Araştırma Makalesi / *Research Article*

İzmir Eğitim ve Araştırma Hastanesi Tıp Dergisi (Medical Journal of İzmir Hospital) 23 (2): 75-81, 2019

BİR EĞİTiM VE ARAŞTIRMA HASTANESİNDE *KLEBSİELLA PNEUMONİAE* KAN DOLAŞIMI ENFEKSİYONLARININ KLİNİK ÖZELLİKLERİ VE MORTALİTENİN DEĞERLENDİRİLMESİ

EVALUATION OF CLINICAL CHARACTERISTICS AND MORTALITY OF *KLEBSIELLA PNEUMONIAE* BLOODSTREAM INFECTIONS IN A TEACHING HOSPITAL

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Anahtar Sözcükler: *Klebsiella pneumoniae*, kan dolaşımı enfeksiyonu, karbapenem direnci, mortalite

Keywords: *Klebsiella pneumoniae*, bloodstream infection, carbapenem resistance, mortality

Yazının alınma tarihi: 02.08.2018 Kabul Tarihi: 15.01.2019 Online basım: 01.04.2019

ÖZ

Giriş: *Bu çalışmanın amacı bir eğitim ve araştırma hastanesine kabul edilmiş Klebsiella pneumoniae kan dolaşımı enfeksiyonu (KPKDE) gelişen hastaların klinik özelliklerini ve bu enfeksiyonlara bağlı genel hasta mortalitesi ile ilişkili risk faktörlerini değerlendirmektir.*

Gereç ve Yöntem: *Bu retrospektif kohort çalışması bir eğitim ve araştırma hastanesinde 2012-2016 yılları arasında yatırılarak izlenmiş hastalarla yapılmıştır. Elektronik hasta izleme sistemindeki veriler kaydedilmiştir.*

Bulgular: *Çalışmaya KPKDE gelişmiş toplam 288 hasta dahil edilmiştir ve yaşları 18-104 aralığında olan hastaların 155 (%53.8)'i erkektir. KPKDE'nin çoğu (% 79.5) hastane kaynaklıdır. İkiyüzseksensekiz KPKDE'nin 64'ü (% 22.2) karbapeneme dirençli K. pneumoniae'ye bağlı gelişmiştir. Karbapenem direnci gelişmesi için en önemli risk faktörü antibiyotik kullanımıdır. İkiyüzseksensekiz KPKDE'nin 28 günlük mortalite oranı % 49.6'dır. Yirmisekiz günlük KPKDE mortalitesi için en önemli risk faktörü ciddi sepsistir.*

Sonuç: *Çalışmamızda KPKDE gelişen hastaların çoğunun hastane kaynaklı enfeksiyonlar olduğunu bulduk. Mortalite için en önemli risk faktörü ciddi sepsistir. Enfeksiyon hastalıkları uzmanları, KPKDE gelişen olgularda uygun ampirik tedavinin erken dönemde başlanmasını gözönünde bulundurmalıdır.*

SUMMARY

Introduction: *The aim of this study was to describe clinical characteristics of Klebsiella pneumoniae bloodstream infection (KPBSI) in patients admitted to a teaching hospital and to evaluate the risk factors related to overall patient mortality from those infections.*

Material and Method: *This retrospective cohort study was conducted with hospitalized patients in a training and research hospital between 2012 and 2016. Data were recorded to the electronic patient data monitoring system.*

Result: *A total of 288 patients with KPBSI were identified, and 155 (53.8%) male patients ranging from 18 to 104 (63.4±17.8) years old were included in the study. Most of the KPBSI (79.5%) were acquired in hospitals.*

Among 288 bloodstream infection (BSI), 64 (22.2%) were due to carbapenem-resistant K. pneumoniae. Exposure to antibiotic use was the most important risk factor for develpoment of carbapenem-resistance. The overall 28-day mortality rate of 288 KPBSI was 49.6%. Severe sepsis was the most important risk factor for 28-day mortality for KPBSI.

Conclusion: *We found that most patients with KPBSI in our study had hospital-acquired infections. Severe sepsis was the most important risk factor for mortality. Infectious disease specialists should consider early initiation of appropriate empirical treatment in cases of KPBSI.*

INTRODUCTION

Klebsiella pneumoniae is a pathogen responsible for severe diseases such as pneumonia and urinary tract, soft tissue, and bloodstream infections (BSI) (1–5). During the past two decades, the spread of extended-spectrum b-lactamase (ESBL)-producing enterobacteriacae has resulted in increased use of broad-spectrum antibiotics, particularly carbapenems (6). Carbapenem-resistant *K. pneumoniae* (CRKP) was first reported in 1996 and has become a worldwide problem (7). The first isolate of *K. pneumoniae* with OXA-48 carbapenemase was identified in Turkey and has been reported in several subsequent reports (4, 5).

