluating beta-lactam antibiotics other than carbapenem in ESBL-producing *Enterobacteriaceae* infections and showed that PTZ can be considered a noteworthy treatment option in mild/moderate urinary and biliary tract infections, especially when the MIC with PTZ is <4 µg/ml. In the same study, it was stated that until more data are available, carbapenem antibiotics should be preferred for severely critical infections in which high inoculum effect may be observed and for infections with higher PTZ MIC value. Due to the lack of MIC values for the isolates in our study, the effect of MIC on treatment response could not be evaluated according to treatment option. In a meta-analysis of 35 studies, carbapenems were compared to other antibiotics active against ESBL-producing *Enterobacteriaceae* and it was reported that beta-lactam/beta-lactamase inhibitors were no less effective as definitive treatment than carbapenems if the microorganism is susceptible[30].

The main limitations of our study are the small patient size, not performing power analysis during study design, the lack of patients' pre-treatment APACHE II scores, which precluded evaluation of disease severity in the patient group, and the insufficient number of deceased patients for an analysis of independent risk factors for mortality. The exclusion of patients who were treated with other antibiotics active against ESBL-producing microorganisms was the most important reason for the small patient sample. Another limitation is that a comparison among the carbapenems (imipenem, meropenem, ertapenem) could not be performed because small numbers of patients were treated with each one. Furthermore, the majority of the patient population had diseases that required surgery. The two main factors in this were the high proportion of patients being followed for malignant etiologies and the fact that our hospital performs a large number of trauma surgeries. Moreover, another limitation of our study is that due to the small and heterogeneous patient groups for each infection focus and the absence of MIC values, the relationships between these factors and treatment response and mortality could not be evaluated.

Conclusion

PTZ is one of the most important alternatives to carbapenems for the treatment of ESBL-producing microorganism infections. A growing number of studies demonstrate that PTZ can be as effective as carbapenems. In our study, there was no difference between PTZ and carbapenem therapy in terms of treatment response or mortality, and PTZ was found to be as effective as carbapenems. With the growing need for rational

use of antimicrobial agents and the increasing importance of carbapenem-sparing treatments, PTZ is currently one of the best alternative agents and has comparable effectiveness to carbapenems against ESBL-producing *E. coli* and *Klebsiella* spp. However, to determine the optimum treatment of ESBL-producing *E. coli* and *Klebsiella* bacteremia and nonbacteremic infections, much larger studies with more homogenously selected patient series are needed.

Ethics

Ethics Committee Approval: Approval for the study was obtained from Ankara Yıldırım Beyazıt University Clinical Research Ethics Committee (approval date: 24.10.2018, no: 214).

Informed Consent: Due to the retrospective study design, informed consent form was not sought.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.A., B.K., A.K.K., İ.H., Concept: M.A., B.K., H.R.G., Design: M.A., B.K., H.R.G., Data Collection or Processing: M.A., D.A., İ.H., A.K.K., Analysis or Interpretation: M.A., B.K., M.A.T., Literature Search: M.A., B.K., Writing: M.A., B.K.

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