To date, few studies have investigated rates of carbapenem resistance and the clinical characteristics and mortality of *Klebsiella pneumoniae* bloodstream infections (KPBSI) in Turkey (8–13).

We describe the clinical characteristics of KPBSI and CRKP-related BSI in patients admitted to a teaching hospital in Turkey and focus on the risk factors related to overall patient mortality from those infections.

MATERIAL AND METHOD

This retrospective cohort study was conducted with hospitalized patients in a training and research hospital between 2012 and 2016. Daily surveillance was performed by infectious disease and clinical microbiology specialists and infection control nurses in our hospital, and data were recorded to the electronic patient data monitoring system.

Medical records included demographic characteristics of patients and comorbid diseases; probable sources of infections; and the presence of risk factors such as surgical procedures, mechanical ventilation, central venous catheter, total parenteral nutrition, and use of antibiotics.

Healthcare-associated infections (HAI) were diagnosed according to Centers for Disease Control and Prevention (CDC) criteria, and primary or secondary bacteremia was defined in accordance with CDC definitions (14). American College of Chest Physicians/Society of Critical Care Medicine criteria were used to diagnose severe sepsis and septic shock (15). Use of an adequate dosage of an antibacterial agent with *in vitro* activity against the isolate initiated within 72 h of the onset of infection was considered appropriate treatment.

The medical records of patients with KPBSI were checked, and the clinical characteristics of patients, carbapenem resistance, risk factors of resistance, and factors affecting 28-day mortality were investigated. Patients younger than 18 years old and patients with polymicrobial bloodstream infections were excluded from the study.

Microbiology

Blood culture bottles (BD BACTEC™ PLUS Aerobic/F Medium; Becton-Dickinson Diagnostic Systems) sent to the microbiology laboratory of our hospital were incubated for 7 days in a BD BACTEC™ FX device (Becton-Dickinson Diagnostic Systems). In samples with positive signals during this period, gram staining was performed, and then samples were incubated in 5% sheep blood agar (Salubris, Turkey), EMB agar (Salubris), and chocolate agar (Salubris) at 37°C for 18–24 h. All positive cultures were further processed for identification of pathogens by colonial morphology, gram staining, and biochemical tests. The bacteria that had grown were identified by conventional methods and the BD Phoenix™ Automated Microbiology System (BD Diagnostics, France). The susceptibility of isolates to antimicrobial agents was tested using the BD Phoenix™ Automated Microbiology System (BD Diagnostics) according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI) (16).

Statistical analyses

Analyses were performed using IBM SPSS Statistics 21. Continuous variables were described as means ± standard deviations and ranges. Categorical variables were analyzed using the chi-square test or Fisher's exact test when appropriate. Univariate and multiple logistic regression analyses (forward stepwise) were performed to better understand thecharacteristics of patients and their relationship with 28-day mortality. Variables were entered into the model when P < 0.05.

The study was approved by the local ethics committee (Date: May 25, 2017, Decision number: 1).

RESULT

A total of 288 patients with KPBSI were identified. Of these, 155 (53.8%) were males ranging from 18 to 104 (63.4±17.8) years old. Off 288 BSI, 64 (22.2%) were due to CRKP. All of those infections were healthcare related, and CRKP isolates accounted for 27.9% of all healthcare-related KPBSI. The results of univariate analyses were shown in Table 1. In multivariate logistic regression analyses, antibiotic use was the most important risk factor for CRKP-BSI (P=0.000, odds ratio: 0.247, 95% confidence interval: 0.132–0.44).

In this study, the overall mortality rate was 49.6%. Mortality was higher in patients with CRKP-BSI than in patients with carbapenem-sensitive *Klebsiella pneumoniae* bloodstream infections (CSKP-BSI) (64% vs. 32.1%, P>0.0001). Antibacterial treatments and clinical outcomes of patients were shown in Table 2. The results of univariate analyses of mortality were shown in Table 3. In multivariate logistic regression analyses, severe sepsis was the most important risk factor for 28-day mortality for KPBSI (P=0.000, odds ratio: 15,147, 95% confidence interval: 5,309–16,393).

Table 1. Characteristics of patients: carbapenem-resistant versus carbapenem-sensitive bloodstream infection

	Total (288) n (%)	Carbapenem resistant (n=64) n (%)	Carbapenem sensitive (n=224) n (%)	P
Age*	63.4±17.8	63.2±17.8	64.2±17.7	0.695
Male sex	155 (53.8%)	32 (50%)	123 (54.9%)	0.487
Healthcare-related infection	229 (79.5%)	64 (100%)	165 (73.7%)	0.000
ICU-acquired infection	106 (36.8%)	37 (57.8%)	69 (30.8%)	0.000
Probable source of infection				
Primary	87 (30.2%)	20 (31.3%)	67 (29.9%)	0.837
Catheter	52 (18.1%)	22 (34.4%)	30 (13.4%)	0.000
Lung	39 (13.5%)	11 (17.2%)	28 (12.5%)	0.334
Urinary	89 (30.9%)	9 (14.1%)	80 (36.7%)	0.001
Intra-abdominal	14 (4.9%)	2 (3%)	12 (5.4%)	0.464
Skin and soft tissue	7 (2.4%)	0 (0%)	7 (3%)	0.152
Comorbidities				
Diabetes mellitus	59 (20.5%)	15 (23.4%)	44 (19.6%)	0.507
Chronic renal failure	70 (24.3%)	21 (32.8%)	49 (21.9%)	0.072
Solid organ malignancy	51 (17.7%)	10 (15.6%)	41 (18.3%)	0.621
Hematological malignancy	48 (16.7%)	9 (14.1%)	39 (17.4%)	0.526
Chronic obstructive pulmonary disease	21 (7.3%)	5 (7.8%)	16 (7.1%)	0.856
Congestive heart failure	22 (7.6%)	6 (9.4%)	16 (7.1%)	0.553
Extrinsic factors				
Trauma	19 (6.6%)	10 (15.6%)	9 (4%)	0.001
Surgical procedure in the previous 3 months	75 (26%)	23 (36.9%)	52 (%23.2)	0.041
Mechanical ventilation	71 (24.7%)	30 (46.9%)	41 (18.3%)	0.000
Central venous catheter	101 (35.1%)	36 (56.3%)	65 (29%)	0.000
Total parenteral nutrition	54 (18.8%)	23 (35.9%)	31 (13.8%)	0.000
Exposure to antibiotic use in the past 30 days	90 (31.2%)	36 (56.2%)	54 (24.1%)	0.002

1. *mean ± standard deviation

Table 2. Therapy and clinical outcomes of patients: carbapenem-resistant versus carbapenem-sensitive bloodstream infection

	Total (288) n (%)	Carbapenem resistant (n=64) n (%)	Carbapenem sensitive (n=224) n (%)	P
Severe sepsis	96 (33.3%)	29 (45.3%)	67 (29.9%)	0.021
Septic shock	25 (8.7%)	4 (6.3%)	21 (9.4%)	0.434
Appropriate empirical therapy	167 (58%)	9 (14.1%)	158 (70.5%)	0.000
28-day mortality	113 (49.6%)	41 (64%)	72 (32.1%)	0.000

Table 3. Clinical variables and associations with 28-day mortality

	Total (n=288) n (%)	Nonsurvivors (n=113) n (%)	Survivors (n=175) n (%)	P
Age*	63.4±17.8	66.4±17.8	61.5±17.5	0.022
Male sex	155 (53.8%)	58 (51.3%)	97 (55.4%)	0.495
Healthcare-related infection	229 (79.5%)	103 (91.2%)	126 (72%)	0.000
ICU-acquired infection	106 (36.8%)	63 (55.8%)	43 (24.6%)	0.000
Probable source of infection				
Primary	87 (30.2%)	38 (33.6%)	49 (28%)	0.310
Catheter	52 (18.1%)	29 (25.7%)	23 (13.1%)	0.007
Lung	39 (13.5%)	23 (20.4%)	16 (9.1%)	0.007
Urinary	89 (30.9%)	20 (17.7%)	69 (39.4%)	0.000
Intra-abdominal	14 (4.9%)	1 (0.8%)	13 (7.4%)	0.012
Skin and soft tissue	7 (2.4%)	2 (1.8%)	5 (2.9%)	0.559
Comorbidities				
Diabetes mellitus	59 (20.5%)	23 (20.4%)	36 (20.6%)	0.964
Chronic renal failure	70 (24.3%)	32 (28.3%)	38 (21.7%)	0.202
Solid organ malignancy	51 (17.7%)	17 (15%)	34 (19.4%)	0.341
Hematological malignancy	48 (16.7%)	25 (22.1%)	23 (13.1%)	0.046
Chronic obstructive pulmonary disease	21 (7.3%)	8 (7.1%)	13 (7.4%)	0.911
Congestive heart failure	22 (7.6%)	13 (11.5%)	9 (5.1%)	0.047
Extrinsic factors				
Trauma	19 (6.6%)	11 (9.7%)	8 (4.6%)	0.085
Surgical procedure in previous 3 months	75 (26%)	29 (25.7%)	46 (26.3%)	0.907
Mechanical ventilation	71 (24.7%)	43 (38.1%)	28 (16%)	0.000
Central venous catheter	101 (35.1%)	55 (48.7%)	46 (26.3%)	0.000
Total parenteral nutrition	54 (18.8%)	36 (31.9%)	18 (10.3%)	0.000
Exposure to antibiotic use in the past 30 days	90	47	43	0.002
Severe sepsis	96 (33.3%)	70 (61.9%)	26 (14.9%)	**0.000**
Septic shock	25 (8.7%)	18 (15.9%)	7 (4%)	**0.000**
Carbapenem resistance	64 (%)	41 (36.3%)	23 (13.1%)	**0.000**
Appropriate empirical therapy	167 (58%)	51 (45.2%)	116 (66.3%)	**0.000**

*mean ± standard deviation

DISCUSSION

We evaluated clinical characteristics, 28-day mortality rate, and risk factors for mortality in patients with KPBSI. We found that most KPBSI (79.5%) were healthcare related, and the sources of KPBSI bacteremia were urinary tract infections (30.9%), catheter-related infections (18.1%), respiratory tract infections (13.5%), and primary BSI (30.2%). The total 28-day mortality rate from KPBSI was 49.6%. According to the literature, the mortality rate from KPBSI is within the range of 23% to 69%, and in several studies the mortality rate was higher for nosocomial-acquired

BSI than community-acquired BSI (17–26). In a study by Wu *et al*., old age; an APACHE II score >15; respiratory tract infections; skin soft tissue infections; inappropriate antimicrobial use; and concomitant malignancy, liver cirrhosis, and chronic renal failure therapy were risk factors associated with higher mortality from KPBSI (26). Kang *et al*. (23) reported that inappropriate antibiotic use, peritonitis, pneumonia, unknown sites of infection, septic shock at the initial presentation, and increased APACHE II scores were independent risk factors for 30-day mortality. In a study by Durdu *et al*., mortality was significantly higher in patients with sepsis, septic shock, ICU-acquired BSI, renal failure, pneumonia as a source of BSI, presence of a central venous or urinary catheter, mechanical ventilation, colostomy, transfusion, hemodialysis, and carbapenem resistance (3). In our study, the mortality rate was higher among BSI patients with pneumonia and catheter-related infections. KPBSI due to lung infection was associated with significantly poorer prognoses (1, 3, 23–26).

The development of severe sepsis and septic shock are among the most important factors affecting mortality from KPBSI (1–3, 11, 17–24). Multivariate logistic regression analyses showed that severe sepsis was the most important risk factor for mortality. Infectious disease specialists should consider early initiation of appropriate empirical treatment in cases of KPBSI with sepsis.

Antibiotic resistance is a major problem for the treatment of KPBSI. In our study group, 64 of 288 patients (22.2%) had CRKP-BSI. We assessed the risk factors of carbapenem resistance among patients with KPBSI. Antibiotic use in the past 30 days was the most significant risk factor for CRKP-BSI in multivariate logistic regression analyses. Several risk factors for carbapenem resistance have been described in the literature. Falagas *et al*. (27) reported that prior use of quinolones and anti-pseudomonal penicillin were independent risk factors for CRKP-BSI. Hussein *et al*. (28) found an independent association between previous exposure to carbapenems or fluoroquinolones and subsequent development of CRKP infections. The existence of serious comorbid diseases, disruption of anatomical barriers due to the use of invasive devices (mechanic ventilation, central venous catheter, etc.), prolonged hospital stay, and immunosuppression were also important factors in the high incidence of carbapenem resistance in the literature (2, 3, 17–30).

In our study, the 28-day total mortality rate was 49.6% in KPBSI patients and 64% in CRKP-BSI patients. Appropriate empirical therapy was performed on 58% of patients with KPBSI, which decreased to 14.1% in CRKP-BSI patients. Carbapenems are usually the antibiotics of choice for treating serious infections in hospitalized patients. The emergence of carbapenem resistance in *Klebsiella pneumoniae* may limit the therapeutic options for treating these infections.The impact of carbapenem resistance on KPBSI-related mortality is controversial. Several studies have found an association between carbapenem resistance and increased mortality, whereas others have not (1, 24, 29, 31). In our study, carbapenem resistance increased mortality from KPBSI, although the presence of severe sepsis was the most important prognostic factor.

Our study has several limitations. The retrospective nature of the study and the small number of patients are the main limitations, and we believe that further multicenter, prospective studies are needed.

In conclusion we found that most patients with KPBSI in our study had hospital-acquired infections. Of the cases of KPBSI, 22.2% were due to CRKP, and all of those infections were healthcare related. Exposure to antibiotic use was the most important risk factor for CRKP-BSI. Mortality was higher in patients with CRKP-BSI than in patients with CSKP-BSI. Severe sepsis was the most important risk factor for mortality. There is no funding or conflict of interest to declare.

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